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**NEUROPSYCHOLOGY OF SLEEP AND BREATHING:  
THE EFFECTS OF OBSTRUCTIVE SLEEP APNEA SYNDROME  
ON COGNITION**

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## SUMMARY

Obstructive Sleep Apnea Syndrome (OSAS) is a common sleep disorder that has drawn the attention of neuropsychologists because of its possible deleterious effects on cognition. Several are the causes of the impairments this syndrome can produce, like fragmentation of sleep, intermittent nocturnal hypoxia and daytime sleepiness. Apolipoprotein E4 (APOE4) may also play a role in OSAS and it has been suggested as a trigger of cognitive impairment and of dementia-like patterns. This dissertation begins with a critical review of the literature, with the aim to provide the current overview of the main controversies about OSAS and its effects on brain and cognition. Three experimental studies aiming to shed light on the nature of the relationship between OSAS and cognition are then proposed. The first two studies focus on the effects of OSAS on information processing speed. Innovative measures have been proposed to clarify whether different components of information processing speed are impaired in OSAS (Study 1), and to evaluate the efficacy over time of the continuous positive airway pressure treatment (Study 2). Finally, Study 3 aims to evaluate the effects of APOE4 on psychometric performance, and to investigate at which sleep stage its presence could be a predictor of cognitive impairments in OSAS patients. Results show that OSAS is associated with impairment of the motor component of information processing speed, which can however be properly recovered after treatment. Furthermore, a retention memory deficit is reported in OSAS patients carrying APOE4, and NREM sleep fragmentation has been found to be directly involved in this impairment. This dissertation supports the hypothesis of a cognitive frailty associated with OSAS, however discouraging its irreversibility, and argues that APOE4 can be considered a risk factor for the memory loss observed in this syndrome.

## Chapter 1

### THE SYSTEMIC DIMENSION OF COGNITION: THE LINK BETWEEN INTERNAL MEDICINE PATHOLOGIES AND CLINICAL NEUROPSYCHOLOGY

#### 1.1 Introduction

One of the main aims of clinical neuropsychology has historically been the evaluation of the effects that neurological disorders have on cognition and behavior. The human brain is extremely complex and its potential dysfunctions can be due to subtle, complex, sometimes unclear and challenging associations of numerous factors. This becomes even truer when signs and symptoms are associated with broad spectrum diseases that do not primarily involve the central nervous system.

The brain is almost entirely dependent on the other organs and systems of the body for the maintenance of its appropriate functioning as it cannot provide by itself all the substances necessary for its livelihood and it cannot store energy. Consequently, stable and efficient metabolic functioning of all the other organs and systems is not only fundamental, it also has to be uninterruptedly adequate. Since a strong relationship exists between the brain and the body, it is clear that some internal medicine pathologies, even if temporary, can potentially have adverse aftermaths on neuropsychological functioning. Anatomical, neurochemical and physiological changes in the brain may originate from more generalized medical diseases and impairment in cognitive functioning and in behavioral regulation may occur. Cerebral integrity can be affected by a number of mechanisms able to alter its normal functioning. For example, an organ or a more complex physiological system may be inefficient in not providing the brain with enough quantities of nourishing substances or not being able to complete its metabolic or physiological functions. Conversely, it may be excessively active, thereby disrupting normal cerebral functioning. A synergistic relationship among all organ systems in the living organism exists so that alteration of

any of them can potentially compromise the functioning of one or all of the others. Therefore, the manifested cerebral dysfunction is usually not caused by damage to a single organ/system, but rather reflects the result of a complex and interconnected chain of different biological events. The link between internal medicine pathologies and clinical neuropsychology could be well represented by the so called “systemic dimension of cognition” (Morin, 1992). According to this view, functional cognitive processes are possible thanks to a healthy and nourished brain whose good functioning depends, in turn, on the wellness of the whole organism which lives and operates in favorable physical and social environments. Any impairment at any of these levels can thus contribute to developing several and disparate dysfunctions. The title of the present dissertation aims to reflect this relationship between the brain and the body: sleep and breathing are directly considered part of the central nervous system, and their impairment can be responsible for neuropsychological deficits, as it will be showed in the following chapters.



## 1.2 Brain Metabolism

The brain is metabolically one of the most active organs of the body and, as mentioned in the Introduction, it has high energy requirements. Although the brain represents only 2% of the body weight, it needs 15% of cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization. Glucose metabolism provides the energy for physiological brain functions through the generation of adenosine triphosphate (ATP), a crucial element for neuronal and non-neuronal cellular maintenance, and generation of neurotransmitters. Appropriate regulation of glucose metabolism is critical to brain physiology and its dysfunction could trigger other diseases affecting the brain itself and the entire organism. The role of glucose in modulating cognitive processes is also well recognized. It has been found to increase learning and memory in both young and old populations of animals and humans (Craft, Murphy, & Wemstrom, 1994; McIlwain, 1959). Conversely, impairments in some cognitive skills have been recognized as a possible aftermath of long-standing non-insulin- and insulin-dependent diabetes mellitus, while enhanced glycemic control can improve performance on selective areas of cognition in these clinical populations (Kodl & Seaquist, 2008).

Oxygen is also extremely important for the healthy functioning of the brain, which is particularly sensitive to its deprivation especially when it occurs over extended periods of time. For example, increased levels of Carbon Dioxide ( $\text{CO}_2$ ) that follow lack of oxygen can impair the cellular oxidative metabolism; consequences vary from slight cardiovascular and neurobehavioral effects at low concentrations, to unconsciousness and death after prolonged exposures, or after acute exposures to high concentrations of  $\text{CO}_2$  (Raub, Mathieu-Nolf, Hampson, & Thom, 2000). Though the neuropathological changes caused by  $\text{CO}_2$  exposure are related to  $\text{CO}_2$ -induced hypoxia (Okeda et al., 1981), other biochemical mechanisms are involved in cellular damage, such as neuro-excitotoxicity (Jarrard & Meldrum, 1993), ischemia/reperfusion injury (Thom, 1990). Deleterious effects of hypoxia are reported not only when it is acute or chronic (conditions which are much

better known), but also when it is intermittent. The present dissertation will focus on the latter, which consists of repeated episodes of hypoxia alternated with normal oxygen supply. Intermittent hypoxia has drawn the attention of researchers and clinicians because of its association with hypertension, developmental deficiencies, enhanced susceptibility to oxidative injury, increased myocardial and cerebral infarction, and neuropathological and neurocognitive deficits (Neubauer, 2001). This intermittent lack of oxygen would also be responsible for changes in the cerebral production of ATP (Benzi, Gorini, Arnaboldi, Ghigini, & Villa, 1994), for impairing cerebral lipid metabolism (Alberghina & Giuffrida, 1981), and the activity of important metabolic enzymes in the brain (Marzatico, Curti, Dagani, Taglietti, & Benzi, 1986). Alterations of the brain concentrations of stem methionine-enkephalin (Gingras-Leatherman, McNamara, & Lawson, 1986) and of serotonin (McNamara, Gingras-Leatherman, & Lawson, 1986) have also been reported as consequences of intermittent hypoxia. In summary, this cascade of events would be caused by episodes of hypoxia producing changes in metabolic pathways, causing inflammatory processes which could underlie short- and long-term changes in neuronal functions (Neubauer, 2001).

A particular example of intermittent episodes of hypoxia is well represented by Obstructive Sleep Apnea Syndrome (OSAS), a sleep disorder characterized by episodic obstructions of airflow during sleep. Intermittent hypoxia is believed to produce the major clinical consequences of OSAS, which are going to be examined in depth in the next chapters of this dissertation.

### **1.3 The importance of sleep**

As well as glucose and oxygen, sleep is also extremely important in warranting the organism good physiological functioning. According to a simple behavioral definition, sleep is a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment (Kriger, Roth, & Dement, 2017). It is a complex combination of physiological and behavioral processes. Sleep is typically accompanied by postural recumbence, behavioral quiescence, closed

eyes and all the other indicators commonly associated with sleeping. Other behaviors can occur when the normal processes of sleep are defected. These behaviors can include sleep-walking, sleep-talking, teeth grinding and other physical and motor activities. Within sleep, two separate states have been defined: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM sleep is conventionally divided into four stages defined by means of an electroencephalogram (EEG). The EEG pattern in NREM sleep is commonly described as “synchronous”, with such characteristic waveforms as sleep spindles, K-complexes, and high voltage slow waves. NREM sleep is usually associated with minimal or fragmentary mental activity. Conversely, REM sleep is defined by EEG activation, muscle atonia, and episodic bursts of rapid eye movements. REM sleep is not usually divided into stages, although atonic and phasic types of REM sleep are occasionally distinguished. The most used marker of REM sleep is the occurrence of rapid eye movements; muscle contractions and cardiorespiratory irregularities and alterations often accompany REM bursts. Several theories have been proposed in order to identify the functions of sleep, and the main ones are reported below:

The Restorative theory maintains that body tissue restoration would be ascribed to NREM sleep, while brain tissue restoration to REM sleep. The restorative processes of sleep would be supported by increased secretion of anabolic hormones (e.g., growth hormone, prolactin, testosterone, luteinizing hormone) (Takahashi, Kipnis, & Daughaday, 1968; Sassin et al., 1973; Boyar, Rosenfeld, & Kapen, 1974; Weitzman & Hellman, 1974) and decreased levels of catabolic hormones (e.g., cortisol) (Weitzman & Hellman, 1974) during sleep, along with the subjective feeling of being refreshed after sleep.

The Energy conservation theory, as the name suggests, asserts that body energy is preserved during sleep. Zepelin and Rechtschaffen (1974) found that animals with a high metabolic rate sleep longer than those with a slower metabolism, thus supporting this theory.

The Adaptive theory suggests that sleep is an adaptive behavior that allows animals and humans to survive under several environmental conditions (Siegel, 2005; Mahowald, Chokroverty, Kader & Schenck, 1997).

The Memory consolidation and reinforcement theory claims that sleep can reinforce new memories. For example, it has been suggested as able to retrieve memories that are lost during wakefulness. Both REM and NREM sleep would be essential during these processes, although with different roles. Vertes and Siegel (2005) suggested that REM sleep is not involved in memory consolidation, which seems instead to be mediated by NREM sleep and, in particular, by slow waves sleep.

The Synaptic and neuronal network integrity theory maintains that sleep is essential for the preservation of synapses that are not adequately stimulated during wakefulness (Siegel, 2005; Krueger, Obal Jr., Kapas, & Fang, 1995). Both REM and NREM sleep would be fundamental for synaptic reorganization (Krueger, Obal Jr, Kapas, & Fang, 1995), although the latter would sustain non-motor activities, and the former would maintain motor circuits (Krueger, Obal Jr, Kapas, & Fang, 1995; Kavanau, 1997).

The importance of sleep can be emphasized by the effects that its deficiency can have on humans (Banks & Dinges, 2007). Numerous studies have investigated the role of sleep deprivation on human well-being. Circadian rhythm and homeostasis are altered by lack of sleep, while among the major effects of sleep deprivation are cognitive impairments (Van Dongen, Maislin, Mullington, & Dinges, 2003) and mood liability (Banks & Dinges, 2007). Modifications observed in electroencephalographic (EEG) recordings (Borbély et al., 1981) proved that sleep dysfunctions can be acknowledged for altering the central nervous system functions and causing cognitive performance deficits (Horne, 1988; Horne, 1993). Decrements of performance, vigilance, attention and concentration are direct effects of sleep deficiency making up the basis for higher-level cognitive function impairments (Chokroverty, 2017).

## **1.4 Sleep breathing disorders: Obstructive Sleep Apnea Syndrome**

The term ‘sleep disordered breathing’ encompasses a range of conditions characterized by abnormal breathing during sleep, associated with narrowing or obstruction of the upper airway (pharynx). Disordered breathing ranges from intermittent, partial obstruction of the airway without sleep disturbance (snoring) to frequent apneas associated with repetitive hypoxia and arousals leading to sleep disruption and daytime sleepiness. Sleep breathing alterations involve different kinds of disorders. An example is central sleep apnea (CSA), in which periodic cessation of breathing occurs without obstruction of the airway and which, in adults, is seen mainly in heart failure. Obesity hypoventilation syndrome (OHS) represents another case in which breathing is reduced throughout sleep, with or without accompanying narrowing or obstruction of the upper airway. However, the most common and studied sleep disordered breathing is Obstructive Sleep Apnea Syndrome (OSAS).

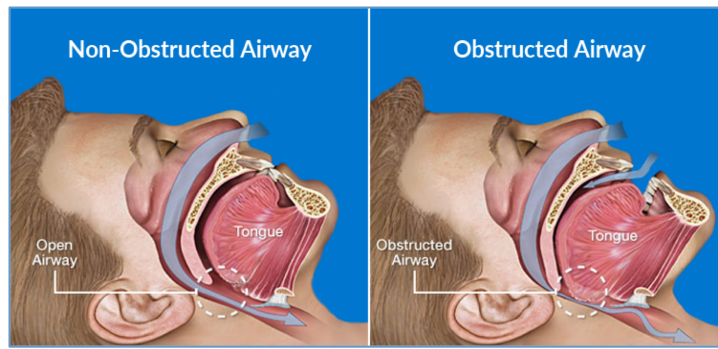
In developed countries, OSAS is reported to affect 10% of men and 3% of women between the ages of 30–49 years, while it is present in 17% of men and in 9% of women between the ages of 50–70 years (Chokroverty, 2017). These data prove that OSAS prevalence increases with age, reaching a plateau after 60 years of age. OSAS is diagnosed based on symptoms (usually daytime sleepiness) reported by the patient him/herself or, more frequently, by his/her caregiver, and by objective evidence of disordered breathing during sleep. The frequent obstruction of the upper airway during sleep results in repetitive breathing pauses accompanied by oxygen desaturation and arousal from sleep. An association between obesity and OSAS has been noted in many studies, with moderate or severe obesity (body mass index (BMI) > 30 kg·m<sup>-2</sup>) in 60–90% of patients with OSAS (Romero-Corral, Caples, Lopez-Jimenez, & Somers, 2010). Central obesity, characterized by a high waist-to-hip ratio or large neck circumference, correlates better with OSAS than BMI, even in people with a normal BMI. As already seen, men are affected by OSAS more commonly than women. This has been attributed to differences in anatomical and functional characteristics of the upper airway, in

craniofacial morphology and fat deposition, and to different ventilator responses to arousal from sleep. First-degree relatives of patients with OSAS have a higher risk of developing this disorder. The genetic determinants of craniofacial features, obesity and regional fat distribution are also relevant.

Smoking is associated with higher prevalence of snoring and OSAS, as is alcohol, which can increase upper airway collapsibility leading to apneas (Chokroverty, 2017). Muscle-relaxant medication (sedative hypnotic drugs, opiates), sleep deprivation and supine posture can all aggravate OSAS, although the degree to which sleep disordered breathing is worsened in an individual may depend on the predominant pathological mechanisms in the patient and his/her own physiological responses (Chokroverty, 2017).

### **1.5 Physiopathology and clinical manifestations of Obstructive Sleep Apnea Syndrome**

The pharynx is the site in which the upper airway obstruction occurs during sleep in OSAS patients. Any pathological change or normal variant of the upper airway can predispose the individual to obstructive apnea or hypopnea during sleep. Obesity is the most common risk factor, but patients with OSAS may have other predisposing factors that narrow the upper airway, such as a large tongue, enlarged tonsils, increased total soft tissue in the pharynx, or a retro-positioned mandible (receding jaw). *Figure 1* shows the collapse of the upper airway (i.e. tongue and soft palate) that causes the obstruction, with consequent episodes of apnea. Each apnea episode is followed by arousals and, as a result, a surge in heart rate and blood pressure occurs. In many individuals, this vascular alteration can persist all day long, with its associated risk of cardiovascular disease and stroke (Young et al., 2002).



**Figure 1** Obstruction of the upper airway

OSAS symptoms can be classified into two categories: those manifested during sleep, and those showed during wakefulness and in daytime. The most common complaint reported by patients with OSAS is excessive daytime sleepiness (EDS) (Engleman & Douglas, 2004). A complete summary of OSAS symptoms is reported in Table 1.

<b>During sleep</b>	<b>During awake time</b>
Loud snoring/snorting	Daytime sleepiness
Witnessed apneas by bed partner	Non-restorative sleep
Awakening with choking	Lack of concentration
Nocturnal restlessness	Cognitive deficits
Vivid, strange or threatening dreams	Changes in mood
Gastro-esophageal reflux	Morning headaches
Insomnia with frequent awakenings	Dry mouth
Nocturia (urination at night)	Impotence or decreased libido
Hyper-salivation, teeth grinding	
Diaphoresis (sweating)	

**Table 1.** Nighttime and daytime symptoms of OSAS

## 1.6 Nighttime and daytime recording and measuring sleep and breathing

Detailed overnight polysomnography (PSG) has been the most commonly used method for the diagnosis of OSAS; however, simpler diagnostic investigations are increasingly being employed, and these can now be used at the patient's home, rather than in hospital. PSG remains the gold standard instrument, simultaneously monitoring nasal and/or oral airflow, thoracic-abdominal movement, snoring, electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG) and oxygen saturation.

According to the American Academy of Sleep Medicine (Westchester, IL), the diagnosis of OSAS can be formulated when the patient presents criterion A or B, plus criterion C, as follows:

- A. Excessive daytime sleepiness not better explained by other factors;
- B. Two or more of the following not better explained by other factors:
  - Choking or gasping during sleep
  - Recurrent awakenings from sleep
  - Unrefreshing sleep
  - Daytime fatigue
  - Impaired concentration;
- C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep.

Three levels of severity of OSAS are proposed, based on the frequency of abnormal respiratory events during sleep:

- *Mild* OSAS: 5–15 events/hour of sleep;
- *Moderate* OSAS: 15–30 events/hour of sleep;
- *Severe* OSAS: More than 30 events/hour of sleep.



Several measures have been proposed for the assessment of excessive daytime sleepiness. Cluydts et al. (2002) divided these measures into behavioral measures and subjective rating scales. Behavioral measures include a performance test, evaluating vigilance and attention (e.g., the psychomotor vigilance task, PVT). Subjective rating scales reflect acute or global sleepiness. The Stanford Sleepiness Scale (SSS) and the Epworth Sleepiness Scale (ESS) (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) are just two of the most commonly used subjective measures of sleepiness. The SSS measures sleepiness at a particular time, while the ESS measures global or typical sleepiness (Johns, 1992).

### **1.7 Consequences of OSAS**

OSAS can cause significant daytime behavioral and adaptive deficits. Functional impairments like sleepiness, impaired driving, increased risk of accidents, and decreased quality of life are frequent consequences of sleep apnea (Engleman & Douglas, 2004; George & Smiley, 1999). OSAS has also been implicated in the etiology of cardiovascular conditions, including hypertension, coronary artery disease, congestive heart failure and stroke (Young et al., 2002). In particular, it has drawn the attention of neuropsychologists because of its possible deleterious effects on cognition. The next chapter will focus on the controversies underlying OSAS and its aftermaths on the brain and on neuropsychological functioning.

## Chapter 2

### OBSTRUCTIVE SLEEP APNEA SYNDROME AND ITS CONTROVERSIAL EFFECTS ON COGNITION

#### 2.1 Introduction

As already mentioned, Obstructive Sleep Apnea Syndrome (OSAS) is a sleep disorder which, because of its typical characteristics, can alter normal global body functioning. Numerous are the cardiovascular, metabolic and cerebrovascular morbidities (Ryan & Bradley, 2005) associated with OSAS. Among other factors, these medical consequences have been found to be directly involved in the cognitive impairments described in OSAS patients. The most frequently affected domains seem to be attention, memory, and, in particular, executive functions, such as problem solving, planning, goal-oriented behavior, and mental flexibility (Décary, Rouleau, & Montplaisir, 2000). However, conflicting effects of OSAS on the brain have been reported. Most studies agree that there is an association between this sleep disorder and important changes in both the amount of cerebral blood flow and its speed (Gillin et al., 2002). The regions more frequently damaged in this syndrome are primarily the pre-frontal cortical lobes (Beebe & Gozal, 2002). The standard treatment of this sleep disorder is the self-administration of continuous positive air-way pressure (CPAP), a prosthetic noninvasive intervention (Stuck, Leitzbach, & Maurer, 2012). Regular use of CPAP has been reported to lower cardiovascular mortality and reduce daily sleepiness (Torraldo, De Nuccio, & Nicolardi, 2011), which may be one of the causes of the cognitive deficits associated with OSAS (Engleman, Kingshott, Martin, & Douglas, 2000) and a significant risk factor in everyday life. Some authors maintain that daily use of CPAP makes cognitive impairments reversible (Canessa et al., 2011; Castronovo et al., 2014; Dalmases et al., 2015). However, it is stated elsewhere that the cognitive deficits associated with OSAS are irreversible, leading to cognitive decline such as a “pseudodementia” pattern of deficits (Bédard, Montplaisir, Malo,

Richer, & Rouleau, 1993). In order to shed light on the current evidence reported in the literature, the presence, the nature and the possible reversibility of cognitive impairments associated with this sleep disorder are discussed in the next paragraphs.

## **2.2 Controversies about the locus of structural brain damage in Obstructive Sleep Apnea Syndrome**

Beebe and Gozal (2002) have developed an etiological model of OSAS and state that the efficacy of sleep and of its restorative function is seriously compromised by the fragmentation of sleep itself and by intermittent hypoxia and hypercapnia directly caused by apneas. All these events trigger a homeostatic imbalance that could alter the normal communication between neuronal and glial cells, thus causing biochemical and cellular stress in different brain areas. The authors suggest that one of the main outcomes of OSAS is damage of the prefrontal regions of the cortex, demonstrated at behavioral level by executive dysfunction. In their model, the “executive system” includes behavioral inhibition, attentional shifting, emotion and arousal self-regulation, working memory, and contextual memory. An executive dysfunction may alter the recruitment of other cognitive abilities, causing maladaptive behavior in daily life (Beebe & Gozal, 2002). Additionally, neuropsychological tests have revealed that working memory and executive functions may be affected most by potential structural damage of the prefrontal cortex (Ferini-Strambi et al., 2003; Naegele et al., 1998). Explanations for structural changes and cognitive damage in OSAS have been put forward, but opinions are contradictory: some studies identify the presence of prefrontal damage, following which an executive dysfunction would occur (Bédard, Montplaisir, Richer, Rouleau, & Malo, 1991; Feuerstein, Naegele, Pepin, & Levy, 1997; Naëgelé et al., 1995), while others consider the cognitive impairment absent or non-significant, in spite of notable structural impairment (Kim et al., 1997; Lee, Givens, Wilson, & Robins, 1999; Redline et al., 1997;

Verstraeten, Cluydts, Pevernagie, & Hoffmann, 2004). Yaouhi et al. (2009) used optimized voxel-based morphometry procedure for the magnetic resonance imaging (MRI) data and resting-state 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET) and found an association between OSAS and structural changes at cerebral level (especially in the right hemisphere) with regard to gray matter density and metabolism. Hypoxia is known to produce extensive damage, in particular to the central nervous system. Gale and Hopkins (2004) compared two groups of patients, one with carbon monoxide poisoning and one with OSAS. Neuroimaging showed a reduction of hippocampal volume in both groups. Other authors claimed that neurons in the hippocampus and other neocortical structures might be selectively impaired by hypoxia (Chen et al., 1998; Daulatzai, 2013; Pulsinelli, Brierley, & Plum, 1982). These findings confirm that long-term effects of protracted intermittent hypoxia can result in cerebral vascular deficits and neurodegeneration, and in possible cognitive impairments due to the cumulative effects of prolonged hypoxia (Neubauer, 2001). Different areas of the brain show a reduction of gray matter density (Joo et al., 2010; Macey et al., 2002; Morrell et al., 2010) and, interestingly, anoxia has been found responsible for this structural damage, in particular for the basal ganglia, for the cerebellum, and, more precisely, in the hippocampal region. These areas are associated, respectively, to attentional skills, motor speed, and fine motor coordination abilities and to episodic memory. All these domains seem to be impaired in OSAS. Macey et al. (2002) confirmed these data and also gave a clear explanation about the structural-functional correspondences mentioned above. They proposed the inappropriate coordination of upper airway muscles from cerebellar dysfunction (due to gray matter loss) as one of the primary mechanisms underlying OSAS. Moreover, in their study, the hippocampus showed a reduction of gray matter volume (see also Algin, Akin, Ocakoğlu, & Özmen, 2016), which in turn would cause a deficit in the resumption of breathing after an apnea episode. Although the hippocampus is rarely considered a breathing control area, there are some hippocampal structures (e.g., dorsal hippocampus) that have been reported to be involved in the inspiratory onset after apnea (Harper, Poe, Rector, & Kristensen,

1998; Lockmann, Laplagne, Leao, & Tort, 2016; Poe, Kristensen, Rector, & Harper, 1996). Therefore, the reduction of gray matter density in the hippocampus would not only corroborate the hypothesis of prefrontal damage, but would also suggest more widespread impact than previously thought. A hippocampal dysfunction may be involved also in inappropriate context-regulation of affect disorders (Davidson et al., 2002). Consistently with this assumption, morphometric studies with MRI have described hippocampal atrophy in patients with major depression (Bremner et al., 2000). A strong link between chronic depression and serum brain-derived neurotrophic factor (BDNF) levels has been proposed. Several authors have showed a significant decrease of this important protein, which plays a pivotal role in the development of neurons of the central nervous system, in patients with depression compared to healthy controls (Brunoni, Lopes, & Fregni, 2008; Bus et al., 2015; Conner, Lauterborn, Yan, Gall, & Varon, 1997; Legge et al., 2015). Moreover, Wang, He, Xiao, Gu, and Chen (2012) suggested that also the serum BDNF level was lower in OSAS patients than in healthy participants. Since BDNF is considered as a key mediator of memory and cognition, the authors refer to its reduction as the cause of the cognitive impairment observed in OSAS (Giacobbo et al., 2016; Jiang et al., 2011; Laske et al., 2011; Wang et al., 2012; Wang, Wang, Zhao, Liu, & Li, 2010). The hippocampus seems to be involved also with BDNF (Fuchikami et al., 2011; Karege et al., 2002; Zafra, Hengerer, Leibrock, Thoenen, & Lindholm, 1990), and the hippocampal connection with breathing, mood, and cognition could explain the mutable pattern of symptoms shown by OSAS patients. Alchanatis et al. (2004) focused on the N-acetylaspartate and choline levels in the brain of patients with OSAS. They found a reduction of these intra-neural molecules in the frontal white matter of these patients, and they associated it with deficits in concentration, memory, and especially executive functions. The authors found that severe OSAS can result in axonal damage, whose lesions in the territory of the frontal cortical and subcortical circuits are often associated with cognitive deficits. Structural damage associated with OSAS has also been reported. Mean diffusivity (MD) procedures based on diffusion tensor imaging (DTI) are also useful in detecting neural pathology. Daulatzai (2015) published a review collecting all data

that showed a significant decrease in global brain MD values in patients with OSAS compared to controls. Many brain areas showed reduced regional MD values in OSAS (i.e. medullary, cerebellar, prefrontal and frontal, temporal, occipital, limbic, and insular, as well as basal ganglia, cingulum bundle, external capsule, corpus callosum, and corona radiata). This reduction would reflect axonal and glial changes, indicating ongoing pathological processes in OSAS (Kumar et al., 2012). Table 2 shows differences across studies on the neuroanatomical areas involved.

<b>Frontal damage</b>	<i>Canessa et al., 2011;</i> <i>Alchanatis et al., 2004;</i> <i>Ferini-Strambi et al., 2003;</i> <i>Beebe &amp; Gozal, 2002;</i> <i>Naegele et al., 1998;</i> <i>Naegele et al., 1995.</i>
<b>Widespread Damage (involving hippocampus, basal ganglia and cerebellum)</b>	<i>Algin, Akin, Ocakoglu &amp; Ozmen, 2016;</i> <i>Daulatzai et al., 2013;</i> <i>Joo et al., 2010;</i> <i>Morrel et al., 2010;</i> <i>Yaouhi et al., 2009;</i> <i>Gale and Hopkins, 2004;</i> <i>Morrel et al., 2003;</i> <i>Macey et al., 2002;</i> <i>Chen et al., 1998;</i> <i>Pulsinelli et al., 1982.</i>

**Table 2.** Brain structures involved in OSAS and the corresponding studies

### 2.3 Controversies about cognitive impairments in Obstructive Sleep Apnea Syndrome

Although cognitive deficits can be found in OSAS patients and become more severe as the disease advances (Kim, Dinges, & Young, 2007), this is not generally agreed upon by all researchers.

Yaouhi et al. (2009), for example, studied a group of patients with moderate-to-severe OSAS evaluating alertness and vigilance, divided attention, working memory, mental flexibility, and episodic memory. Their patients' neuropsychological data indicated mild memory and motor impairment and no evident cognitive deficits in any other domain compared with the control group. The authors explained the contrasting results between an evident metabolic and structural deficit and a minor cognitive impairment in terms of cognitive reserve of their subjects, which could have acted as a protective factor. Similarly, studies on executive dysfunction in OSAS have reported performance deficits also in other cognitive abilities (see Bédard et al., 1991; Feuerstein et al., 1997; Naëgelé et al., 1995), suggesting widespread impairment in many areas of cognitive functioning (not only in executive functions). However, other authors maintain that the cognitive deficits associated with OSAS are not meaningful, despite the extensive neuroanatomical changes observed (Sforza et al., 2010). Engleman et al. (2000) suggested the presence of deficits in attention, working memory, and executive functions with resulting disturbances in everyday life. The authors identified four main difficulties: daytime sleepiness, cognitive deficits, reduced driving competence, and impaired psychosocial well-being. In the previous section, we discussed Beebe and Gozal's (2002) prefrontal model, which greatly contributed to the comprehension of ensuing OSAS deficits. Besides explaining how OSAS can lead to damage of the prefrontal cortex because of events during sleep, the authors' model describes the main unfavorable effects experienced by OSAS patients during the day. The most investigated and predominant effect is daytime drowsiness, conventionally defined as the tendency to fall asleep during the day. However, adults with OSAS also show malaise in their social context due to their emotional liability and low motivation. Their performance at work is poor, and they must cope with failures in their job due to inadequate planning, disorganization, and diminished ability to make judgments (Day, Gerhardstein, Lumley, Roth, & Rosenthal, 1999; Doghramji, 1993; Redline & Strohl, 1998). All these aspects could be linked to the concept of "fatigue", which is defined as a gradual and cumulative process associated with a defeat of efficiency and a disinclination for any kind of effort

(Grandjean, 1979). It comprises tiredness, reduced strength, lack of vitality, lethargy, and difficulty with concentration often experienced and self-reported by patients with OSAS (Bardwell, Moore, Ancoli-Israel, & Dimsdale, 2003). It has been suggested that both fatigue and sleepiness impair the perceived quality of life of these patients and, in some cases, they can lead to minor psychiatric morbidity, having strong, negative consequences on many daytime functions and activities (Cheshire, Engleman, Deary, Shapiro, & Douglas, 1992). In particular, some authors argue that sleepiness and fatigue are the crucial responsible factors for cognitive impairment in patients with OSAS (Lis et al., 2008; Verstraeten, 2007). Sleep fragmentation and the ensuing daytime drowsiness are among the most important causes related to the decline of neurocognitive functions in OSAS patients. However, individuals with non-treated OSAS show a dysfunction that cannot be attributed to mere sleepiness. For example, in a multicenter, randomized, double-blind study which included a very large sample of patients with OSAS, Quan et al. (2011) did not find any relationship between disease severity and neurocognitive functions. In line with these results, Jurádo-Gámez, Guglielmi, Gude and Buéla-Casal (2016) did not report significant correlations between sleepiness and neurocognitive functions. According to some authors (e.g., Bardwell, Ancoli-Israel, Berry, & Dimsdale, 2001; Naëgelé et al., 1995), the neuropsychological impairment showed by patients with OSAS might be directly linked to disease severity, while others suggest that oxygen desaturation is responsible for these patients' poorer cognitive performance (e.g., Aloia et al., 2003; Quan et al., 2011). Gelir et al. (2014) conducted a study to examine the effects of OSAS on cognitive abilities to understand whether there is an association between hypoxemia and the cognitive performance of these patients. The authors used event-related potentials (ERPs) and analyzed the P300 component as an index of global cognitive functioning. This and other studies (e.g., Gosselin et al., 2014) have showed consistent changes in the P300 component, suggesting attentional deficits in patients with OSAS. To evaluate attention, working memory, procedural memory, and executive functions they used the n-back task, mirror-drawing, and Trail-Making Task A and B, showing a significant global slowdown of performance in patients with OSAS



compared to the control group, and a negative effect on learning, highlighted by reduced P300 amplitude. The attentional arousal and memory disturbances described in these patients are generally attributed to excessive daytime sleepiness, while their hypoxemia is correlated with the executive function deficit. Thus, their cognitive impairment is directly correlated with the severity of the obstructive syndrome itself, although the trend is not linear. In patients with OSAS the executive dysfunction is usually shaded, and it only occurs in complex activities that require great attentional resources, such as driving, working tasks, and social relationships (Engleman et al., 2000). Table 3 shows differences across studies on the cognitive functions impaired. Scanty evidence is available to quantify the impact of OSAS on individuals' work performance, security, and productivity as well as on the potential, additional, and indirect costs of lost productivity due to sleep disorders (Rosekind et al., 2010). Mulgrew et al. (2007) found that blue-collar workers with OSAS have time management and mental/interpersonal interactions impaired, while Sjösten et al. (2009) identified, more in general, selected indicators of work disability due to this sleep disorder, such as "total sickness absence," "long-term absence," and "disability pensions." To the best of our knowledge, not many studies have been carried out on this topic; however, it can be concluded that OSAS is associated with an increased risk of occupational accidents, reduced working ability, and poorer work efficacy.

<b><i>Executive Function Deficits</i></b>	<i>Beebe &amp; Gozal, 2002;</i> <i>Decary, Rouleau, &amp; Montplaisir, 2000;</i> <i>Engleman et al., 2000;</i> <i>Day, Gerhardstein, Lumley, Roth, &amp; Rosenthal, 1999;</i> <i>Redline &amp; Strohl, 1998;</i> <i>Doghramji et al., 1993.</i>
<b><i>Multiple Cognitive Deficits</i></b>	<i>Gelir et al., 2014;</i> <i>Yaouhi et al., 2009</i> <i>Feuerstein, Naegele, Pepin &amp; Levy, 1997</i> <i>Naegele et al., 1995</i> <i>Bedard, Montplaisir, Richer, Rouleau, &amp; Malo, 1991.</i>
<b><i>Absence of Cognitive Deficits</i></b>	<i>Sforza et al., 2010</i> <i>Verstraeten, Cluydts, Pevernagie, &amp; Hoffmann, 2004;</i> <i>Lee, Givens, Wilson, &amp; Robins, 1999;</i> <i>Kim et al., 1997;</i> <i>Redline et al., 1997.</i>

**Table 3.** Cognitive Deficits in OSAS and corresponding studies which found the indicated evidence

## **2.4 Reversibility versus non-reversibility of structural brain damage and cognitive impairments**

Another issue widely debated in the OSAS literature is the reversibility (or non-reversibility) of cognitive deficits and of brain structural changes due to sleep fragmentation and hypoxia. As seen above, intermittent hypoxemia is associated with higher vasoconstriction leading to decreased protective vascular mechanisms, which in turn can contribute to the development of structural and functional changes of brain vascularization (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004; Lanfranchi & Somers, 2001; Zimmerman & Aloia, 2006). Some studies based on voxel morphometry have showed a diminished density of the gray matter in frontal, parietal, temporal, and hippocampal areas, as well as in cerebellar regions in patients with OSAS (Macey et al., 2002). Similarly, Yaouhi

et al. (2009) reported a gray matter loss in frontal and temporo-parieto-occipital cortices and in hippocampal and cerebellar regions despite minimal cognitive and motor deficits. O'Donoghue and his research group (O'Donoghue et al., 2005) have long studied the possible reversibility of the several sequelae associated with this sleep disorder. At first, the authors documented no significant gray matter differences (by means of voxel-based morphometry) between OSAS patients and healthy controls. Furthermore, they did not report any change in brain volume after six months of CPAP treatment. This may suggest that there was no evidence of significant and permanent structural brain damage (O'Donoghue et al., 2005). However, in a second study, the same authors found a significant difference between OSAS patients and healthy controls in frontal lobes N-acetylaspartate/choline ratios (cited in the previous review as "markers" of cerebral damage) and in the hippocampus. After six months of CPAP, the frontal lobe damage in patients with OSAS did not reverse, while no difference between groups was observed in the hippocampus (O'Donoghue et al., 2012). In 1993 Bédard et al. published one of the most important studies about the reversibility of OSAS effects through CPAP. In their work, the authors aimed to further investigate the topic of reversibility of neuropsychological deficits (memory, attention, and executive functions) and to document possible anoxic damage to the brain. They found that CPAP was effective at both physiological and respiratory levels but a few cognitive deficits persisted (in the Verbal Fluency task, in the Trail- Making Test Part B, and, more in general, in those tasks tapping executive functions). According to Bédard and colleagues (1993), the cognitive deficits and sleepiness observed in OSAS were related to hypoxemia severity, and thus a structural, anoxic, and irreversible brain damage might be suspected. Contrasting results were also obtained by Kotterba et al. (1998) who showed a reversibility of deficits in some of the neuropsychological tests assessing alertness, sustained attention, and information processing, but also highlighted cognitive deficits (i.e., in selective and divided attention, and in vigilance) in the same study. Bardwell and colleagues (2001), instead, showed no beneficial effects of CPAP in any specific investigated cognitive domain. Canessa et al. (2011) hypothesized that neuropsychological impairments in short- and

long-term memory, executive functions, constructional abilities, vigilance, attention, and abstract reasoning observed in patients with OSAS might be associated with localized changes in the brain and could be reversible through treatment with CPAP. Before treatment, their patients greatly differed from controls regarding body mass index (BMI; OSAS patients had a much higher index), somnolence, and results of neuropsychological tests (performance of OSAS patients was significantly poorer than that of controls). After treatment with CPAP, the patients showed significant improvement in somnolence and on all cognitive tests. Also Mood and Quality of life significantly improved after treatment. With respect to structural brain changes, there was a significant reduction of gray matter volume in different brain areas of the patients before treatment, in particular at the hippocampal level. After CPAP, it was possible to observe an increase in the density of specific hippocampal clusters (left subiculum and bilateral entorhinal cortex) and the frontal area, such as superior gyri and frontal and orbitofrontal medial cortex (Canessa et al., 2011). These results contrast with those reported by O'Donoghue et al. (2005), who found no significant difference in gray matter between patients and controls either before or after treatment. Recently, Dalmases et al. (2015) supported the reversibility of impairment in elderly adults newly diagnosed with severe OSAS. Patients benefited from the use of CPAP and after a three-month treatment showed a significant improvement in short-term and episodic memory. Speed of mental processing and mental flexibility were enhanced after treatment. The CPAP group reported a significant gain in intensity of connectivity (Dalmases et al., 2015). Other recent findings show that just one month of CPAP treatment can restore several cognitive and morphometric deficits in patients with moderate-to-severe OSAS, assuming that 30 days are a sufficient timeframe for primary neuroplastic and neurocognitive changes (Rosenzweig, 2016). However, other studies, some of them very recent, have not confirmed these results, increasing the complexity of the overall picture. Jurádo- Gámez et al. (2016) showed limited effectiveness of four-month CPAP treatment in improving neuropsychological symptoms, reporting significant changes only in memory. Table 4 summarizes outcomes on the efficacy of CPAP treatment across studies.

<b>Reversibility</b>	<i>Rosenzweig, 2016; Dalmases et al., 2015; Canessa et al., 2011; O'Donoghue, 2005</i>
<b>Partial Reversibility*</b>	<i>Jurado-Gamez et al., (2016) O'Donoghue, 2012; Bardwell et al., 2001; Kotterbaa et al., (1998); Bedard et al., 1993.</i>
<b>Non Reversibility</b>	<i>Engleman &amp; Douglas, 2004</i>

**Table 4.** Outcomes after CPAP treatment and corresponding studies

## 2.5 Conclusions

The present work has focused on the cognitive dysfunction possibly caused by OSAS considering neuropsychological evidence (Engleman et al., 2000), structural brain changes (Macey et al., 2002), and reversibility (Canessa et al., 2011) or non-reversibility (Bédard et al., 1993; Engleman & Douglas, 2004) of signs of this sleep disorder. As reported, some authors (Alchanatis et al., 2004; Beebe & Gozal, 2002; Naëgelé et al., 1995) argue the existence of a specific and localized frontal lobe damage that could be responsible for the executive dysfunction observed in OSAS. However, there is also evidence showing how anoxia impairs different and widespread cortical and subcortical areas of the brain, compromising also other cognitive abilities (Joo et al., 2010; Macey et al., 2002; Morrell et al., 2010). Some researchers, however, have not confirmed the executive function impairment, stating that it is absent or just not significant (Kim et al., 1997; Lee et al., 1999; Redline et al., 1997; Verstraeten et al., 2004), while other studies show no cognitive impairment at all (Sforza et al., 2010). Controversies have also emerged about the possible reversibility of cognitive impairment due to OSAS. Canessa et al. (2011) and more recently Dalmases et al. (2015) are among those who support the reversibility of both structural and cognitive damage. On the other hand, O'Donoghue et al. (2012) and Bédard, Montplaisir, Malo, Richer and Rouleau (1998) only

partially support this possibility. In light of these contradictory data, we can affirm that it is not possible to draw definitive conclusions. Other factors taken into account in this review are the important sequelae associated with OSAS, which should be considered as a common occurrence in daily life. For instance, OSAS patients often face challenges in social and professional situations as a consequence of executive dysfunction (Day et al., 1999; Doghramji, 1993; Redline & Strohl, 1998). Many daily activities involve executive processes, and one clear case is driving a car. This is an example of a complex activity in daily life that often becomes problematic for OSAS patients. Findley, Unverzagt and Suratt (1988) stated that OSAS patients have a greater risk of car accidents than people without apneas. George, Boudreau and Smiley (1996) found that, during a simulated driving test, OSAS patients performed even worse than a control group impaired by alcohol abuse. Car accidents occurring to drivers with OSAS can help public opinion realize that they could have been prevented and may lead to increased awareness and recognition of this “silent” problem. We believe that the cognitive and behavioral features of OSAS represent an interesting matter for investigation, given the direct connection with quality of life (McMillan et al., 2014). This in turn is related to many other factors, such as the nutritional status, body mass (Browman et al., 1984), and mood. Drowsiness could potentially reflect changes in depressed mood, known to be common in OSAS (Peppard, Szklo-Coxe, Hla, & Young, 2006). Guilleminault (1989) showed that a high percentage of patients with OSAS had previously been evaluated by a psychiatrist because of anxiety or depression. This repeated and almost steady association was subsequently confirmed by several other authors (BaHammam et al., 2016; Pillar & Lavie, 1998; Schröder & O’Hara, 2005). It was suggested that the association between OSAS and depression may underlie a common neurobiological risk factor -that is, the level of serotonin. Adrien (2002) suggested that the serotonergic system has a central role for mood regulations, sleep-wakefulness cycle, and upper airway muscle tone control during sleep. Therefore, the decrease of serotonergic neurotransmission is the potential, common biological substratum in patients with depression and OSAS. According to Beebe and Gozal (2002), cognition and mood regulation are

neuroanatomically linked to the same areas, and thus disorders might derive from the same brain region. Their model, in fact, suggests that self-regulation of affect and arousal is fundamental to maintain the outcome. Mood, motivation and arousal frailties are consistent with a weakness in executive functions and derive from the same prefrontal cortex impairment. From all these findings it is difficult to draw a clear picture of OSAS deficits. Many investigations show divergent results and only partial clear and coherent reasoning on the relationship among neuroanatomy, neurophysiology, neuropsychology, and mood regulation. For example, even if the involvement of the prefrontal cortex is widely accepted, not all deficits of the executive type are the result of damage to these areas. Furthermore, the hippocampus is repeatedly reported as impaired with also a reduction in volume, but its involvement in several and different functions (i.e., memory, mood, arousal, and breathing) increases the complexity of the general frame of this syndrome. It is indeed difficult to have a definite overall picture of this syndrome because of the many controversial data reported in the literature. The absence of a clear trend could be due both to the different methodologies used in the studies and to the complexity and comorbidity of the syndrome. The challenge for better understanding OSAS is finding an explanation that considers all different results in light of comorbid conditions and the multiple neural dysfunctions potentially involved. The conflicting results concerning neurocognitive deficits in OSAS may be associated with other confounding factors such as age, obesity, educational level, and intelligence. For example, Alchanatis et al. (2005) showed that cognitive decline in OSAS is age-dependent: older patients were more compromised than younger patients with the same disease severity. The authors proposed that younger patients were able to compensate for the cognitive losses of sleep deprivation and nocturnal hypoxia through greater brain plasticity. Another possible factor is mood disorder. This could become more relevant if we consider that early diagnosis may limit consequences of the potential reversibility of the impairments. Povitz et al. (2014) suggested that CPAP, besides reducing respiratory disturbances, may even decrease severity of depression, although this is an additional controversial issue (Lee, Bardwell, Ancoli-Israel, Lored, & Dimsdale, 2012).

Nevertheless, as mentioned before, Dalmases et al. (2015) demonstrated the role of CPAP in improving the cognitive impairment associated with OSAS. In agreement with the authors, we think it is necessary to verify the effects of CPAP in people affected by mild or moderate apneas and exploit its potential to limit the further collateral disabilities previously observed, and possibly increase the chances of their reversibility. The lack of consensus among the authors may be due, as mentioned, to differences in methodology and neuropsychological tasks, heterogeneity of patients' clinical symptoms, and possible adherence to CPAP. This is the future line of research for better understanding the complete picture of OSAS in terms of brain structures involved, cognitive deficits, and reversibility after continuous positive oxygen treatment.



## CHAPTER 3

### COGNITIVE AND MOTOR REACTION TIMES IN OBSTRUCTIVE SLEEP APNEA SYNDROME: A STUDY BASED ON COMPUTERIZED MEASURES

#### 3.1 Introduction

The critical review of the literature proposed in Chapter 2 described brain and cognitive impairments associated with Obstructive Sleep Apnea Syndrome (OSAS). Although authors agree in recognizing executive functions as the cognitive domain most impaired by OSAS, it is not clear at which level this impairment would occur. Certainly, the pre-frontal cortex (PFC) is responsible for adequate executive functioning, and for the appropriate integration of different information coming from the environment. Information processing speed is the ability required to integrate these stimuli and to adaptively select a response. It can then be considered as a very sensitive measure to detect both clinical and subclinical cognitive disorders. Reaction times (RTs), which are observable and quantifiable indexes of information processing speed and of attention, are often measured in order to evaluate the ability to respond quickly and accurately to simple and complex target stimuli. A delay in information processing and psychomotor speed can be observed in individuals with OSAS. Although, as described in the previous chapter, a debate is underway on the existence of cognitive dysfunction in OSAS patients, some authors highlight a cognitive impairment (see Devita et al., 2017) that can be largely explained by alteration of the pre-frontal cortex (PFC), which is most sensitive to both intermittent nocturnal hypoxia and sleep disruption (Beebe & Gozal, 2002). The PFC has been chiefly assumed to control attention and executive functions, and may be damaged in their functioning even by a single night of sleep deprivation, as demonstrated in some neuroimaging studies (Drummond, Brown, Sticker, Buxton, Wang, & Gillin, 1999; Thomas et al., 2000). In their etiological model, Beebe and Gozal (2002) suggested that one of the main

consequences of OSAS is indeed functional damage of the prefrontal regions of the brain, demonstrated at behavioral level by executive dysfunction (i.e. behavioral inhibition, attentional shifting, emotion and arousal self-regulation, working memory, and contextual memory).

Although it is well established that frontal dysfunction plays a pivotal role in explaining the neuropsychological consequences of this sleep disorder, other brain areas could also suggest a link between neuroanatomy correlates and cognitive functioning in OSAS symptomatology. Hypoxia has been found to be responsible for structural brain damage in basal nuclei and in the cerebellum (Mattay et al., 2002), areas that are associated with attentional skills, motor speed and fine motor coordination movements, which seem to be impaired in OSAS. A strong link between the PFC and the cerebellum has been described (Diamond, 2000), and both structures have been reported as being involved in information and psychomotor speed (Eckert, Keren, Roberts, Calhoun, & Harris, 2010). In their study, Eckert et al. (2010) found two putative networks related to information processing speed: a frontal and a cerebellar one, which are also the most compromised areas in OSAS (see Devita et al., 2017).

In the organization of brain cognition, executive functions are required to integrate new introspective, sensory, and situational information by focusing on appropriate stimuli and planning a response (Jackson, Croft, Kennedy, Owens, & Howard, 2013). However, according to Verstraeten and colleagues (2004) executive functions may be worsened by lower-level cognitive deficits, and OSAS patients clearly show impairment in some basic mechanisms (e.g., information processing speed, short-term memory span, and attention). Spikman and van Zomeren (2010) focused on the assessment of such basic processes. They suggested that attentional skills and psychomotor speed are closely linked to each other, and that they are composed of three sub-levels based on task difficulty and time pressure. The “operational” level provides a measure of the basic speed of information processing; the tasks are relatively simple but there is always a strong time pressure. The “tactical” level requires both speed and planning skills and characterizes more complex and challenging tasks. Finally, the “strategic” level, where autonomous strategies are conceived,

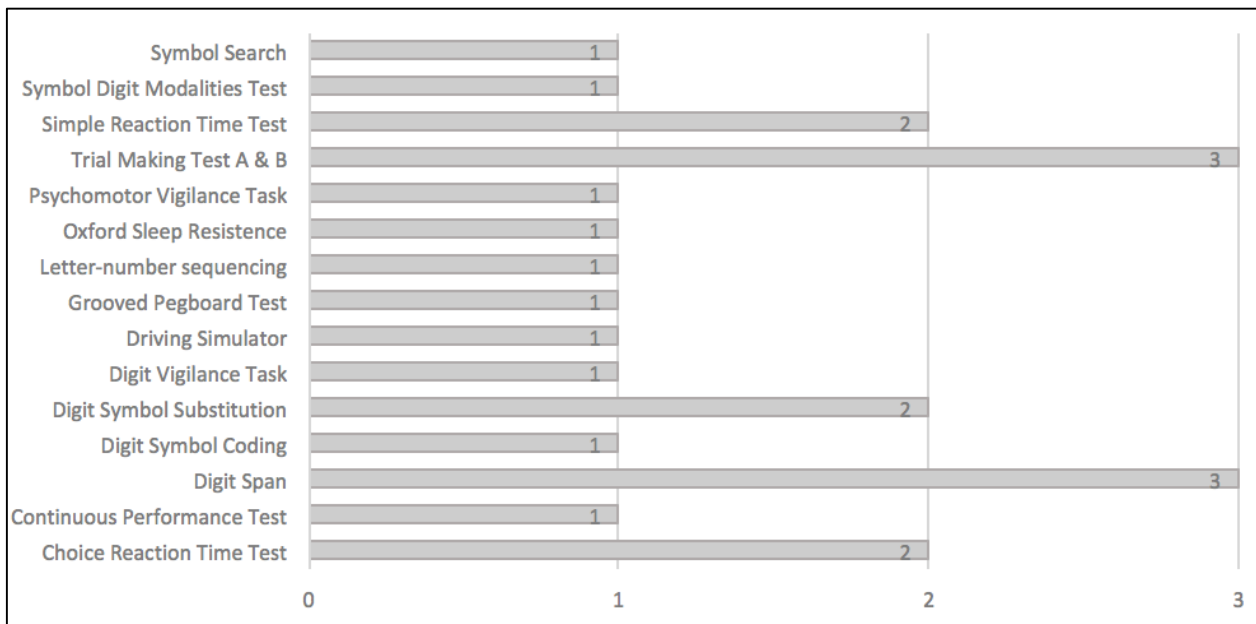
involves more executive demands, with a minimum time pressure. As a result of this differentiation, the construct of processing speed can be more clearly defined than that of executive functions. In the majority of studies, however, processing speed is measured together with other cognitive variables producing a confounding effect across factors. Salthouse (2000) has greatly contributed to the better comprehension of this mechanism by distinguishing between *decision speed* (“the time to respond to cognitive tests with moderately complex content”) and *perceptual speed* (“the speed of responding with simple content in which everyone would be perfect if there were no time limits”).

In the last decade a number of studies investigating the difference between cognitive and motor reaction times have been reported in the literature (e.g., Salthouse, 1996; Cerella, 1991; Sleimen-Malkoun, Temprado, & Berton, 2013). Cerella (1991) supported the so-called General Slowing Hypothesis (GSH) in the cognitive domain, explaining that behavioral slowing is mediated by a generalized deficit in the processing speed of the Central Nervous System (CNS) responsible for the decline in a variety of tasks. According to the GSH, a generalized decline occurs in all cognitive processes or, at least, in all non-peripheral ones (Cerella 1991; Salthouse, 1996). “Slowed synaptic transmission, increased information loss, longer cycle time per calculation, greater neural noise” are all primary features of GSH, resulting in global behavioral slowing down (Cerella 1991; Salthouse, 1996). This hypothesis has been frequently associated with age-related slowing and it is often also used to explain attentional and cognitive loss in several disorders (e.g., Shura et al., 2017; Choi, & Feng, 2016). Although GSH has been mostly associated with decision times and with cognitive processes, some authors have claimed that it may also affect motor responses. For example, Cerella (1991) found moderate sensory motor slowing in groups of middle-aged and old-aged participants, while marked cognitive slowing was observed only in the old-aged group. According to the author, these findings give further support to the existence of a network divided into two different regions: “a cognitive core and a sensory motor fringe”. More recently, Sleimen-Malkoun et al.’s (2013) study aimed to determine if GSH could be extended to the motor domain by comparing age-related cognitive and motor slowing. They found age-related co-variation of behavioral slowing in both

cognitive and motor domains, due to unspecific limitation of processing speed in the CNS. In other words, according to Sleimen-Malkoun et al. (2013) a decrease in processing speed would act as a common cause of behavioral slowing in both cognitive and motor tasks. However, most neuropsychological tasks typically used to assess information processing speed might not be sensitive and accurate enough to quantify the two components. In the field of OSAS investigation this aspect becomes crucial. For example, a number of studies (for a review see Kilpinen et al., 2014) used paper-and-pencil tests like the Trial Making Test A or the Digit Symbol to assess responsiveness, but very few adopted digital tasks like the Simple Motor Reaction Time Test (see Jackson et al., 2013). Also Jackson et al. (2013) did not distinguish clearly between higher-level cognitive processing speed and lower-level psychomotor speed. Table 5 lists some studies and the methods used to assess information processing and psychomotor speed (see also *Figure 1*).

<b>Authors</b>	<b>Abilities investigated</b>	<b>Methods</b>
<i>Jackson et al., 2013</i>	<b>Psychomotor speed</b> , focused and sustained attention, visuomotor coordination	Simple Reaction Times, Choice reaction times, Digit Vigilance Task, Psychomotor Vigilance Task
<i>Sharma et al., 2010</i>	Concentration/ <b>psychomotor slowing</b>	Digit Symbol Substitution, Digit Span
<i>Quan et al., 2006</i>	<b>Motor speed, processing speed</b>	Digit Span, Letter-number sequencing, Digit Symbol coding, Symbol Search, Trail Making Test B, Grooved Pegboard Test
<i>Mazza et al., 2005</i>	Vigilance as: wakefulness, sustained and selective attention, divided attention	Continuous performance test, driving simulator
<i>Naismith et al., 2004</i>	<b>Processing Speed</b> , executive functions	Simple reaction times, Choice reaction times, Trial Making Test A, Symbol Digit Modalities Test
<i>Verstraeten et al., 2004</i>	Executive functions, <b>information processing speed</b> , arousal	Trial Making Test A & B, Digit Span Task

*Table 5.* Studies and methods to assess information processing and psychomotor speed.



**Figure 2.** Frequency of tasks used to assess information processing and psychomotor speed in the studies cited.

### 3.2 Study 1

The aim of the present study was to provide sensitive and reliable measures to determine whether different components of information processing speed like cognitive and motor reaction times are equally impaired in OSAS. This issue can be addressed with a specific methodological approach allowing to determine and evaluate two qualitatively different mechanisms underlying the observed performance. Firstly, the target stimulus has to be dealt with by visuospatial attentional processes (stimulus encoding, decision process) and, secondly, a motor response must be appropriately selected and given (motor reaction times). The use of specific computerized tests disentangles the two cognitive and motor components and, at the same time, provides reliable RTs allowing better comprehension of different levels of information processing. This methodology can be ascribed to the aforementioned “operational” level hypothesized by Spikman and van Zomeren (2010), contributing to the investigation of psychomotor speed of OSAS patients through accurate measures of this basic ability.

### 3.3 Material and Methods

Thirty-three OSAS patients never treated before (29 men and 4 women; Mean age=  $60.42 \pm 13.04$ ) were recruited. In accordance with the International Classification of Sleep Disorders (1997) the inclusion criteria were: clinical OSAS profile with subjective report of symptoms, and an apnea-hypopnea index (AHI)  $>5/h$  (Mean apnea per hour:  $39.5 \pm 17.79$ ). Exclusion criteria were: current continuous treatment with positive airway pressure (CPAP), use of drugs acting on the central nervous system (e.g., benzodiazepines), current or planned intervention for weight reduction, hypertension, diabetes, and other neurological or psychiatric disorders. Patients were evaluated by a full-night attended polysomnography (PSG). Given the difficulty in defining the interval between disease onset and its diagnosis, we asked our patients to estimate when they had experienced apnea symptoms for the first time. They reported onset as far back as ten years previously, making them chronic patients with a long history of the disease.

Thirty healthy controls (26 men and 4 women; Mean age =  $59.9 \pm 13.33$ ) without any history of snoring or sleep complaints were recruited. OSAS patients and healthy controls were matched for age ( $t_{(61)} = -.158, p = .875$ ), education ( $t_{(61)} = .069, p = .945$ ) and cognitive reserve ( $t_{(61)} = -.455, p = .651$ ). The latter was measured using the Cognitive Reserve Index questionnaire (CRIq; Nucci, Mapelli, & Mondini, 2012), administered at the beginning of the evaluation. The study was approved by the local Ethics Committee. *Table 6* shows demographic data of all participants.

Characteristics (M ± DS)	OSAS Patients (n = 33)	Min-Max	HC (n = 30)	Min-Max
Age	60.42 ± 13.04	31 - 80	59.9 ± 13.33	30 - 79
Education	9.63 ± 3.56	5 - 17	9.7 ± 3.7	5 - 18
Cognitive Reserve Index (tot)	98.54 ± 13.59	82 - 124	97 ± 13.3	74 - 134
Apnea – Hypopnea Index/h	36.2 ± 16.67	8.1 – 74.1	-	-

**Table 6.** Characteristics of Obstructive Sleep Apnea Syndrome (OSAS) patients and healthy controls (HC); (HC did not undergo PSG).

After giving their consent, OSAS patients and healthy controls (HC) underwent one paper-and-pencil test (i.e. the Montreal Cognitive Assessment, MoCA) and four computerized tests (i.e. the Simple Reaction Time Test, RT/S1, the Complex Reaction Time Test, RT/S3, the Movement Detection Time Test, MDT/S2, and a more complex version of this same test, MDT/S3), all taken from the Vienna Test System ([www.schuhfried.at](http://www.schuhfried.at)). For the administration of the computerized tests, participants were seated in front of a 13-inch monitor placed 50 cm from their eyes. The answers were given through an interactive panel equipped with colored buttons and a sensor key (i.e. rest button). During the paper-and-pencil test, participants were seated in front of the examiner in a well-lighted quiet room. The administration of the tests lasted around one hour. All the tests used are described below:

- The MoCA test (Nasreddine et al., 2005) evaluates global cognitive functioning. It assesses visuospatial abilities, executive functions, short-term memory recall, language, and orientation in time and place. The time required for administration is about 10 minutes, making the test a quick and reliable measure of neuropsychological functioning.
- The RT/S1 is a computerized test administered in order to evaluate information processing speed and, in particular, both cognitive and motor reaction times. Participants are asked to perform a simple reaction time task: when the target stimulus (a yellow light) appears on the

screen, the participant has to answer as fast as possible by pressing a button on the keyboard. Five practice stimuli precede the test. In the test phase, 28 stimuli are presented, each requiring a response. The time needed for administration (including instructions) is about seven minutes.

This computerized Reaction Time task allows to measure both a Cognitive reaction time (RT/S1 COG) and a Motor reaction time (RT/S1 MOT) for each stimulus. The former measures the time (msec) between the appearance of the target and the moment the finger leaves the rest button; the latter is the time (msec) that elapses between the moment the finger leaves the rest button and the time the reaction button is pressed in response to the target.

- The RT/S3 is a more complex version of the RT/S1 seen above. In this test format a sequence of yellow and red lights, a tone and combinations of these stimuli are presented. The critical combination to which the respondent is required to answer consists of simultaneous visual and acoustic stimuli (yellow light and a tone at 2000 Hz). A minimum of nine practice stimuli are presented. In the test phase, 48 stimuli are showed on the screen, 16 of which require a reaction. The time needed for administration (including instructions) is about nine minutes. This test, as the RT/S1, allows to measure both a Cognitive reaction time (RT/S3 COG) and a Motor reaction time (RT/S3 MOT).
- The MDT/S2 is used to evaluate a participant's reaction to a moving visual stimulus with a congruent motor response. The stimulus (a small ball) moves very fast from the center of the screen toward one of the four corners, each marked by a different color. Participants have to detect as quickly as possible the direction of the movement, lift their finger from the rest button, and press the corresponding key (same color) on the response panel. A total of 32 stimuli are presented at an interval of between 1025 and 6000 milliseconds, and each stimulus remains on the screen for 750 milliseconds. The MDT/S2 allows to measure the median cognitive reaction time between the presentation of the stimulus and the moment the



finger is released from the rest button (MDT/S2 COG). It also allows to measure the median motor time based on the time between the start of the motor reaction and the time (msec) the corresponding key is pressed (MDT/S2 MOT).

- The MDT/S3 evaluates the participant's reaction to a moving visual stimulus with an incongruent motor response. As for MDT/S2, a small ball moves from the center of the screen to one of the colored corners. Movements are preceded by pauses between 1025 and 6000 milliseconds and each of them lasts for 750 milliseconds. Movement direction is random, as are the colors in the corners, which change at each trial. Compared with the previous task (MDT/S2), this one requires greater involvement of executive functions because the color of the corners changes at every trial. Participants have to detect as quickly as possible the direction of the movement, lift the finger from the rest button and press the corresponding key (same color) on the response panel. In this test format, as in the other computerized tests, it is possible to measure a cognitive reaction time (MDT/S3 COG) and a motor reaction time (MDT/S3 MOT).

All the computerized tasks used in this study are based on the Parallel Distributed Processing (PDP) model which describes an interaction between top-down and bottom-up processes (Rumelhart, Hinton, & McClelland, 1986). Although the distinction between a cognitive and a motor component of RTs could be seen as an oversimplification, it has been supported by a series of previous studies (Magnuson, Robin, & Wright, 2010; Klapp 1996; Klapp, 1995). In our investigation, the cognitive component of RTs would correspond to the decision time and to the pre-motor time (see Klapp, 1996). According to the PDP model, in this phase two pathways between sensory input and memory processes are active: participants have to compare the received instructions with the presented stimuli. Conversely, the motor component would correspond to the selection and the implementation of an appropriate motor response. During this phase, the planned movements are activated and nervous impulses drive the muscles that allow those movements to take place. While

human and mental processes are certainly more complex than this oversimplification, nonetheless the distinction between cognitive and motor RTs has been supported over time by numerous studies (Mierau et al., 2016; Vlagsma et al., 2016).

### **3.4 Statistical analysis**

Three logistic regression models were built starting from a baseline model with GROUP (OSAS vs. HC) as the dependent variable and AGE and EDUCATION as predictors. In order to avoid potential confounding effects, each model was built by adding variables of interest as predictors to the baseline model, thus adjusting results for the effect of AGE and EDUCATION. In Model 1 the MoCA score was considered as the only predictor of interest. In Model 2 the mean values of cognitive reaction times obtained in the computerized tests (RT/S1 COG, RT/S3 COG, MDT/S2 COG, MDT/S3 COG) were taken into account. In Model 3 the mean values of motor reaction times of each test (RT/S1 MOT, RT/S3 MOT, MDT/S2 MOT, MDT/S3 MOT) were added to the baseline model as predictors. In Models 2 and 3 one observation was deleted due to missing values. Collinearity across predictors was checked in all logistic regression models by means of variance inflation factors (VIF). For all the models, VIF values were lower than 10, thus suggesting no potentially harmful collinearity (Bowermann & O'Connell, 1990; Myers, 1990). Moreover, the existence of influential outliers was checked with Cook's distance ( $D_i$ ). No values of  $D_i$  were greater than 1, thus suggesting absence of influential outliers (Cook & Weisberg, 1982). All analyses were performed by means of R Software (R Core Team, 2013) and considering an alpha level of 0.05 for defining significance.

### 3.5 Results

For each model we checked through a Likelihood Ratio (LR) Test whether adding our variables of interest might significantly improve their fit, compared with the baseline model. In Model 1, adding the MoCA score as predictor produced a significant improvement in the fit of the model ( $\chi^2(1)=21.16, p<.001$ ) and MoCA was highlighted as a significant predictor for discriminating between OSAS patients and Healthy Controls ( $z= -3.45, p<.001$ ). In Model 2, the addition of Cognitive RTs did not significantly improve the model fit ( $\chi^2(4)= 2.33, p= .68$ ) and no significant effects emerged for any of the considered predictors. In Model 3, the addition of Motor RTs produced a significant improvement in the fit of the model ( $\chi^2(4)= 20.29, p< .001$ ). In particular, Motor RTs significantly predicted the GROUP to which participants would belong, when considering RT/S1 ( $p= .012$ ) and RT/S3 ( $p= .012$ ) tasks, while only a trend to significance emerged for MDT/S2 ( $p= .051$ ). No significant effect emerged for Motor RTs obtained in the MDT/S3 task ( $p= .24$ ). Table 7 shows means and standard deviations of each measure. Logistic regression results are reported in Table 8. The Odds-Ratio (OR) of significant predictors in Model 1 suggests that an increased MoCA score is related to diminished likelihood of belonging to the OSAS group (OR = 0.6; CI<sub>2.5%</sub> = 0.43; CI<sub>97.5%</sub> = 0.78). On the other hand, Model 3 ORs suggest that slower Motor RTs in the RT/S1 task increase the odds of having OSAS (OR= 1.03; CI<sub>2.5%</sub>= 1.009; CI<sub>97.5%</sub>= 1.06), while slower Motor RTs in the RT/S3 task diminish the odds of having OSAS (OR= 0.97; CI<sub>2.5%</sub>= 0.94; CI<sub>97.5%</sub>= 0.99).

	<b>OSAS</b>	<b>HC</b>
<b>MoCA</b>	22.9 ± 3.46	26.6 ± 2.38
<b>RT/S1 COG</b>	331.4 ± 63.4	342.5 ± 95.7
<b>RT/S1 MOT</b>	211.4 ± 64.4	180.7 ± 61.7
<b>RT/S3 COG</b>	487.7 ± 81.6	508.3 ± 107.02
<b>RT/S3 MOT</b>	219.8 ± 73.4	200.5 ± 67.7
<b>MDT/S2 COG</b>	446.9 ± 113.5	437.8 ± 74.5
<b>MDT/S2 MOT</b>	273 ± 69.7	233.4 ± 67.6
<b>MDT/S3 COG</b>	606.1 ± 140.7	586.03 ± 89.6
<b>MDT/S3 MOT</b>	396.9 ± 321.9	281.2 ± 97.5

**Table 7.** Performance of Obstructive Sleep Apnea (OSAS) patients and healthy controls (HC) on MoCA and computerized tests (RT/S1; RT/S3; MDT/S2; MDT/S3); COG= cognitive reaction times; MOT= motor reaction times

Logistic regression results are reported in *Table 8*

	<b>beta</b>	<b>SE</b>	<b>OR</b>	<b>Z</b>	<b>p-value</b>
<b>Model 1</b>					
<b>MoCA</b>	-.051	.147	.602	-3.45	<.001
<b>Model 2</b>					
<b>RT/S1 COG</b>	.0006	.005	1.0006	.13	.89
<b>RT/S3 COG</b>	-.005	.004	.99	-1.14	.25
<b>MDT/S2 COG</b>	.002	.006	1.002	.36	.72
<b>MDT/S3 COG</b>	.0013	.004	1.001	.32	.75
<b>Model 3</b>					
<b>RT/S1 MOT</b>	.033	.013	1.033	2.5	.012
<b>RT/S3 MOT</b>	-.03	.013	.97	-2.5	.012
<b>MDT/S2 MOT</b>	.019	.009	1.018	1.95	.051
<b>MDT/S3 MOT</b>	.004	.003	1.004	1.16	.24

**Table 8.** Logistic regression models and results for predictors of interest. Tests: MoCA; RT/S1; RT/S3; MDT/S2; MDT/S3); COG= cognitive reaction times; MOT= motor reaction times.

### 3.6 Discussion

The aim of the present study was to separately determine the potential deficits of OSAS patients in cognitive and motor reaction times. Kilpinen et al. (2014) reviewed a series of studies showing general slowness in information processing and psychomotor speed in OSAS patients. However, to the best of our knowledge, all of these investigations did not distinguish between these two constructs and did not separately measure them. In our study we used extremely sensitive and reliable computerized tests which provided separate measures of cognitive and motor reaction times. This distinction has been repeatedly reported in the literature, but there is no consensus on both the definition of mechanisms and the way in which we can measure them. The differences in

defining cognitive and motor RTs may be due to changes in the theoretical approaches underlying the different experimental designs. In the present study, we found that OSAS patients performed worse than controls on the MoCA test, showing that this syndrome globally impairs cognitive functioning. OSAS scores, however, were not at pathological level (see Table 7) when compared with the available Italian normative data (Santangelo et al., 2015). Nonetheless, it is known that OSAS patients do not have optimal global functioning in daily life and that the most noticeable clinical sign seems to be psychomotor slowness. As to psychomotor speed, our data highlight that OSAS patients show slower reaction times, which we found to be restricted to the motor component in three of the tasks, but not on the MDT/S3. In this task the two groups did not seem to specifically differ in any components and this could be due to the high complexity of the cognitive processing load and to the number of cognitive, mainly executive, functions involved. Another controversial result was found between RT/S1 and RT/S3 odd ratios. In RT/S1 the odds of having OSAS increased with the increasing of RTs, while the opposite pattern emerged in RT/S3. As for MDT/S3, the increased complexity of the task may have confounded the effects observed in the simplest tasks. Despite these and other theoretical controversies about a clear distinction between cognitive and motor RTs, some neurophysiological findings seem to sustain our results, especially the slowing down of the motor component. According to Bashore, Osman and Heffley III (1989), supporting data for component-specific slowing down can be achieved by conducting studies on brain potentials. RTs and the latency of the P300 component of event-related brain potentials allowed the authors to separate the reaction process into two sub-components: the time required for stimulus processing, indexed by P300 latency, and the time involved with response selection and activation, measured as the difference between RTs and P300 latency. Bashore and colleagues (1989) suggested that the response-related component (i.e. motor) is more exposed to the negative age-related effects than the stimulus-related component (i.e. cognitive), as indexed by P300 latency. In patients with OSAS motor slowdown could have a substantial impact on daily activities by worsening cognitive efficiency. This is in agreement with those authors who do not confirm a

primary cognitive impairment in OSAS patients (Verstraeten et al., 2004) but, rather, hypothesize these deficits as secondary to the motor slowness derived from daily sleepiness and/or non-restorative sleep. Thus, motor slowness might also be at the basis of their mild global cognitive impairment.

A number of studies have investigated motor movements and reaction times in aging. Smith et al. (1999) found that the slowing down of motor movements and the loss of fine motor skills reflect underlying age-related motor slowing. Furthermore, Mattay et al. (2002) showed that in normal aging a strong relationship exists between motor behaviors and prefrontal cortex activation (BOLD fMRI): the faster the motor behaviors, the greater the prefrontal cortex activation. Therefore, it could be hypothesized that hypoxia, which mostly impairs frontal brain areas, might accelerate aging processes, which in turn would compromise the motor component of reaction times. Houx and Jolles (1993) also found age-related slowing and the greatest effect emerged in “motor execution times”. Further important evidence comes from Eckert et al. (2010). Besides identifying the networks implicated in processing speed, they also found that the frontal and cerebellar areas reveal age-related structural alterations that would explain changes in processing speed linked to aging. The authors suggested that these structural networks appear to share topological features with functional networks (He et al., 2007; Honey et al., 2007), highlighting the action of long- and short-range fiber connections among regions. Impaired coordination between cerebellar and frontal regions could be one reason why some older adults show slower perceptual-motor learning (Rodrigue et al., 2005). The prefrontal cortex and the cerebellum have been reported as the most age-related impaired brain areas (Bernard & Seidler, 2014) and this evidence represents a starting point to understand the neural underpinnings of age-related cognitive and motor decline. Our results suggest that what happens to healthy people with aging occurs in patients with OSAS regardless of age. These findings become more interesting within the current debate about OSAS and safety in daily life as evidence is being found on the increasing risk of work and driving accidents because of OSAS (George, 2004; Pizza, Contardi, Ferlisi, Mondini, & Cirignotta, 2008). Karimi and

colleagues (2015) showed that delays and protracted RTs are directly associated with a history of motor vehicle accidents in patients with OSAS. Moreover, others (e.g., Engleman, Kingshott, Martin, & Douglas, 2000) report that this and other serious life-threatening factors are strictly connected with sleepiness and drowsiness during the day. Our results encourage us to think that delayed motor reaction times might prevent prompt and effective responses to complex requests, thus causing many of the everyday life problems experienced by OSAS patients. To our knowledge, this clear impairment of the motor component has not been reported in other studies and we believe that its evolution over time would be a very interesting aspect to investigate in a longitudinal study within this clinical population.

We are aware of some limitations in this study. First of all, lack of measures of vigilance and somnolence, which would allow us to evaluate micro-sleep episodes as adverse factors for cognitive functioning. Extensive literature shows that short and recurrent transitions from wakefulness to sleep (i.e. micro-sleep episodes) might disrupt the steadiness of cognitive functioning itself (Blatter et al., 2006; Tirunahari et al., 2003). Engleman and Joffe (1999) suggested that the nocturnal physiological events of sleep disruption and the intermittent hypoxia would explain almost all the neuropsychological impairments observed in OSAS patients. Moreover, as a result of their inability to stay awake in both monotonous and stimulating settings, the patients with OSAS examined by Mazza et al. (2005) showed important difficulties in all attentional processes and vigilance tasks. However, as mentioned in the Introduction, it is difficult to draw conclusions because of the controversies reported in the literature. The wide inter-individual variability characterizing patients with OSAS is suggestive of extremely complex interactions between neuroanatomy, neurophysiology and neuropsychology, so that the behaviors observed in this syndrome cannot be attributed to just one factor.

Another limitation is the lack of measures of partial oxygen pressure ( $PO_2$ ) and of oxygen-saturation ( $SO_2$ ). Oxygen desaturation is an immediate consequence of OSAS and it increases sympathetic activity and norepinephrine levels, leading to several medical complications, such as hypertension



and diabetes (McNicholas & Bonsignore, 2007; Peppard, Young, Palta, & Skatrud, 2000). Most of the sequelae associated with OSAS have been reported to be strongly linked to the degree and duration of oxygen desaturation rather than to the number of apnea or micro-sleep episodes. The lack of body mass index (BMI) measure is another limitation of our study, since BMI might be responsible by itself for cognitive dysfunction. Therefore, the interpretation of our results should be considered with attention.

### **3.7 Conclusions**

Study 1 has confirmed that patients with Obstructive Sleep Apnea Syndrome have a slight global cognitive impairment and show slowness in motor reaction times. As a result of such cognitive impairment, these patients experience difficulty in daily activities, due to worsening of their global cognitive efficiency and acceleration of their aging processes.

## CHAPTER 4

### GLOBAL COGNITIVE PROFILE AND DIFFERENT COMPONENTS OF REACTION TIMES IN OBSTRUCTIVE SLEEP APNEA SYNDROME: EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE OVER TIME

#### 4.1 Introduction

The possible reversibility of cognitive impairment associated with Obstructive Sleep Apnea Syndrome (OSAS) is another important issue of debate, as remarked in Chapter 2.

It has been highlighted that the most damaged brain area seems to be the pre-frontal cortex (PFC), which is extremely sensitive to the effects of intermittent nocturnal hypoxia and sleep disruption (Beebe & Gozal, 2002). A selective and preminent involvement of PFC has not always been confirmed, since some authors have underlined that hypoxia may also affect other brain areas. A reduction in gray matter density has been described in the basal ganglia, in the cerebellum and in the hippocampus (Castronovo et al., 2014; Joo et al., 2010; Morrell et al., 2010; Macey et al., 2002). Such neuroanatomical correlations confirm the clinical symptomatology usually observed in patients with OSAS. They are reported to show slowness in information processing and psychomotor speed, difficulty in shifting between tasks, in updating and monitoring working memory representations and in inhibiting predominant responses (Olaithe & Bucks, 2013). Furthermore, the involvement of the cerebellum and subcortical areas supports the deficiency of motor skills and fine motor coordination movements showed by OSAS patients. The actual occurrence and the variety of cognitive deficits possibly triggered by this sleep disorder has been previously debated, as has the reversibility of these impairments, which is not clearly established yet (see Devita et al., 2017).

As mentioned, the most effective treatment for OSAS at present is a Continuous Positive Airway Pressure (CPAP), which, by delivering a stream of compressed air, avoids the collapse of the upper airway and the obstruction of the air flow.

However, there are studies suggesting that even after adequate treatment cognitive deficits associated with OSAS are irreversible, leading to permanent cognitive decline (Bédard, Montplaisir, Malo, Richer, & Rouleau, 1993). An association between OSAS and the early onset of cognitive deterioration has been described, while growing clinical evidence and data from experiments on animals support claims that OSAS should be acknowledged as one of the atypical modifiable risk factors for Alzheimer's dementia (Rosenzweig et al., 2015; Osorio et al., 2015; Yaffe et al., 2014). Thus, it was suggested that OSAS may lead to a "pseudodementia" symptomatology, and that executive functions and psychomotor speed are the abilities most damaged and least responsive to treatment (for reviews, see Devita et al., 2017; Kilpinen et al., 2014; Sanchez et al., 2009).

## **4.2 Study 2**

The second study carried out aimed to compare over time the global cognitive profile of newly diagnosed patients with OSAS who underwent the CPAP treatment (group "CPAP+") with those who did not (group "CPAP-"); both groups were additionally matched with healthy participants (group "HC"). More importantly, participants' RTs were evaluated over time with a specific methodological approach allowing to distinguish between the cognitive and the motor component, which reflect information processing and psychomotor speed, respectively. This methodology is a novel and original approach to the study of RTs in general and, above all, it allows better comprehension of the psychomotor impairment reported in OSAS patients.

### 4.3 Materials and Methods

Our sample included sixty-three participants: twenty-three patients newly diagnosed with OSAS who chose to undergo the CPAP treatment, (CPAP+; 3 F; mean age = 60.08, SD = 13.20), ten newly diagnosed patients with OSAS who chose not to undergo the treatment (CPAP-; 2 F; mean age = 61.02, SD = 11.93) and thirty healthy controls (HC; 3 F; mean age = 59.9, SD = 13.11) recruited among the authors' acquaintances and patients' family members. In accordance with the International Classification of Sleep Disorders (2014) inclusion criteria were: a clinical OSAS profile and the subjective report of symptoms, and an apnea-hypopnea index (AHI) > 15/h. Exclusion criteria were: CPAP treatment already ongoing, use of drugs acting on the central nervous system (e.g. benzodiazepines), current or planned intervention for weight reduction, hypertension, diabetes, and other neurological or psychiatric disorders. The OSAS diagnosis was made by means of a portable four-channel device composed of a nasal flow detector, an oximeter, a chest and an abdominal belt able to detect the muscle activity of these regions and the respiratory efforts. Our sample was made up of patients with a severe level of disease (Mean apnea per hour:  $39.5 \pm 17.79$ ). For those who decided to undergo the CPAP, three or four nights in hospital were sufficient for the CPAP titration. Our device was equipped with a memory card recording respiratory events, based on which the airway pressure was set (10-12 cmH<sub>2</sub>O of positive pressure were usually sufficient to reduce the AHI to <5). All patients who started titration to treatment retained it throughout the follow-up period.

The groups were matched for age and education. Table 9 shows the descriptive statistics of participants.

This study was approved by the local ethics committee and all participants gave their written consent to be interviewed and tested.

Group	Age Mean (SD)	Education (years) Mean (SD)
HC	59.9 (13.1)	9.7 (3.7)
CPAP+	60.1 (13.2)	8.9 (3.3)
CPAP-	61.2 (11.9)	11.4 (3.4)
Total	60.2 (12.9)	9.7 (3.6)

**Table 9.** Descriptive statistics of healthy participants (HC), OSAS patients who underwent the CPAP treatment (CPAP+) and OSAS patients who did not undergo the CPAP treatment (CPAP); SD= Standard Deviation.

All groups underwent a neuropsychological assessment at baseline (T0), after three (T1) and six months (T2). The psychometric evaluation included a paper-and-pencil test (MoCA; Nasreddine et al., 2005) and four computerized RTs tasks, all taken from the Vienna Test System ([www.schuhfried.at](http://www.schuhfried.at)).

- The MoCA test evaluates the global neuropsychological functioning through items assessing visuospatial abilities, executive functions, short-term memory recall, language and orientation to time and place.
- The RT/S1 is a simple reaction time test. Cognitive (RT/S1 COG) and a motor reaction times (RT/S1 MOT) are separately measured. RT/S1 COG measures the time (msec) between the appearance of the target and the moment the finger leaves the rest button; RT/S1 MOT consists in the time (msec) that elapses between the moment the finger leaves the rest button and the time the reaction button is pressed in response to the target. Participants have to answer as fast as possible pressing a response button on the keyboard, as the target stimulus (yellow light) appears on the screen.
- The RT/S3 is a more complex version of RT/S1. Stimuli are presented in a sequence of yellow and red lights, a tone and combinations of them. Participants have to respond only when the combination of a visual and an acoustic stimulus (yellow light and a tone) appears simultaneously. Both cognitive reaction times (RT/S3 COG) and motor reaction times (RT/S3 MOT) are measured.
- The MDT/S2 evaluates a subject's reaction to a visual moving stimulus with a congruent motor response. A small ball moves very fast from the center of the screen toward one of the

four corners, each of a different color. Participants have to detect as quickly as possible the direction of the movement, lift the finger from the rest button and press the corresponding key (same color as the corner toward which the small ball is directed) on the response panel. As well as the previous tasks, the MDT allows to measure cognitive reaction times (MDT/S2 COG) and motor times (MDT/S2 MOT).

- Finally, the MDT/S3 evaluates a subject's reaction to a visual moving stimulus with an incongruent motor response. As well as in MDT/S2, a small ball moves from the center of the screen to one of the colored corners. Direction of movements is random, as is the color of each corner, which changes at each trial. Participants have to detect as quickly as possible the direction of the movement, lift the finger from the rest button and press the corresponding key (same color as the corner) on the response panel. Cognitive reaction times (MDT/S3 COG) and motor reaction times (MDT/S3 MOT) are computed.

#### **4.4 Statistical analysis**

A generalized linear mixed-effects model approach (Pinheiro & Bates, 2000) was adopted to investigate the effects of AGE, EDUCATION, TIME (T0, T1 and T2) and GROUP (HC, CPAP+ and CPAP-) on three behavioral measures adopted as dependent variables: MoCA score, cognitive and motor reaction times, both obtained in the same computerized tests (RT/S1, RT/S3, MDT/S2, MDT/S3). This statistical approach has been applied in many research areas (e.g., Goldstein, 2005; Faraway, 2006; Malcolm et al., 2008; Levitan et al., 2015), and it has been proposed for the analysis of RTs (Baayen & Milin, 2010) given its ability to deal with complex data. Mixed-effects models allow to simultaneously take into consideration all factors potentially contributing to data understanding (Baayen et al., 2008), including not only those under experimental control (fixed effects), but also those characterized by the fact that their levels are randomly drawn from a population (Di Giorgio et al., 2012), the so-called random effect factors (e.g., participants).

Thus, in the present study generalized linear mixed-effects models have been adopted to properly deal with repeated measures, to model participants' individual differences on MoCA score and in RTs distribution as random effect factors, and to deal with skewness of data distribution. Moreover, this approach allowed to perform analyses focusing on the number of observations ( $N = 757$ ) and on their subject-specific distribution rather than simply on the number of participants ( $N = 63$ ). For each dependent variable (MoCA score, cognitive RTs and motor RTs, respectively) four Generalized Linear Mixed-Effects nested regression models were built after scaling all variables. The baseline model - Model 0 - contained SUBJECT as the random effect, AGE and EDUCATION as fixed effect predictors. In Model 1 the effect of TIME was added to the baseline model. Model 2 included the effect of GROUP, while Model 3 considered also the interaction between TIME and GROUP. The contribution of each model toward explaining data was quantified by means of the Akaike Information Criterion (AIC; Akaike, 1987) and through Likelihood-Ratio Tests (LR) in order to see if adding a variable to a model could significantly improve model performance in explaining the data. In particular, we evaluated AICs (see Table 10) to have an additional measure of goodness of fit and of model parsimony, that is, the balance between the inclusion of more predictors and the corresponding increase in model fit. Furthermore, when needed, least-squares contrasts were performed to investigate in detail TIME\*GROUP interaction. Given the non-orthogonality of these comparisons,  $p$ -values were adjusted by means of Bonferroni correction to control Type I error rate.

In contrast to Study 2, in which cognitive and motor reaction times were separately considered, in this investigation we obtained the reaction times' values by merging the four tests. This choice was due to the different purposes of Study 2 and Study 3; in this latter, indeed, all measures combined allowed to cover a greater proportion of RTs variability, rather than considering each single test separately.

All reported analyses were performed by means of R Software (R Core Team, 2013), and the R packages lme4 (Bates & Maechler, 2010) and lsmeans (Lenth, 2016) were used for generalized mixed-effects models and post-hoc comparisons.

Model	MoCA score			Dependent Variables					
	$\chi^2$	p	AIC	Cognitive RTs			Motor RTs		
	$\chi^2$	p	AIC	$\chi^2$	p	AIC	$\chi^2$	p	AIC
Model 0	-	-	-1532.2	-	-	-5.48	-	-	257.65
Model 1	102.34	<.001	-1630.6	1.03	.59	-2.51	1.14	.57	260.52
Model 2	7.54	.023	-1634.1	.95	.62	.54	1.16	.56	263.36
Model 3	29.63	<.001	-1655.7	9.6	.048	-1.06	22.97	<.001	248.39

**Table 10.** Goodness of fit measures for each model: Likelihood Ratio Test  $\chi^2$ , corresponding  $p$ -value and Akaike Information Criterion (AIC). Model 0 = model with Subject (Random Effect), Age and Education (Fixed Effects) as predictors; Model 1 = model with Subject (Random Effect), Age, Education and Time (Fixed Effects) as predictors; Model 2 = model with Subject (Random Effect), Age, Education, Time and Group (Fixed Effects) as predictors; Model 3 = model with Subject (Random Effect), Age, Education, Time, Group and Time\*Group (Fixed Effects) as predictors.

## 4.5 Results

Likelihood-Ratio Tests showed that adding TIME\*GROUP interaction - Model 3 - significantly improved the fit of the model to the data both when considering MoCA score ( $\chi^2_{(4)} = 29.63$ ,  $p < .001$ ), cognitive RTs ( $\chi^2_{(4)} = 9.6$ ,  $p = .048$ ) and motor RTs ( $\chi^2_{(4)} = 22.97$ ,  $p < .001$ ) as dependent variables.

As for MoCA score and motor RTs, the smallest AIC value was associated to Model 3 (-1655.7 and 248.4, respectively), thus confirming that adding the TIME\*GROUP interaction improved the model fit. Conversely, in cognitive RTs the smallest AIC value was associated with the baseline model - Model 0 - including only AGE and EDUCATION as fixed effects factors (AIC = -5.48), indicating Model 0 as having the best balance between goodness of fit and parsimony. Moreover, for cognitive RTs, the interaction was not significant in Model 3. For this reason, in this study, only



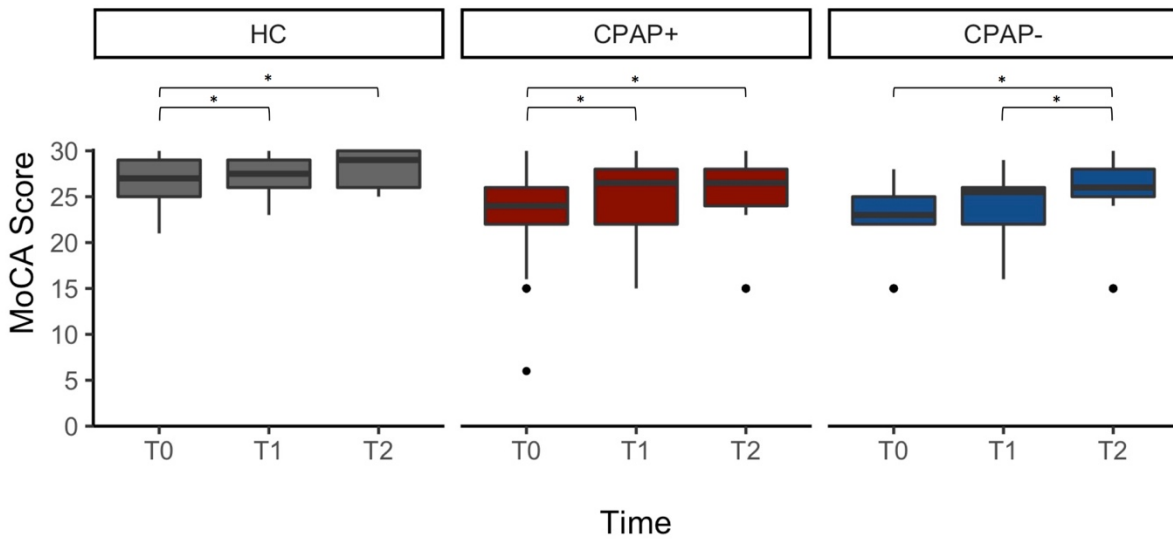
results based on Model 3 for MoCA score and motor RTs, and on Model 0 for cognitive RTs will be reported.

For MoCA scores (see *Graph 1*), main effects of TIME ( $\chi^2_{(2)} = 117.9, p < .001$ ) and GROUP ( $\chi^2_{(2)} = 7.15, p = .028$ ) emerged as significant, as well as TIME\*GROUP interaction ( $\chi^2_{(4)} = 31.81, p < .001$ ).

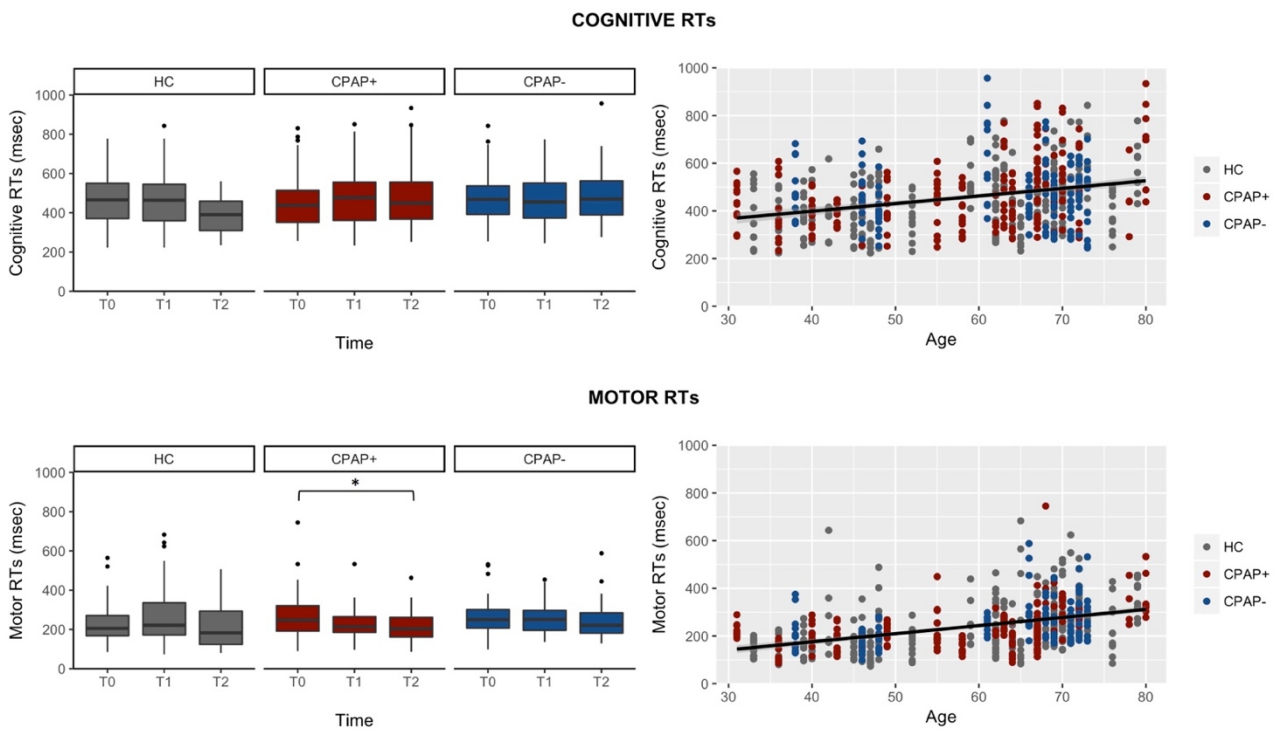
Least-squares means contrasts did not show differences between groups in any of the assessments (T0, T1, T2). Significant improvements in MoCA score emerged between T0 and T1 in both HC ( $z = 3.29, p = .036$ ) and CPAP+ ( $z = 4.19, p = .001$ ), while no difference emerged for CPAP-. Conversely, only CPAP- showed significant improvements in MoCA score between T1 and T2 ( $z = 5.94, p < .001$ ). Furthermore, for all groups significant differences emerged between T0 and T2 (HC:  $z = 3.92, p = .003$ ; CPAP+:  $z = 7.27, p < .001$ ; CPAP-:  $z = 8.5, p < .001$ ), showing improved scores.

When considering RTs as a dependent variable (see *Graph 2*), the significant main effect of AGE emerged both for the cognitive ( $\chi^2_{(1)} = 10.81, p = .001$ ) and the motor ( $\chi^2_{(1)} = 24.33, p < .001$ ) component, while the interaction TIME\*GROUP was significant only for motor RTs ( $\chi^2_{(4)} = 23.44, p < .001$ ). Importantly, least-squares means contrasts on motor RTs model showed a significant difference between T0 and T2 only in CPAP+ patients ( $z = -3.28, p = .038$ ), showing faster motor RTs. Although it was not an aim of the present study, we analyzed differences between groups at each time point (T0, T1 or T2), but no significant differences emerged for any of the cognitive measures.

## MoCA SCORE



**Graph 1.** MoCA scores over time of healthy participants (HC), OSAS patients who underwent the CPAP treatment (CPAP+) and OSAS patients who did not undergo the CPAP treatment (CPAP-). T0= baseline, T1= after three months, T2= after six months.



**Graph 2.** Cognitive and motor reaction times (RTs) over time of healthy participants (HC), OSAS patients who underwent the CPAP treatment (CPAP+) and OSAS patients who did not undergo the CPAP treatment (CPAP-). T0= baseline, T1= after three months, T2= after six months.

## 4.6 Discussion

The present study aimed to evaluate global cognitive profile by comparing over time a group of OSAS patients who underwent CPAP with a group of patients who did not. Both groups were compared with healthy participants and reaction times were also assessed. More importantly, in this study it was possible to distinguish between the cognitive and the motor component of RTs which reflect information processing and psychomotor speed. These goals were pursued in order to investigate, albeit for a limited period of six months, how global cognitive function, information processing and psychomotor speed can change over time according to whether OSAS patients are either treated or not with CPAP. Our findings show that on the MoCA test both CPAP+ and HC performed already significantly better just after three months, further increasing their scores after six months and highlight that their performance was very similar and comparable. As for CPAP-, improvement of performance emerged only after six months. A practice effect could justify this change in all groups; however, CPAP+ and HC showed an equal behavioral pattern, exhibiting similar practice effect over time. Conversely, CPAP- took longer than the other groups to show a practice effect and to improve their performance. These longer response times can be considered as a result of vulnerable cognitive functioning and it can be said that if OSAS patients are not treated they need longer to learn.

“Cognitive frailty” rather than real “Cognitive impairment” can be supposed to characterize the profile of OSAS patients that do not undergo CPAP, as, in fact, at the baseline no significant differences emerged between groups in any of the examined cognitive functions. The term frailty is commonly used for clinical geriatric purposes and refers to a multisystem impairment resulting in a general vulnerability (Ensrud et al., 2009). Definitions of frailty usually include a component of lack of energy and feelings of fatigue that have been considered as the main outcomes of OSAS and among the primary causes of cognitive weakness in patients with this sleep disorder (Engleman & Douglas, 2004; Verstraeten, Cluydts, Pevernagie, & Hoffmann 2004). Few studies have

investigated the relationship between sleep disorders and cognitive frailty, and independent associations between them have been described (Ensrud et al., 2012; Bardwell et al., 2003). Although the majority of OSAS findings tend to confirm a decline in cognitive functioning, our results would suggest that slight and sometimes partially silent inefficiencies are definitely plausible and reasonable in this sleep disorder. A different trend emerged in information processing and psychomotor speed measures: decreased RTs were found over time, but only in the CPAP+ group, who performed significantly better than CPAP-. In the patients who underwent CPAP treatment improvement was observed only in the motor component, suggesting that CPAP treatment improves psychomotor speediness without effects on cognitive RTs. Our findings highlight the potential important role that CPAP may have in slowing down the negative effects of OSAS by fostering sufficient cognitive functioning and adequate motor speed. The efficacy of CPAP limited to the motor component of RTs might seem difficult to explain, but also other findings have confirmed a selective efficiency of this treatment on the motor behaviors of OSAS patients (Ryan et al., 2011).

Our results are not completely in line with those reported by Kilpinen et al. (2014), who claimed a general inefficiency of CPAP in improving psychomotor speed. A longer follow-up would have been undoubtedly more useful in drawing conclusions, and further research exploring motor behaviors in OSAS is certainly required to achieve more solid knowledge on this issue. A limitation of this and other similar studies involving optional rather than mandatory treatments is the method of patient selection, which usually produces small samples. There may have been other dissimilarities between our groups which we are not aware of, and this could possibly have affected the acceptance or the refusal of the treatment, thus causing an enrollment bias. The absence of body mass index (BMI) measure is another limitation of our study, since BMI might be responsible by itself for cognitive dysfunction. Therefore, our results should be considered with caution. These limitations notwithstanding, the methodological approach used in this study has undoubtedly some strength as it allows to discriminate between different components of the same behavior, which in

other cases has been considered as a whole mechanism. This could be the reason why such controversial results exist about this topic, together with the adoption of measures not always appropriate or sensitive to the evaluation of information processing and psychomotor speed.

#### **4.7 Conclusions**

The present study aimed to evaluate the global cognitive profile and the different components of RTs of OSAS patients, assessing the effects of CPAP over six months.

Our results seem to support “cognitive frailty” and a consequent vulnerability of non-treated OSAS patients. In addition, the innovative and sensitive methodological approach allows to show that, following treatment with CPAP, patients can improve over time, at least as regards the motor component of RTs. Since motor impairments are related to underlying early aging processes, our study suggests that treated patients can benefit from CPAP because it may protect them against accelerated cognitive loss.

## CHAPTER 5

### REM AND NREM OBSTRUCTIVE SLEEP APNEA SYNDROME AND COGNITIVE FUNCTIONING: INTERACTIONS WITH APOE4 STATUS

#### 5.1 Introduction

As widely showed along the present dissertation, an increasing number of studies have investigated the role that various conditions and pathologies may have in compromising the normal brain and neuropsychological functioning, and Obstructive Sleep Apnea Syndrome (OSAS) is certainly one example. It has been seen that OSAS has been associated with a number of other medical problems that hamper a proper cardiovascular, metabolic and cerebrovascular functioning (Ryan & Bradley, 2005). Furthermore, an association between OSAS and cognitive impairment has been suggested, although a debate still persists on which cognitive domains are most compromised (Devita et al., 2017). Several review studies suggest that OSAS mainly impairs executive functions and memory, while other domains may be less affected (Devita et al., 2017; Gagnon et al., 2014). In particular, many investigations confirmed the executive functions impairment, while more controversial are the results about memory. However, clinical observation and self-reports of patients with OSAS suggest that further research is needed in order to better explore the memory deficits reported (Salorio et al., 2002). The relationship between sleep and cognition has been broadly investigated (Chokroverty, 2017).

Furthermore, an increasing interest is arising in more deeply exploring the role of the different sleep stages (i.e. REM and NREM sleep) in this association. Some authors investigated whether

there are clinical and polysomnographic differences between the measured level of the apnea/hypopnea index (AHI) during NREM and REM sleep. Although Liu et al. (2011) found that there are no differences between these two stages and that both of them should be considered part of the OSAS spectrum, instead of a specific clinical entity, other studies did not confirm these findings. Siddiqui, Walters, Goldstein, Lahey and Desay (2006) found that the half of patients with OSAS had a higher NREM AHI than REM AHI, and Sunnetcioglu, Sertogullarindan, Ozba, Gunbatar and Ekin (2015) showed that severe OSAS was more common among the patients with a higher NREM AHI than REM AHI.

Associations between AHI levels during REM and NREM sleep with various outcomes have begun to be investigated. For example, among participants in the Wisconsin Sleep Cohort Study (WSCS), Mokhlesi et al. (2014) investigated the association between NREM and REM OSAS and hypertension, finding that the latter is cross-sectionally and longitudinally associated with hypertension. Additionally, Mokhlesi et al. (2015) found that REM OSAS is independently associated with incident non-dipping of blood pressure.

Because of several physiological and cognitive comorbidities associated with OSAS, researchers have investigated its genetic etiological factors (Larkin et al., 2006). An association between Apolipoprotein E4 (APOE4) and this sleep disorder has been suggested but not fully established (Uyrum et al., 2015; Gottlieb et al., 2004; Kadotani et al., 2001).

APOE4 is a genetic risk factor for several neurologic disorders, and in particular for dementia, (Van Giau, Bagyinszky, Soo A An, & Kim, 2015) and it has been directly associated with cognitive impairment (Farlow et al., 2004). An increasing number of studies is being published about the role that the APOE4 may have in determining cognitive impairments also in non-demented populations (Anstey & Christensen, 2000), as well as in OSAS population. Genetic

data, some of which from the WSCS, have been combined with neuropsychological measures highlighting that OSAS patients carrying APOE4 show worse cognitive performances (Nikodemova et al., 2013; Cosentino et al., 2008; O'Hara et al., 2005). However, studies that have investigated whether there is significant modification of the association between OSAS and cognition by APOE4 status are not consistent. On the one hand, a major executive dysfunction related to the relationship between APOE4 and OSAS was highlighted by Small et al. (2004). On the other hand, Nikodemova et al. (2013) reported poorer performance, occurring in APOE4 carriers suffering from a moderate to severe AHI, chiefly in memory abilities. This study represented an important evidence investigating the role of APOE4 in modulating the association between OSAS and cognitive functioning. Because of the findings previously reported (Siddiqui et al., 2006; Mokhlesi et al., 2014; Mokhlesi et al., 2015; Sunnetcioglu et al., 2015) and because an increasing number of evidence highlighted that the NREM sleep is mainly involved in consolidating long-term memories (Maestri et al., 2015; Aricò et al., 2010; Marshall, Helgadottir, Molle, Born, 2006; Stickgold, 2005), the Nikodemova et al.'s study of the WSCS (2013) was a starting point to further explore in which stage of sleep the AHI can be a predictor of memory loss in OSAS. The fragmentation of NREM sleep was not only reported to affect memory skills, but some authors suggested that it could also contribute to an increased production of amyloid (Hayes et al., 2014). Although OSAS is usually worse during the REM sleep (Findley, Wilhoit, & Suratt, 1985), 50% of patients showed a NREM apnea/hypopnea index (AHI) higher than REM AHI (Siddiqui et al., 2006; Loadsman & Wilcox, 2000). Hence, in the present study it has been hypothesized that an increased AHI during NREM sleep could trigger a memory impairment, and that this latter would be more evident in APOE4 carriers. As a matter of facts, NREM sleep was found to be responsible of long-term memories consolidation (Mander et al.,



2013). It indeed limits the offline decline of episodic memories over time, resulting in greater retention (Takashima et al., 2006). Also the electrical facilitation of NREM slow waves was found to increase the retention of episodic memories (Marshall, Helgadóttir, Mölle, & Born, 2006). The reason why these mechanisms should occur finds an answer in the hypothesized existence of a hippocampal-neocortical framework of memory consolidation (Buzsáki, 1996; Frankland, & Bontempi, 2005). The NREM sleep promotes the transformation of episodic memories from an initially hippocampal-dependent to a progressively hippocampal-independent state (Diekelmann, & Born, 2010; Walker, 2009). Consistently with this framework, it has been suggested that NREM sleep can be associated with the degree of increasing hippocampal independence during post-sleep memory retrieval (Takashima et al., 2006). On the contrary, sleep deprivation after learning impairs long-term declarative memory retention, potentially resulting in a greater reliance of memory retrieval on the hippocampus (Gais et al., 2007). Fragmentation of NREM sleep has been also associated with an augmented deposition of amyloid plaques (Porter, Buxton, & Avidan, 2015; Mander, Marks, & Vogel, 2015; Lucey & Bateman, 2014; Kang, Lim, & Bateman, 2009). Mander and colleagues (2013) described a theoretical model highlighting how amyloid deposition is associated with NREM sleep disruption. This latter would be indeed responsible of endorsing an increased synaptic tone and metabolic activity in the brain that in turn leads to the accumulation of toxic metabolites in the cerebrospinal fluid, resulting in the amyloid plaques deposition that further impairs sleep (Lucey & Bateman, 2014; Kang et al., 2009).

Building on the previous finding that AHI is more strongly associated with cognitive impairment among APOE4 carriers than non-carriers (Nikodemova 2013), in this study we aim to investigate associations between memory and other cognitive impairments and AHI during REM and

NREM sleep. Our second objective is to evaluate where APOE4 status modifies these associations between cognition and OSAS during REM and NREM sleep.

### **5.2 Study 3**

The aim of this investigation was so to verify if the AHI registered during different sleep stages (i.e. REM vs NREM) can be a predictor of cognitive impairments in OSAS patients. Likewise, also the presence or the absence of APOE4 were examined in order to better understand the role of APOE4 in the association between OSAS and cognition.

### **5.3 Material and Methods**

#### *Participants and Data collection*

A total of 1545 middle-aged adults were enrolled on the Wisconsin Sleep Cohort Study (WSCS), approved by the University of Wisconsin Health Sciences Institutional Review Board. Written informed consent was obtained from all participants, who participated in a broad and thorough epidemiologic study in order to explore the natural history, the causes and consequences of sleep disordered breathing (Young et al., 2009). Body habitus measures, questionnaires about lifestyle, health and medications, neuropsychological tests and overnight polysomnography were collected. Genetic data were also collected in order to identify APOE genotypes, by using the polymerase chain reaction-restriction fragment length method, described in previous studies (Kadotani et al., 2001; Hixson & Vernier, 1990). This third and last study was possible thanks to a period of five months spent at the University of Madison-Wisconsin, as part of my PhD

program. For the present investigation, 1253 adults, age 30- to 60- years, were selected and, according to our aims, analyzed by means of overnight polysomnography, neuropsychological and genetic data.

### *Polysomnography*

Polysomnography recordings have been described in details in previous studies from the WSCS (Peppard, Ward and Morrel, 2009; Kadotani et al., 2001; Young et al., 1993). Apneas were defined as a cessation of breathing for at least 10 seconds, while hypopneas were defined as a reduction of breathing of 20% or greater. The AHI was calculated as the mean number of apneas and hypopneas associated with oxygen desaturation 2% or greater per hour of sleep.

### *Neuropsychological Assessment*

A neuropsychological paper-and-pencil battery of tests was administered by trained technicians after the polysomnography recordings. Tasks have been chosen based on findings highlighting a greater impairment in OSAS patients in executive functions, psychomotor speed and memory. The overall neuropsychological assessment, which lasted about 45 minutes, is shortly described below:

- The Trial Making Test (Part B) commonly used to assess executive functions, motor speed, attention and task switching. It consists of 25 circles numbered from 1-13 and lettered from A-L. Participants are asked to connect in sequence, as quickly as possible, all the circles alternating, in increasing order, between numbers and letters. The main outcome is the Time, measured in seconds, required to complete the task;

- The Symbol Digit Modalities Test also used to evaluate executive functions, attention and motor skills. In this test, a visual key consisting of 110 paired geometric figures and numbers is provided. Participants are asked to apply a key to supply the proper number that is associated with the specific symbol. The outcome is the Number of correct responses in a timeframe of 90 seconds;
- The Controlled Oral Word Association Test used to assess both executive functions and language skills. Participants are asked to name as many words as possible starting with a selected letter of the alphabet. The outcome is measured as the Number of total words in a limited timeframe (1 minute);
- The Digit Cancellation Test used to evaluate psychomotor speed. Participants are asked to detect and delete, as quickly as possible, the target stimulus among a series of distractors. The outcome is the Time, measured in seconds, required to complete the task;
- The Grooved Pegboard Test used to evaluate psychomotor speed. In this test, participants are asked to insert, as quickly as possible, 25 grooved pegs into randomly oriented, slotted holes with, alternately, both the right and the left hand. The outcome is the Time, measured in seconds, to complete the task (sum of right and left hand);
- The Auditory Verbal Learning Test used to assess memory and learning skills. It is composed of several sub-tests consisting of five presentations of a 15-word list with immediate recall (*Learning*), one presentation of a second 15-word list to distract, sixth recall trial of the first list (*Retention*), a recall of the words from the first list after 30 minutes (*Delay*), and a circling words in a short story (*Recognition*). Different outcomes are so measured for each sub-test. The *Learning* score consists of the sum of recalled words in trial 1-5; the *Retention* score is provided by the number of recalled words; the

*Delay* score is the percentage of recalled words and, finally, the *Recognition* score is represented by the number of words correctly identified.

#### **5.4 Statistical Analyses**

Two sets of linear mixed-effects models were performed, in which REM AHI and/or NREM AHI were considered as predictors, and cognitive measures as dependent variables. The first set of models included REM AHI as the main predictor, and the second set included NREM AHI as the main predictor. Separate models were estimated for each cognitive outcome. Each model included an interaction term between REM or NREM AHI and presence of APOE4 to test whether associations between REM and NREM AHI varied by APOE4 status. For cognitive outcomes where the interaction term was significant, the sample was stratified and results are presented separately by APOE4 status. All models were adjusted for the following covariates: age, sex, education level, and BMI. Two-sided  $P < 0.05$  was considered for statistical significance. Data were analyzed with SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

#### **5.5 Results**

Selected demographic, neuropsychological and sleep characteristics of the sample are presented in Table 11.

	<b>n=1253</b>
<b>Demographic and life style characteristics</b>	
Age, mean $\pm$ SD	62.3 $\pm$ 8.1
Male, n (%)	553 (44.1)
Body Mass Index, mean $\pm$ SD	31.7 $\pm$ 7.2
Education (y), mean $\pm$ SD	14.2 $\pm$ 2.5
Alcohol (drinks/week), mean $\pm$ SD	3.7 $\pm$ 5.3
Current Smoking, n (%)	102 (8.1)
<b>Sleep Measures</b>	
Sleep Efficiency, mean $\pm$ SD	79.4 $\pm$ 10.5
PtstI90 <sup>a</sup> , median (IQR)	0.1 (0.0 – 1.3)
Sleepiness <sup>b</sup> , n (%)	239 (19.1)
AHI, median (IQR)	8.3 (3.8 – 19.4)
CPAP <sup>c</sup> treatment, n (%)	182 (14.5)
<b>Neuropsychological Measures, mean <math>\pm</math> SD</b>	
Trial Making Test, Part B (seconds)	83 $\pm$ 37.3
Symbol Digit Modalities Test (n. correct)	48.8 $\pm$ 9.1
Oral Word Controlled Association Test (n. correct)	41.41 $\pm$ 11.04
Digit Cancellation Test (seconds)	396.4 $\pm$ 93.4
Grooved Pegboard Test (seconds)	159.8 $\pm$ 45.8
Rey Auditory verbal Learning Test recognition (n. correct)	13.7 $\pm$ 1.7
Rey Auditory verbal Learning Test learning (n. correct)	47.4 $\pm$ 9.3
Rey Auditory verbal Learning Test delay (%)	79.4 $\pm$ 18.4
Rey Auditory verbal Learning Test retention (n. correct)	9.6 $\pm$ 2.9
<b>Medical history</b>	
Stroke, n (%)	31 (2.5)
Epilepsy, n (%)	22 (2.1)
Hypertension, n (%)	521 (41.6)
<b>Prescribed medication use</b>	
Antidepressants, n (%)	239 (19.1)
Sedatives, n (%)	91 (7.3)
Stimulants, n (%)	7 (0.6)
<b>Genetic Data</b>	
APOE $\epsilon$ 2, n (%)	191 (15.2)
APOE $\epsilon$ 4, n (%)	364 (29.1)

**Table 11.** Selected sample's characteristics.

AHI= apnea/hypopnea index; SD= standard deviation; IQR= inter-quartile ratio; APOE= presence of apolipoprotein.  
<sup>a</sup>Percentage of total sleep time spent with low than 90% of oxygen; <sup>b</sup>self-reported excessive daytime sleepiness on most or all days of the week 9yes, no); <sup>c</sup>Continuous Positive Airway Pressure treatment.

Table 12 shows the estimated association and main effects between REM and NREM AHI and each of the cognitive outcomes, including the interaction term between REM or NREM AHI and presence of APOE4. After adjusting for age, sex, education and BMI, significant associations between NREM AHI and APOE4 emerged at the Controlled Oral Word Association test ( $t_{(489)} = -2.49, p = 0.01$ ), and at the retention AVLT subtest ( $t_{(489)} = -2.50, p = 0.01$ ). As a result of the significant associations found between NREM AHI and presence of APOE4 at the Controlled Oral Word Association test and at the retention AVLT subtest, the sample was stratified by APOE4 status for these two neuropsychological tests. No significant associations were found between REM AHI and presence of APOE4 at any of the cognitive tests.

Neuropsychological Measures	REM AHI			N-REM AHI		
	$\beta$	SE	p	$\beta$	SE	p
Trial Making Test, B	-0.002	0.10	0.98	0.02	0.14	0.85
Symbol Digit Modalities Test	-0.03	0.02	0.12	-0.06	0.02	0.03
Controlled Oral Word Association	-0.02	0.02	0.29	-0.09	0.03	<b>0.01</b>
Digit Cancellation Test	0.32	0.24	0.18	-0.14	0.34	0.67
Grooved Pegboard Test	-0.03	0.12	0.78	0.16	0.17	0.32
Auditory Verbal Learning Test						
Recognition	-0.007	0.005	0.14	-0.008	0.007	0.25
Learning	-0.004	0.02	0.86	-0.04	0.03	0.19
Delay	0.06	0.05	0.23	0.11	0.07	0.12
Retention	-0.005	0.007	0.47	-0.02	0.01	<b>0.01</b>

**Table 12.** Associations between REM and NREM AHI and presence of APOE4 at neuropsychological tests.

REM AHI= apnea/hypopnea index during rapid-eye movement sleep; NREM AHI= apnea/hypopnea index during non rapid-eye movement sleep

Table 13 shows the results stratified by APOE4 status. After adjusting for age, sex, education and BMI, it was found that a higher NREM AHI is a predictor of lower cognitive performances for the retention (memory) ( $t_{(142)} = -2.34, p = 0.02$ ) subtest of AVLT in APOE4 carriers. A significant association occurred between NREM AHI and the absence of APOE4 at the Controlled Oral Word Association test ( $t_{(489)} = -2.49, p = 0.01$ ).

No significant associations were found for REM AHI in predicting any of the cognitive outcomes. None of the interaction terms between REM AHI and APOE4 status were significant, suggesting that APOE4 status did not affect this lack of association between REM AHI and cognitive performance (Table 12).

Neuropsychological Measures	APOE4			NO APOE4		
	$\beta$	SE	p	$\beta$	SE	p
Controlled Oral Word Association	-0.04	0.02	0.15	0.05	0.02	<b>0.01</b>
Auditory Verbal Learning Test - Retention	-0.02	0.009	<b>0.02</b>	0.004	0.006	0.52

**Table 13.** Association between NREM AHI and neuropsychological tests, stratified by APOE4 status.

APOE4= presence of apolipoprotein epsilon 4; NO APOE4= absence of apolipoprotein epsilon 4.

## 5.6 Discussion

As stated in the Introduction section, an increasing number of studies suggested an association between APOE4 and OSAS, which has been considered as a cause of the possible cognitive impairment occurring with this sleep disorder (Small et al., 2004). Nikodemova et al. (2013) corroborated this association, claiming that a memory impairment is the result of the role of APOE4 in modulating the association between OSAS and cognition. The consolidation of long-term memories has been mainly attributed to the NREM stage, which was also found to be the most fragmented by apnea/hypopnea producing, in turn, the deposition of amyloid plaques (Porter, Buxton, & Avidan, 2015; Mander, Marks, & Vogel, 2015; Lucey & Bateman, 2014; Kang, Lim, &



Bateman, 2009). As chiefly described in the Introduction section of this study, some authors suggested that beta-amyloid might cause memory impairments because of the disruption of NREM sleep (Backhaus et al., 2007; Carrier et al., 2011; Mander et al., 2000). Several explanations have been provided in order to better understand this association. One example has been reported in Mander et al. (2015) according to which, in older adults, the reductions in NREM sleep can be associated with the severity of memory impairment observed.

Our results showed that NREM AHI is a predictor of worse memory performances and, in particular, of long memory retention, among APOE4 carriers; according to the Backhaus et al., 2007, Carrier et al., 2011, and Mander et al.'s (2000) studies, our findings might represent further evidence that there may be brain changes due to elevated AHI during NREM sleep. Our results suggest that encoding processes are not damaged, as performances in the recognition of the words previously recorded was not associated with REM or NREM AHI. A selective deficit emerged in retention (i.e. the ability of recovering words from memory), highlighting a long-term memory loss specifically that might be due to the NREM AHI fragmentation. Although significance is not reached, a similar trend can be observed also for the other cognitive measures, potentially suggesting that the higher the fragmentation of NREM sleep, the worse the overall cognitive performance in APOE4 carriers. Cosentino et al. (2008) also described a selective deficit for words retrieval in this population; however, the authors did not analyze the possible differences between REM and NREM sleep, drawing more general conclusions.

To the best of our knowledge, this is the first study to investigate AHI in different sleep stages as a predictor of cognitive performances and whether these associations are modified by APOE4 status. We did not find an association between REM or NREM AHI and tests of recognition, consistent with other studies (Cosentino et al., 2008). This finding may be consistent with the hippocampal/subcortical-frontal dissociation theory. According to this idea, the hippocampus would be more involved in encoding and storage processes, while the subcortical-frontal networks would be responsible for retrieval (Frisoni et al., 2006; Kramer et al., 2004). Our results suggest that

among individuals with OSAS, a hippocampal memory damage would not occur, since the unimpaired recognition suggests proper encoding processes. Conversely, a subcortical-frontal dysfunction, entirely well established in OSAS patients (Beebe & Gozal, 2002), would explain the retention deficit. Also these findings are consistent with the already mentioned Mander et al.'s study (2015) that suggested that the amyloid deposition burden would mostly occur in medial prefrontal cortex, further supporting our findings.

The unimpaired hippocampal memory might discourage the idea that OSAS could be a cause of Alzheimer Disease (Rosenzweig et al., 2015; Osorio et al., 2015; Yaffe et al., 2014) in which a hippocampal memory damage typically occurs. As a matter of facts, the presence of APOE4 does not necessarily imply a direct association between OSAS and Alzheimer Disease. Rather, it can be considered as a risk factor in developing cognitive impairments due to other diseases (i.e. ischemic cerebrovascular disease) showing a “dementia-like” clinical manifestation of symptoms (McCarron, DeLong, & Alberts, 1999).

Although fMRI studies showed OSAS-due structural hippocampal damages (Algin, O., Akin, B., Ocakoğlu, G., & Özmen, 2016), a retention memory deficit was not always highlighted (if not completely excluded) by clinical neuropsychological evaluations. Limited to this specific results, it can be proposed that the potential cognitive impairment observed in OSAS patients might be due to different neurological sequelae rather than a real dementia-related pattern.

Although the present study provided a first, overall distinction of the effects that AHI registered in different stages of sleep may have on cognition, further research is necessary. Our findings suggest an association between AHI during NREM sleep and the consolidation of long-term memories. However, in our study a lack of information about NREM sub-stages exists. In particular, further research should explore NREM stages 3 and 4 which are characterized by slow waves sleep that, in turn, could be important for memory consolidation (Genzel, Kroes, Dresler, & Battaglia, 2014; Aricò et al., 2010; Marshall, Helgadóttir, Mölle, & Born, 2006).

## **5.7 Conclusions**

The present study showed that a higher apnea/hypopnea index during NREM sleep predicts worse performance on a memory task among APOE4 carriers. In OSAS, memory processes seem to be strongly mediated by NREM sleep, whose fragmentation is suggested to be responsible of their impairments.

## **GENERAL CONCLUSIONS AND PRACTICAL IMPLICATIONS**

The aim of the present dissertation was to show that Obstructive Sleep Apnea Syndrome (OSAS) is an extremely complex disease, able to compromise overall body and brain functioning. Notwithstanding the controversies underlying this sleep disorder that have been discussed in the previous chapters, the general conclusion is that cognition is affected by OSAS and that there is a particular involvement of the executive functions. Thus, this dissertation supports the hypothesis of a cognitive frailty associated with OSAS which, with adequate treatment, can be reversed at least in some sub-cognitive domains. Our results show that apolipoprotein Epsilon 4 (APOE4) can be considered a risk factor for the retention memory loss described, and that NREM sleep is particularly fundamental in this process.

The results of our research work and the consequences associated with OSAS have some important practical implications that we think clinicians should take into account. The described executive dysfunction is directly linked to the social and occupational difficulties experienced by patients with OSAS. As mentioned in Chapter 2, the impact of OSAS on individuals' work performance, security and productivity as well as on the potential, additional and indirect costs of lost productivity, needs to be investigated in depth (Rosekind et al., 2010). Poor work performance and occupational injuries have been associated with excessive daytime sleepiness (AlGhanim, Comondore, Fleetham, Marra, & Ayas, 2008). In addition, the economic burden related to untreated OSAS is considerable, amounting to billions of dollars per year (AlGhanim et al., 2008). The mood alterations previously described in the literature (Engleman & Douglas, 2004; Devita et al., 2017) have also been considered an important worsening factor for the work efficiency of OSAS patients. This research project is part of a PhD program focusing on "Human Capital Formation and Labour Relations" that well represents the need to keep a multidisciplinary approach when dealing with human and psychological sciences. Accordingly, the investigation on OSAS fits well into this approach, since, as showed in our 3 studies, it cannot be considered just as a disease limited to sleep

or to nighttime. Rather, it should be seen as a complex condition involving different and large areas of patients' and caregivers' life and functioning. OSAS does not only affect the restorative function and the quality of sleep, but also cognitive functioning and mood regulation, social and interpersonal exchanges, and work and occupational performances and efficiency.

As reported above, OSAS is still underdiagnosed and its effects are usually underestimated by the general population, even if early diagnosis is of crucial importance to limit the social and occupational issues due to it. The results achieved in this work should encourage clinicians to investigate the presence of OSAS by default during routine clinical interviews and medical anamneses, also bearing in mind patients' poor awareness of their condition. Adequate and well-timed treatment would then be prescribed in order to avoid the cognitive, behavioral, social and occupational difficulties described in this dissertation.

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**Devita M**, Montemurro S, Zangrossi A, Ramponi S, Marvisi M, Villani D, Raimondi MC, Merlo P, Rusconi ML, Mondini S (2017). Cognitive and motor reaction times in Obstructive Sleep Apnea Syndrome. A study based on computerized measures. *Brain and Cognition*, 117C, 26-32.

**Devita, M**, Montemurro, S, Ramponi, S, Marvisi, M, Villani, D, Raimondi, MC, Rusconi ML, & Mondini, S. (2017). Obstructive sleep apnea and its controversial effects on cognition. *Journal of clinical and experimental neuropsychology*, 39(7), 659-669.

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