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OBSTRUCTIVE SLEEP APNEA: THE EFFECTS OF APNEA-HYPOPNEA INDEX, OXYGEN DESATURATION AND DAYTIME SLEEPINESS ON COGNITIVE FUNCTION.

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Trabalho efetuado sob a orientação de:
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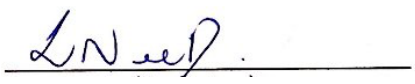
Signature: 

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Abstract

Background: Obstructive sleep apnea (OSA), a sleep-disordered breathing, is recognized for having deleterious effects on cognition, however, the mechanisms mediating this effect as well as the specific cognitive functions affected remain unknown. The most reported deficits are in executive functions, attention and memory. An aetiological model suggests that sleep fragmentation and intermittent hypoxemia account for the development of cognitive impairment in OSA and may produce different patterns of cognitive decline (Beebe & Gozal, 2002). Additionally, research shows that excessive daytime sleepiness (EDS), a common symptom of OSA, plays an important role in neurocognitive dysfunction. Whether EDS is a result of sleep disruption, hypoxemia or it is an independent risk factor for neurocognitive dysfunction in OSA remains unclear.

Research questions: This study investigated whether neuropsychological performance of OSA patients varies across group of patients with different OSA severity as well as from normative data and a comparative group. Moreover, this study explored whether the mean number of apneic events per hour (Apnea-Hypopnea Index/AHI), the length of time patients remain hypoxemic during sleep or EDS could predict particular neuropsychological deficits, while taking into account common OSA-related comorbidities. Finally, the relationship between AHI, desaturation indexes and EDS were analysed.

Methods: Fifty-three participants were included (30 men, 23 women) aged 57.7 ± 10.9 years (range: 39–78 years); 38 were newly diagnosed, untreated OSA patients and 15 were controls. Participants were recruited from a group of patients referred for an evaluation of clinically suspected OSA. All participants underwent ambulatory PSG and neuropsychological evaluation. Degree of hypoxemia was operationalised by the average number of desaturations per hour (ODI) and time spent with saturation below 90% (SpO2<90%). Degree of disease severity/sleep fragmentation was represented by the AHI and EDS was characterized by Epworth Sleepiness Scale (ESS) scores.

Findings: Compared to normative data, severely affected OSA patients presented mild impairment in a global cognitive measure (MoCA; z= -1.2). An analysis of the entire OSA cohort revealed moderate to severe deficits in attention, immediate verbal recall and delayed recall in 18.9%, 15.8% and 39.5% of the patients, respectively; mild to moderate deficits in visual memory in 18.4% of the patients as well as deficits in cognitive flexibility

performance in 31.6% of the total OSA sample. Significant difference in the Digit Span Backward performance was detected between mild and moderate OSA patients (p=.017). However, this difference disappeared after the impact of slowed information processing was controlled (p>.05). Higher levels of EDS were associated with lower performance in the Stroop Test, regardless of disease severity (.20 ± .52 vs. -.33 ± .63 vs. -.35± .35, mild vs. moderate vs. severe EDS, p= .016). AHI and ODI were highly correlated (r=.90), AHI and ODI were moderately correlated with SpO2<90% (r=.45, r=.55, respectively). EDS did not significantly correlate with AHI or ODI, yet it was weakly, negatively correlated with SpO2<90% (r=-.40).

Conclusion: The relationship between cognition and apnea severity is not completely linear. Severely affected patients presented deficits in general cognitive performance, yet no such deficits were observed in mild and moderate OSA patients. Although no further evidence of profound cognitive impairment was found in OSA patients when analysed according to disease severity, an analysis of the whole OSA sample revealed sustained attention, memory and cognitive flexibility deficits. Disease severity, desaturation indexes and EDS were not significant contributors to the prediction of these deficits, suggesting that perhaps another unexplored factor may account for cognitive impairment in OSA. Results revealed that increased subjective EDS was associated with poorer inhibitory control performance in apneic patients, substantiating the well-known detrimental effects of poor sleep on the prefrontal cortex circuitry. EDS was not associated with apnea or desaturation index, however, longer desaturations were associated with less sleep complains. Overall, this study emphasizes the impact of OSA on cognition as well as the importance of the psychological aspects of the disorder. The lack of access to full polysomnographic data and the modest sample size may have limited the investigation of the OSA-cognitive dysfunction association.

Key words: Obstructive Sleep Apnea, cognitive impairment, hypoxemia, daytime sleepiness, sleep fragmentation, neuropsychology.

Resumo

Contexto: A síndrome de apneia obstrutiva do sono (AOS) é uma perturbação respiratória do sono, caracterizada por episódios repetitivos de interrupção do fluxo aéreo, que causam a queda da saturação de oxigênio no sangue, resultando em esforço respiratório e (micro)despertares. Consequentemente, pessoas que sofrem de AOS frequentemente apresentam sono fragmentado e sonolência diurna excessiva (SDE). Os efeitos deletérios da AOS na saúde são bem conhecidos, particularmente na cognição. Embora muitos estudos demonstrem uma relação entre AOS e comprometimento cognitivo, os mecanismos que medeiam esse efeito permanecem desconhecidos, bem como as funções cognitivas específicas afetadas. Os défices mais relatados na literatura são nas funções executivas, atenção e memória. Embora a gravidade da doença tenha sido descrita como um dos principais contribuintes para o declínio cognitivo, estudos mostram que a gravidade do comprometimento cognitivo e a gravidade da AOS não se correlacionam inteiramente, sugerindo que alguns parâmetros na AOS podem explicar melhor esta associação subjacente do que outros. Beebe e Gozal (2002) ofereceram um modelo etiológico sugerindo que a fragmentação do sono e a hipoxemia intermitente são responsáveis por desencadear o comprometimento cognitivo na AOS, podendo produzir diferentes padrões de declínio cognitivo. Além disso, pesquisas indicam que a SDE desempenha um papel importante na disfunção neurocognitiva, no qual doentes apneicos não-sonolentos tendem a apresentar menos défices cognitivos do que os doentes sonolentos. Ainda não está claro se a SDE resulta da fragmentação do sono, hipoxemia ou se é um fator de risco independente para disfunção neurocognitiva na AOS.

Objetivos: O objetivo deste estudo foi investigar se a performance neuropsicológica de doentes com AOS varia entre grupos de doentes com diferentes graus de apneia, bem como se há variação em relação a dados normativos e a um grupo comparativo. Além disso, este estudo explorou se o número médio de eventos apneicos (Índice de Apneia-Hipoapneia/IAH, relacionado a microdespertares, podendo ou não envolver dessaturação), o tempo em que os doentes permanecem hipoxémicos durante o sono ou a SDE podem prever défices neuropsicológicos específicos, enquanto comorbidades comuns relacionadas à AOS são controladas. Por fim, analisou-se a relação entre IAH, índices de dessaturação e SDE.

Métodos: Foram incluídos 53 participantes (30 homens, 23 mulheres), com idade de 57,7 ± 10,9 anos (variação: 39-78 anos). A amostra consistiu em 38 doentes recentemente diagnosticados com AOS e não tratados, e 15 controlos. Todos os participantes foram recrutados de um grupo de doentes encaminhados para avaliação de suspeita de AOS, os

quais foram submetidos a polissonografia ambulatorial e a uma avaliação neuropsicológica completa. O grau de hipoxemia foi operacionalizado pelo número médio de eventos de dessaturação por hora de sono (IDO) e o tempo gasto com saturação abaixo de 90% (SpO_2 <90%). A gravidade da doença/fragmentação do sono foi representada pelo índice de apneia-hipoapneia (IAH) e a sonolência diurna excessiva (SDE) foi caracterizada pelas pontuações na Epworth Sleepiness Scale (ESS).

Resultados: Comparados a dados normativos, os doentes com AOS gravemente afetados apresentaram comprometimento ligeiro em uma medida cognitiva global (MoCA; z = -1,2). Uma análise da amostra envolvendo todos os doentes apneicos revelou também défices moderados a graves na atenção, recuperação imediata de estímulo verbal e recuperação diferida de material verbal em 18,9%, 15,8% e 39,5% dos pacientes, respetivamente. Défices ligeiros a moderados na memória visual foram observados em 18,4% dos doentes, bem como défices no desempenho da flexibilidade cognitiva em um total de 31,6% da amostra (AOS). Não foram detetadas diferenças significativas entre as performances neuropsicológicas de doentes com diferentes gravidades da doença, exceto no desempenho do teste de Memória de Dígitos Inversa (p = 0,017) de doentes com AOS ligeira e moderada. Essa diferença, no entanto, desapareceu após o impacto da lentificação do processamento de informação ser controlado (0,35 ± 0,13 vs. -14 ± 0,15, ligeira vs. moderada, p>.05). Após controlar certas características clínicas, a SDE foi associada de forma independente a um pior desempenho no teste Stroop em doentes com AOS (0,20 ± 0,52 vs. -0,33 ± 0,63 vs. -0,35± 0,35, EDS ligeira vs. moderada vs. grave, p = 0,016). IAH e IDO apresentaram correlações fortes (r = 0,90), enquanto IAH e IDO foram moderadamente correlacionados com SpO2 <90% (r = 0,45, r = 0,55, respetivamente). A EDS não se correlacionou significativamente com o IAH ou com o ODI, mas foi fracamente e negativamente correlacionada com SpO_2 <90% (r = -. 40).

Conclusão: Este estudo mostra que a relação entre cognição e gravidade da apneia não é completamente linear em adultos de meia-idade/idosos. Os resultados revelaram comprometimento no desempenho cognitivo geral de doentes gravemente afetados em relação a dados normativos, mas nenhum défice foi observado em doentes com AOS ligeira e moderada. Embora nenhuma outra evidência de comprometimento cognitivo tenha sido encontrada nos doentes quando analisados de acordo com a gravidade da doença, uma análise incluindo todos os doentes apneicos revelou um aumento de défices de atenção, memória e flexibilidade cognitiva. Os índices de gravidade da doença, dessaturação e SDE não contribuíram significativamente para o desenvolvimento da maioria destes défices, o que sugere que outros mecanismos não explorados neste estudo podem estar envolvidos. Os

resultados revelaram, no entanto, que a SDE influencia negativamente a capacidade de controle inibitório em doentes com AOS, o que confirma os efeitos prejudiciais da interrupção e má qualidade do sono no circuito do córtex pré-frontal. Enquanto a hipoxemia não foi um fator relevante para a previsão de défices neuropsicológicos, os resultados mostraram que indivíduos com dessaturações mais longas demonstram um número menor de queixas de sono, o qual pode estar associado a uma perceção errónea de sono causada por danos cerebrais. No geral, este estudo enfatiza o impacto da AOS na cognição, independentemente da gravidade da doença, assim como a importância dos aspetos psicológicos do distúrbio. A falta de acesso a dados polissonográficos completos pode ter limitado a investigação da associação entre AOS e disfunção cognitiva. Além disso, o tamanho modesto da amostra utilizado neste estudo pode ter levado a uma subestimação da magnitude do efeito dos fatores da AOS no funcionamento neurocognitivo.

Termos chave: Apneia Obstrutiva do Sono, declínio cognitivo, hipoxemia, sonolência diurna, fragmentação do sono, neuropsicologia.

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List of Abbreviations

AD = Alzheimer's Disease

AHI = Apnea-Hypopnea Index

COPD = Chronic Obstructive Pulmonary Disease

CR = Cognitive Reserve

CVD = Cerebrovascular Disease

CPAP = Continuous Positive Airway Pressure

EDS = Excessive Daytime Sleepiness

EEG = Electroencephalogram

ESS = Epworth Sleepiness Scale

MCI = Mild Cognitive Impairment

PSG = Polysomnography

ODI = Oxygen Desaturation Index

OSA = Obstructive Sleep Apnea

RDI = Respiratory Disturbance Index

SD = Standard Deviation

SDB = Sleep-Disordered Breathing

SpO_2<90% = Length of sleep time spent with saturation below 90%

Chapter 1. Introduction

1.1 Literature review

1.1.1 Overview.

Obstructive sleep apnea syndrome (OSA) is a sleep-disordered breathing (SDB) characterised by repetitive episodes of airflow cessation or significant decrease in airflow during sleep (Jackson, Howard & Banes, 2011). The obstruction of the upper airway (i.e., recurrent apneas and hypopnea) causes blood oxygen saturation to drop, which leads to respiratory effort and arousals from sleep (Aloia, Arnedt, Davis, Riggs & Byrd, 2004; Jurádo-Gámez, Guglielmi, Gude & Buela-Casal, 2015). Consequently, patients suffering from OSA frequently present snoring, intermittent hypoxemia, sympathetic overactivity and fragmentation of sleep, which often results in excessive daytime sleepiness (EDS).

OSA can have a great impact on both physical and mental health and it is regarded as a risk factor for the development of arterial hypertension, cardiovascular diseases, stroke, white matter change, anxiety and depression (Bahia & Pereira, 2015). Furthermore, OSA has been associated with an increased risk of both Alzheimer's Disease (AD) and vascular dementia (Shi et al., 2018). Cognitive decline has in fact been one of the most mentioned consequences of OSA in the literature. Over the past decades, the study of the relationship between OSA and neurocognitive dysfunction has been increasingly growing. The most reported deficits related to OSA are in executive functions, attention/vigilance, and memory (Bédard, Montplaisir, Richer, Rouleau & Malo, 1991; Daurat, Sarhane & Tiberge, 2016; Krysta, Bratek, Zawada & Stepanczak, 2016). Other authors have indicated further cognitive domains impaired in OSA patients, including psychomotor speed, constructional abilities, language and visuospatial skills (Aloia et al., 2004; Ferini-Strambi et al., 2003; Jackson et al., 2011; Kim, Lee, Lee, Jhoo & Woo, 2011). While many studies have demonstrated a relationship between OSA and cognitive impairment, the mechanisms mediating this effect as well as the specific cognitive functions affected remain unknown.

Conflicting findings may be partly explained by the severity of the disease, where a minor cognitive deficit is observed in mild OSA patients and a greater impairment in moderate to severe cases, particularly in terms of executive function (Sforza & Roche, 2012). However, the severity of cognitive impairment and OSA severity do not correlate entirely, suggesting that some physiologic parameters in OSA may be reflective of the underlying association more than others (Bédard et al., 1991). Studies on the effects of OSA on cognitive functions have

proposed different mechanisms to explain cognitive impairment in apneic patients, where sleep disruption and blood gas abnormalities are seen as the main determinants of cognitive decline (Olaithe, Bucks, Hillman & Eastwood, 2018). Different authors have argued that the number of apneas per hour of sleep (represented by the apnea-hypopnea index/AHI), associated with sleep fragmentation and EDS, explains cognitive dysfunction in these patients (Aloia et al., 2001; Bardwell, Ancoli-Israel, Berry & Dimsdale, 2001; Olaithe, Skinner, Hillman, Eastwood & Bucks, 2015). On the other hand, nocturnal hypoxemia has been repeatedly mentioned in the literature as the main causative factor for these deficits (Findley et al., 1986; Gale & Hopkins, 2004; Quan et al., 2011). Conflicting findings over the causal factors of cognitive impairment in OSA may be partly explained by the different methodologies applied (e.g., self-reported OSA, adjusted confounding factors; such as body mass index, cerebrovascular disease (CVD), hypertension, diabetes mellitus and definitions used to characterize the disease.

Overall, despite the remarkable growth of scientific research on OSA and its effects on cognition, the mechanisms underlying this association are still debatable. Whether the different components of OSA can explain the neurocognitive deficits seen in these patients or whether they coexist independently from SDB remains unknown. This study aims to contribute to the current understanding of the relationship between OSA and cognitive impairment, with a specific focus on the neuropsychological domains affected in apneic patients, the degree of impairment and how certain aspects of OSA may affect the nature of these deficits differently.

The next section will provide an overview of the epidemiology of OSA, with a particular emphasis on issues related to the population prevalence, comorbidities and cardio-/cerebrovascular complications. Within this subsection, the relationship between OSA and depression is reviewed as well as their collective impact on cognitive functioning. The relationship between OSA and cognitive impairment is then discussed. This is followed by the analysis of empirical evidence of the potential contributing factors for this association, which include the effects of AHI (disease severity), oxygen desaturation (hypoxemia) and EDS. The potential associations between these three last factors are also considered.

1.1.2 Obstructive Sleep Apnea: Epidemiology.

1.1.2.1 Definition and Diagnosis.

According to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events, an OSA diagnosis is made if the number of obstructive events (apneas and hypopneas) is greater than 15 events/hr or greater than 5 events/hour in a patient who reports any of the following: unintentional sleep episodes during wakefulness, daytime

sleepiness, unrefreshing sleep, fatigue, insomnia, waking up breath holding, gasping, or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient's sleep (American Academy of Sleep Medicine, 2005).

According to the AASM, sleep apnea severity is typically measured by the apnea-hypopnoea index (AHI) defined as the number of complete (apneas) or incomplete (hypopneas) obstructive episodes per hour of sleep (Garvey, Pengo, Drakatos & Kent, 2015). OSA severity is defined as mild for AHI ≥ 5 and < 15, moderate for AHI ≥ 15 and ≤ 30, and severe for AHI > 30/hr (Epstein et al., 2009). Apneas are defined as a continuous decrease of airflow of at least 90% from baseline for at least 10 seconds. They can be categorized as central, obstructive or mixed, based on whether attempt to breathe is present during the episode. Hypopneas are characterized by constant reduction of airflow of at least 30% from baseline for at least 10 seconds, accompanied by oxygen desaturation of at least 3% from pre-event baseline or an arousal (Zuurbier et al., 2016). For both clinical and research purposes further measures of disease severity may include degree of nocturnal hypoxemia and extent of sleep fragmentation (Punjabi, 2008).

Traditionally, overnight polysomnography (PSG) is considered the gold standard test for the diagnosis of OSA, so that the following physiological signals can be monitored: electroencephalogram (EEG), electrooculogram, chin electromyogram, airflow, oxygen saturation, respiratory effort, and electrocardiogram and heart rate. While PSG is considered the gold-standard method for diagnosing OSA, it has several disadvantages. It requires an overnight stay at a sleep clinic with qualified staff that can gather and interpret complex physiologic data. The process is also expensive, time consuming and labour intensive (Punjabi, 2008). Furthermore, the discrepancies in PSG data collection, analysis and interpretation across many sleep centres have made the comparison between numerous investigations on the health impact of OSA complicated (Punjabi, 2008). These limitations have led to growing interest in in-home diagnosis of OSA using portable monitors. Clinical guidelines support the use of home monitors in the diagnosis of OSA when used as part of a comprehensive sleep assessment in patients with a high pretest probability of moderate to severe OSA (Epstein et al., 2009). Portable monitors are cost-effective and have shown high sensitivity and specificity, therefore obviating the need for PSG testing in patients with suspected OSA (Xu et al, 2017).

1.1.2.2 OSA Prevalence and Risk Factors.

Notwithstanding the great clinical and scientific progressions with regard to OSA in the last decades, many adults suffering from this condition remain undiagnosed (Punjabi, 2008). The reason for this may be explained by the fact that patients are often unaware of the associated symptoms that are frequently recognized by a bed partner. In spite of being an undiagnosed pathology, OSA is considered one of the most common respiratory disorder, especially among men. It is estimated that 24% of men aged 30 to 60 years old have OSA compared to 9% of women of this age group (Garvey et al., 2015). The reason for the discrepancy of OSA incidence among sexes is not well established. The higher prevalence of OSA in the male population could be explained by anatomical upper airway abnormalities, more frequently seen in men (Jackson et al., 2011). It is also possible that the different types of complaints presented by women (e.g., low energy and fatigue) compared to the classical OSA symptoms commonly exhibited by men (e.g., loud snoring, witnessed apneas and excessive daytime sleepiness) may lead to diagnostic errors (Garvey et al., 2015).

Age is another recognized risk factor for OSA. It is estimated that adults face a 30% higher risk after 65 years old (Jurádo-Gámez et al., 2015). Studies have shown that the prevalence of OSA in men and women between 65 and 99 years of age goes up to 70% and 56% respectively, when AHI is defined as ≥ 10 events/hr (Punjabi, 2008). While the incidence of OSA increases progressively with age, the community-based Sleep Heart Health Study has revealed that the syndrome reaches a plateau after the age of 60 (Young et al., 2002). The higher incidence of OSA in older adults may be due to increased fat deposition in the parapharyngeal space and changes in the pharyngeal area (Punjabi, 2008).

Numerous epidemiologic studies have also repeatedly described body weight as the strongest risk factor for OSA (Jurádo-Gámez et al., 2015). According to the Sleep Heart Health Study, an increase in body weight over time can speed up the progression of OSA or increase disease severity (Young et al., 2002). Knowledge of the risk factors for OSA is therefore crucial for diagnostic, prognostic and treatment purposes in both clinical and research areas.

1.1.2.3 Comorbidities and Complications:

The prevalence of patients with comorbidities associated with OSA has been consistently growing. Numerous studies support an independent role for OSA in promoting harmful cardiovascular consequences, particularly with regard to hypertension. A study performed with 11,911 participants with suspected OSA has shown that chronic intermittent hypoxia seems to be an independent predictor of hypertension (Tkacova et al., 2014). Intermittent hypoxemia in

OSA is considered one of main contributors for the development of an extensive range of cardiovascular and other morbidities (Lavie, 2019). Recurrent hypoxia provokes the overproduction of reactive oxygen species, generating oxidative stress by inducing mitochondrial dysfunction (Lavie, 2019). This may lead to endothelial dysfunction, a hallmark of atherosclerosis, a condition which causes substantial reductions in blood flow through the affected artery (Badran, Ayas & Laher, 2014). Severity of intermittent hypoxia and the presence of moderately severe OSA has also been linked to glucose intolerance and insulin resistance, which could result in type 2 diabetes mellitus (DM2) (Punjabi et al., 2004). Not surprisingly, numerous studies have further demonstrated that OSA increases the chance of stroke incident (Lavie, 2019). Badran et al. (2014) have revealed a significant positive correlation between AHI and ischemic stroke in men (Badran et al., 2014). OSA and CVD appear to have a bidirectional relationship, where adults who have had a stroke or transient ischaemic attack are more likely to suffer from OSA than the general population, and the prevalence of CVD increases with OSA severity (Garvey et al., 2015).

Previous research has also indicated a high prevalence of insomnia in OSA patients, varying from 32% to 84% in Western countries (Cho et al., 2018). It has been suggested that recurring episodes of apnea and subsequent arousals can cause maintaining sleep difficulties and thus poor sleep quality, supporting the idea that sleep disruption may promote the development of insomnia (Beneto, Gomez-Siurana & Rubio-Sanchez, 2009). Patients suffering from both conditions may present worse sleep quality and increased risk for cardiovascular disease, cerebrovascular disease, dementia and depression (Cho et al., 2018).

These sleep, metabolic, cardiovascular and cerebrovascular disorders are considered to affect selected cognitive domains (Incalzi et al., 2004). The association between OSA and neurocognitive impairment is therefore a complex one as it may involve several overlapping physiological processes (Zhou, Camacho, Tang & Kushida, 2016). It is possible that comorbidities can make some apneic patients more or less at risk of developing cognitive impairment (Yamout, Goldstein, Lah, Levey & Bliwise, 2012).

As previously mentioned, depression is another common mental health condition in apneic patients. It is estimated that for every two apneic patients one suffers from depression (Rezaeitalab, Moharrari, Saberi, Asadpour & Rezaeetalab, 2014). Adults suffering from OSA often present lower mood states with higher levels of anxiety and depression (Jurádo-Gámez et al., 2015). These psychological symptoms may be a result of hypoxemia, sleep fragmentation and/or EDS (Gale & Hopkins, 2004; Jaussent et al., 2011; Kerner & Roose, 2016). Past studies have shown that depressive symptoms are commonly seen in individuals

who suffer from hypoxemia, such as OSA and carbon monoxide poisoning patients (Gale & Hopkins, 2004). The link between OSA and hypoxemia is supported by available evidence which suggests that Continuous Positive Airway Pressure (CPAP) reduces these emotional symptoms in apneic patients (Gale & Hopkins, 2004).

Neuroimaging studies have suggested that these associations are likely to be explained by pathologic processes in the cerebral microvascular and neurovascular systems (Kerner & Roose, 2016). Tahmasian and colleagues (2016) have detected structural atrophy and functional disturbances in the amygdala and the right central insula of apneic patients, concluding that the negative impact of the disease on these structures might play a role in the affective changes observed in these patients.

Depression may also mediate or contribute to the relationship between sleep apnea and cognitive impairment (Shi et al., 2017). The longitudinal Maastricht Ageing Study (MAAS) has revealed that depressive symptoms mediate the relationship between sleep complaints and cognitive impairment in middle aged and older adults, suggesting that poor sleep may lead to higher levels of depressive symptoms and consequently resulting in cognitive decline (Jelicic et al., 2002). Hence, based on the overwhelming evidence confirming the deleterious impact of depression on cognitive functions, particularly in the domains of memory, attention and executive function (e.g., problem solving, decision making, and judgment), it is important that depressive symptoms are assessed and taken into account when analysing the relationship between OSA and neurocognitive dysfunction (Richardson & Adams, 2018).

Overall, OSA has a multidimensional influence on health and increase the risk of morbidity of physical and mental conditions (Shi et al., 2017). The challenge for better understanding the link between OSA and cognitive dysfunction is finding an explanation that considers all different results in light of comorbid conditions.

1.1.3 OSA and Cognitive Dysfunction

The association between OSA and cognitive dysfunction has been increasingly investigated. The overall pattern of cognitive impairment in apneic patients is complex, yet, alterations are most likely to take place in the domains of attention, memory, and executive functions. A meta-analysis by Aloia and colleagues (2004) has revealed that these functions are compromised in at least 60% of the studies reviewed. In the attention domain, sustained attention seems to be most impaired, whereas in the memory domain, impairment occurs in verbal and visual delayed long-term memory, and in visuospatial/constructional memory

(Olaithe et al., 2018). Executive function is believed to be one of the most affected cognitive domains in patients with severe OSA (Bédard et al., 1991; Gale & Hopkins, 2004). Decline in executive functions has been observed in shifting, updating/working memory, inhibition, generativity and fluid reasoning (Olaithe et al., 2015). Neuroimaging studies confirm a relationship between changes in neuropsychological functions in OSA and localized brain change. Gale and Hopkins (2004) demonstrated an association between hippocampal atrophy and memory deficits in apneic adults, whereas Canessa et al. (2011) found that executive and visuoconstructional impairment are likely to reflect a decrease in grey matter volume in the superior parietal and frontal regions, also involved in attention and working memory. While some studies have also reported a general cognitive domain, the majority of papers reviewed in two meta-analyses have found intact global cognitive functioning (Aloia et al., 2004; Olaithe et al., 2018). It is possible that the absence of impairment in general cognitive ability in these studies is a result of the lack of categorisation of patients according to disease severity. Few studies have demonstrated that OSA may also affect other abilities, including psychomotor speed and language (Daurat et al., 2016; Ferini-Strambi et al., 2003). Yet, most studies have indicated that language function is typically spared in apneic patients. Researchers maintain that there is no theoretical reason to think that language capacities would be impaired by either intermittent hypoxia or sleep fragmentation (Aloia et al., 2004).

In 2016, a meta-analysis revealed that the greatest deficits in OSA are observed in the domains of psychomotor speed and executive function, while memory functions, attention, speed of processing and constructional abilities are affected but to a lesser extent (Stranks & Crowe, 2016). These findings are in line with a former meta-analysis performed by Beebe, Groesz, Wells, Nichols and McGee (2003). While several earlier studies reveal mixed findings with regard to memory functions (Fulda & Schulz, 2001), many recent studies point out that apneic patients are indeed prone to memory problems (Stranks & Crowe, 2016). Memory processes are nevertheless believed to be affected differently by OSA. Naegelé and colleagues (2006) have found that patients with moderate to severe OSA presented poorer retrieval of verbal and visual episodic memory (recollection of particular experiences) yet, normal maintenance, recognition, and forgetfulness compared to healthy subjects. The pattern of deficit in episodic memory is indicative of prefrontal, subcortical, or both prefrontal and subcortical dysfunction (Naegelé et al., 2006). Furthermore, OSA patients exhibited an inferior performance on a procedural memory test (memory for skills), despite normal learning pattern; and working memory deficits (temporary maintenance and manipulation of information), yet, intact short-term memory (temporary recall of information). All these memory deficits were

nevertheless mild. Contrary to many previous studies, there was no significant association between memory impairment and OSA severity (respiratory disturbance index/RDI or O_2 desaturation) (Roche, 2016). This inconsistency may be a result of the variability in disease severity among patients and consequently the vulnerability to cognitive effects of sleep fragmentation and intermittent hypoxia. Alternatively, other factors may influence the OSA-memory dysfunction association.

Besides being considered a risk factor for neurocognitive dysfunction in older adults, a bidirectional relationship between OSA and neurodegenerative diseases has been repeatedly demonstrated in the literature (Bahia & Pereira, 2015). In a recent meta-analysis of the association between the most common sleep complaints and several types of dementia, it was reported that SDB increases the risk of AD and vascular dementia in the elderly (Shi et al., 2018). Likewise, a meta-analysis of six prospective studies carried out with 212,943 individuals aged 40 years or older reported that apneic adults were 26% more likely to develop significant cognitive decline or dementia at the 3 to 15-year follow-up (Gosselin et al., 2018). The apolipoprotein E epsilon4 (ApoE e4), a protein involved in lipid metabolism and considered a major risk factor for AD, may also increase the risk for OSA (Kim et al., 2011). This protein has been repeatedly linked to OSA, particularly when cognitive deterioration is present (da Silva, 2015). A population-based longitudinal study has shown that the AHI is considerably higher in adults with ApoE e4, irrespective of age, sex, and body mass index (Naegelé et al., 2006). It is possible that OSA and ApoE e4 may have negative synergistic effects on cognition.

Research shows that the reverse is also true, the greater the severity of dementia, the higher the incidence and severity of OSA (Kim et al., 2011). It has been estimated that nearly 50% of AD patients will have experienced OSA at some point after their initial diagnosis (Polsek et al., 2018). It is possible that disturbance of sleep-wake rhythm, poor sleep quality, and OSA, commonly observed in people with AD, are connected to neuronal degeneration involved in sleep-wake generation and respiration (Kim et al., 2011). However, up until now, neither the time course of alterations in the sleep parameters from preclinical to the clinical stages of dementia nor its trajectory during the course of OSA process have been entirely recorded or understood (Polsek et al., 2018).

Numerous studies have endeavoured to find the causative factors leading to neurocognitive changes in OSA patients (Jurádo-Gámez et al., 2015). In 2002, Beebe and Gozal offered an aetiological model based on significant roles for sleep fragmentation and intermittent hypoxia in the development of cognitive impairment in apneic patients. In this model, sleep is

considered a vital restorative and regulating process, which includes reinforcing foundations for learning and memory, and modulating neuroendocrine demands. These processes are compromised by the fragmentation of sleep, which results in homeostatic imbalance, impairing neural function (Beebe & Gozal, 2002). Moreover, the model proposes that hypoxia and hypercapnia (high levels of carbon dioxide in the bloodstream) compound this damage. The authors suggest that both hypoxemia and sleep fragmentation contribute to cognitive impairment in OSA. It is currently recognized that both sleep fragmentation and oxygen desaturation can produce different patterns of cognitive decline and response to treatment, which may reflect different neuropathological mechanisms (Aloia et al., 2004). Research indicates that these two factors do not only exacerbate the existing neuropsychological deficits in patients with moderate OSA but also generate new deficits in severe apneic patients (Bédard et al., 1991).

Numerous studies were nonetheless unsuccessful in finding a relationship between OSA parameters and neuropsychological performance. The inconsistency in results across studies may be explained by the great diversity of measures of sleep fragmentation and disease severity (e.g., AHI, RDI, Apnea Index/AI or arousals), as well as measures of hypoxemia (e.g., mean oxygen saturation/SpO_2 during sleep, lowest level and percentage of sleep time below a threshold saturation level, often 80% or 90%) and daytime sleepiness (e.g., self-report questionnaires or behavioural measures).

1.1.3.1 Contributing Factor: Apnea-Hypopnea Index (AHI).

OSA severity, as indicated by the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index, AHI), may play a significant role in cognitive decline. AHI has been linked to distinctive patterns of cognitive change. As reported by Sforza and Roche (2012), patients presenting mild OSA (AHI> 5) are more likely to present self-assessed concentration difficulties but not memory deficits. In contrast, older adults with severe OSA (AHI≥ 30) are more prone to manifest attention, memory and executive function impairment compared to mild cases (Aloia et al., 2004). Similarly, a systematic review has shown that studies conducted with community samples with low levels of OSA demonstrated that these patients present minor cognitive deficits, not statistically different from healthy individuals (SD= .3 or less). Whereas impairment effect size for patients with mean AHI of 30 events/hour was 1, 0.5, and 0.9 SD for attention, memory and executive performance respectively (Engleman & Douglas, 2004). That is, moderate to large impairment effect sizes were detected in clinical samples,

which progressively increased with mean AHI (Engleman & Douglas, 2004). These findings are largely consistent with the study conducted by Bédard et al. (1991), who reported more and severer deficits in severely affected patients and smaller deficits in individuals with moderate OSA. Deficits in attention, immediate and delayed recall of verbal and visual information, planning, and fine motor skills were progressively worse from moderate to severe OSA patients. A decline in general intellectual functioning and executive functions (shifting and constructive skills) were nonetheless only observed in patients with severe OSA. Bédard and colleagues (1991) also found that poor performance in general intellectual measure, as well as in executive and psychomotor tasks were all related to the severity of hypoxemia, whereas attention and memory deficits were associated with reduced vigilance. Such results indicate that there is a contrast between the neuropsychological profiles found in moderate and severe OSA. This may explain why studies that considered these groups as a homogenous population have not found consistent linear relationships between the severity of apneas and neuropsychological deficits.

Despite considerable evidence confirming the cognitive impact of OSA, some studies have found that most cognitive functions were preserved in older apneic patients (Quan et al., 2011; Sforza et al., 2010). A study by Sforza and colleagues (2010) has revealed small deficits only in older adults with severe OSA (AHI>30), who demonstrated a trend toward lower cognitive scores on delayed recall and inhibitory control/executive function (Stroop test). There were nevertheless no significant or strong relationships observed between neuropsychological performance and AHI, ODI, and EDS, suggesting that perhaps other factors outside respiratory sleep disorder affect cognitive performance in these patients (Sforza et al., 2010). It is possible that participants' high level of formal education could have influenced the results. Based on the cognitive reserve (CR) hypothesis, these individuals have more resources available to confront cognitive decline, hence, CR may act as an adaptive compensatory mechanism for accumulated hypoxemia and sleep loss (Stern, 2002). However, this cannot be confirmed as the study lacks a comprehensive measure that quantifies CR. Moreover, a key limitation of this research is that participants were recruited from a cross-sectional community-based study and strict exclusion criteria considering associate medical disorders were applied. The exclusion criteria may restrict the assessment to "very healthy" older adults; thus, the study design may make the cohort different from the general population and findings may not be generalized to clinical samples.

A major limitation of studies investigating the sequelae of OSA on cognitive functioning is that the effects of sleep disturbance are often not separated from oxygen desaturation effects

(Hoth, Zimmerman, Meschede, Arnedt & Aloia, 2013). Although the AHI may include episodes that cause arousals or awakenings from sleep simultaneously with desaturation, it may occur without affecting oxygen levels. Additionally, the AHI does not contain information on the duration aspect of the breathing interruptions and related oxygen desaturations (Wu, Zhan, Zhao & Wei, 2016). While the AHI is a quantitative measure, the degree of physiological stress of different patients with similar AHI severity can be very different. Astonishingly, some investigators have found that when the depth and length of the apnea events increase, AHI may paradoxically decrease (Kulkas, Tiihonen, Julkunen, Mervaala & Töyräs, 2013). Thus, isolating these potential contributing factors is essential to better understand their effects on cognitive function.

In an attempt to overcome the problem of separating the effects of co-occurring episodes of hypoxemia and arousals, different authors have compared the cognitive profiles of OSA and other disorders that affect either sleep architecture or cause hypoxemia (Incalzi et al., 2004; Roehrs et al., 1995). This approach assists in identifying the shared or exclusive cognitive deficits taking place between OSA and other pathologies, and therefore it may help clarifying the underlying mechanisms of cognitive harm in OSA. A study comparing the cognitive profiles of patients with OSA and chronic obstructive pulmonary disease (COPD), postulated that since airflow obstruction is a central element of both conditions, any differences between these groups could be ascribed to sleep disturbance (Roehrs et al., 1995). The findings revealed that apneic adults demonstrated inferior performance on a sustained attention task, considered sensitive to sleepiness, whereas individuals with COPD exhibited poorer performance on a motor skill task, sensitive to hypoxemia. Thus, it could be said that the deficits in attention and psychomotor abilities seem to be specifically associated to sleep disruption and hypoxemia, respectively (Roehrs et al., 1995). Yet, other deficits observed in complex reasoning and memory were nonspecific, that is, both sleep disruption and hypoxemia contributed to the impairment. While the respiratory events index (number of apneas and respiratory event-related arousals) did not provide unique predictability of cognitive impairment in apneic patients in this study, mean sleep latency (an objective measure of EDS) was found to be the best predictor of the cognitive deficits observed (moderate correlation), followed by time spent with oxygen saturation under 85%.

Using the same approach, Incalzi and co-workers (2004) compared the cognitive pattern of apneic patients, COPD, AD and multi-infarct dementia patients. They revealed that OSA patients present a well-defined neuropsychological profile which stems from a predominant constructive and reasoning deficit (Incalzi et al., 2004). This study has nevertheless failed to

find a relationship between neuropsychological deficits and OSA severity indexes. It is possible that the small number of severely hypoxic apneic patients could have hamper the probability of detecting a significant correlation. Moreover, this study has not administered tests to measure attention and it has not measured many executive functions that are often impaired in apneic patients.

In addition to the limitations that have been discussed, the absence of consistent association between OSA parameters and neuropsychological deficits in previous studies may stem from the fact several studies have only used the RDI or AHI to analyse the relationship between OSA and cognitive impairment, which is a crude measure of assessing sleep apnea since it does not consider the duration of each separate event involved in OSA. Whether the AHI can predict the degree of specific cognitive alterations in apneic patients or it only provides redundant information and not unique predictability remains unknown.

1.1.3.2 Contributing Factor: Oxygen Desaturation (Hypoxemia).

The impairments in neuropsychological function in OSA have been repeatedly ascribed to chronic intermittent hypoxemia (Rohers et al., 1995). While the AHI measures the number of apneas (shallow breathing or pauses in breathing which may or not occur with desaturations) per hour of recording, the Oxygen Desaturation Index (ODI) is typically used to assess the number of desaturations per hour, that is, the severity of nocturnal hypoxemia. The ODI is graded like the AHI, where an ODI of 5<15 is considered mild, 15<30 moderate and ≥30 severe. The effects of moderate and severe ODI on general intellectual slowing and more specific deficits in executive functions have been confirmed by many studies (Devita et al., 2016; Gale & Hopkins, 2004). Both daytime and nocturnal hypoxemia are known to disrupt the biochemical and hemodynamic sate of the central nervous system (CNS) (Findley et al., 1986). Hypoxemia and hypercapnia alter neural functions, increase sympathetic vasoconstriction and therefore considerably increase cerebral blood flow (Canessa et al., 2011; Findley et al., 1986). These CNS disturbances may justify the relationship between hypoxemia and neurocognitive impairment in individuals who undergo hypoxemic episodes, such as individuals at high altitudes, severely affected COPD and OSA patients (Findley et al., 1986; Gale & Hopkins, 2004).

OSA research has focused primarily on deficits in executive functions (Sforza & Roche, 2012). The most affected domains of executive functions are working memory, phonological fluency, cognitive flexibility, and planning (Saunamäki & Jehkonen, 2007). These deficits support the idea that the areas normally damaged in this disorder are predominantly the

prefrontal cortical lobes (Beebe & Gozal, 2002; Devita et al., 2016). Research findings are nevertheless heterogeneous, some studies pointing out to an executive dysfunction, whereas others indicate an attentional deficit. Sharma and colleagues (2010) have revealed that severely hypoxemic patients were substantially impaired on working memory, response inhibition, alertness and problem-solving measures. However, after controlling for delayed information processing, the differences in most executive function performance between groups disappeared (apart from in inhibitory control), indicating that perhaps these patients present slowed information processing rather than deficits in executive function (Sharma et al., 2010). Another study has also shown that OSA patients may perform weakly on a working memory measure (Digit Span Backward test) not necessarily because of a deficit in the central executive, but because of deficits in basic attentional processes and slowed mental processing (Verstraeten, Cluydts, Pevernagie & Hoffmann, 2004). These findings highlight the importance of controlling for attentional capacity when evaluating executive functions.

Neuropsychological research suggests that further cognitive impairment and neuropathological changes may be caused by accumulative hypoxia, in addition to executive dysfunction. Findley et al. (1986) have observed that hypoxemic OSA patients demonstrate inferior neuropsychological performance on measures of attention, memory, and global cognitive functioning compared to apneic patients without hypoxemia. In a comparison between OSA and COPD patients, Olaithe and colleagues (2018) have revealed that both pathologies are associated with deficits in executive function, attention, memory, psychomotor function and language abilities, indicating that hypoxemia may be the foremost determinant of deficits in these domains in apneic patients. A recent study by Johnson and colleagues (2017) has reported that cumulative sleep time percentage with oxygen saturation under 90% (SpO_2<90%; another desaturation measure often used in OSA studies) and ESS (Epworth Sleepiness Scale) score were both associated with reduced attention and memory in apneic patients assessed by the Digit Span Forward Test score. Additionally, it was observed that ApoE e4 carriers presented poorer attention as desaturation increased. Along similar lines, a study with Mild Cognitive Impairment (MCI) and dementia patients has provided further support for the negative consequences of severe ODI and SpO_2<90% on attention and executive functions (Yamout et al., 2012). However, this association was only clear in OSA patients with cardiovascular disease history, indicating that medical comorbidity may serve as a key moderator of this effect. Given the significant impact of cardiovascular disease on the brain, it is important to consider this group of medical conditions when investigating cognitive functioning in apneic patients.

There is also compelling evidence to argue that hypoxemia related to OSA causes brain changes. Nocturnal oxygen desaturation has been linked to whole brain white matter atrophy independent of covariates, particularly in relation to the hippocampus and white matter parietal volume (Zuurbier et al., 2016). Hippocampal atrophy has indeed been associated with inferior memory performance in severe apneic patients in a study conducted by Gale and Hopkins (2004). While the AHI has also been associated with white matter atrophy, Zuurbier et al. (2016) have reported that this relationship disappears when oxygen desaturation is added to the model. Additionally, no relationship between arousals and white matter atrophy was observed by the authors. These findings support the idea that hypoxemia may account for the association between OSA and brain damage (Zuurbier et al., 2016). Grey matter reductions in the anterior cingulate cortex of OSA patients have also been consistently reported in neuroimaging studies (Shi et al., 2017). An atrophy in this structure may partially explain deficits in attention and executive functions in these patients (Carter, Botvinick, & Cohen, 1999). Moreover, based on the finding that grey matter volume in the cingulate cortex is reduced both before and after surgical treatment in apneic individuals, it is possible that these deficits might be irreversible (Shi et al., 2017).

Because only some of these sleep apnea-related cognitive deficits improve with CPAP treatment (Bédard et al., 1993; Henke, Grady & Kuna, 2001) while others do not (Barbé et al., 2001; Bardwell et al., 2001), it has been proposed that chronic intermittent hypoxemia experienced by apneic patients may lead to cerebral vascular deficits, neurodegeneration and cognitive decline (Beebe & Gozal, 2002), which would explain the link between OSA, MCI, AD and vascular dementia (Naegelé et al., 2006). Past studies have demonstrated an association between elevated average desaturation index (≥15 events/hour) and increased risk of developing MCI and dementia (Bédard et al., 1991; Yaffe et al., 2011). It has been suggested that as the disease progresses, and hypoxemia aggravates, structural brain lesions occur. These lesions may account for the greater cognitive changes and the absence of normalization of certain cognitive functions after CPAP treatment (Beebe & Gozal, 2002).

Several studies have nevertheless failed to find a strong and consistent correlation between hypoxemia severity and specific cognitive deficits in apneic patients (Aloia et al., 2004). Severity of oxygen desaturation was only weakly associated with worse cognitive performance on some measures of intelligence, attention, and speed of processing, based on the baseline assessment of the sample from the large scale Apnea Positive Pressure Long-term Efficacy Study (APPLES) (Quan et al., 2011). However, the strength of the correlations may have been underestimated as the sample had high education level and above average intelligence. As

previously mentioned, individuals with higher intelligence levels are deemed more resilient to the negative effects of OSA on cognition (Quan et al., 2011). In an OSA study by Kingshott and co-workers (2000) none of the neuropsychological domains assessed were significantly related to hypoxemia (or other severity measures), apart from attention. It is possible that the inconsistency in oxygen measures may have affected the results since some studies have used nadir oxygen (i.e., lowest level of oxygen) whereas others have utilised the number of desaturations as well as a specific criterion. Although these measures are possibly associated, they correspond to distinct aspects of hypoxemia and could restrict the probability of finding a significant relationship (Aloia et al., 2004). Moreover, it is possible that the effect of hypoxemia may not be significant unless the saturation is below a specific threshold, which suggests that conventional PSG parameters, such as the ODI, may not sensitive enough to predict the negative impact of hypoxemia (Wu et al., 2015).

According to a systematic review by Saunamäki and Jehkonen (2007), studies in the OSA literature may also be affected by the heterogeneity of patient samples, since hypoxemia may affect individuals differently. Hypoxemia with a desaturation of 10% can have a greater impact on older patients with OSA, while hypoxemia with the same desaturation may only have a mild impact on healthy young individuals (Wu et al., 2015). Moreover, Saunamäki and Jehkonen (2007) have shown that factors such as the definitions of the different executive functions used and the low number of executive functions assessed (one or two tests administered per study) may also affect research findings. It is therefore important that the assessments of different domains of executive functions are included in OSA studies.

1.1.3.3 Contributing Factor: Excessive Daytime Sleepiness (EDS)

Great effort has also been devoted to the study of another potential contributor to cognitive deterioration in OSA: excessive daytime sleepiness (EDS). Due to its great impact on patients' daily life, the presence of EDS frequently motivates patients to present for evaluation (Jurádo-Gámez et al., 2015). Daytime sleepiness consists of the main complaint in 31% of apneic adults, second only to stop-breathing incidents at 42% of chief complaints (Rosenthal & Dolan, 2008). The AASM defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentional or at inappropriate times almost daily for at least 3 months (Garbarino et al., 2018). Current research suggests that EDS, possibly caused by recurring sleep arousals associated with obstructive events, might be one of the reversible causative factors for the development and severity of cognitive decline in OSA patients (Roche, 2016).

Much research has been done on the relationship between OSA, EDS and cognitive dysfunction. Findings from the APPLES, a six-month, randomized controlled trial, has shown that patients who displayed improvement in subjective sleepiness performed better in a working memory measure after six months of treatment and those presenting improvement in objective sleepiness exhibited better performance after two months, implying that sleepiness may be linked to a domain of OSA-related neurocognition (Kushida et al., 2012). There are nevertheless inconsistent findings regarding working memory deficits through variable measures which may be attributable to the influence of vigilance and attention impairment in these patients (Zhou et al., 2016). The impact of sleepiness on attention has been well documented in the literature. In a systematic review conducted by Fulda and Schulz (2001), in which the neuropsychological profiles of patients with OSA and narcolepsy were compared, it was found that both groups of patients demonstrated poor performance in attention tasks in one third to half of all comparisons made. Similarly, in 2018, Olaithe and co-workers carried out a meta-review comparing cognitive impairment in sleep deprived and OSA patients which has revealed that both groups of patients show similar patterns of cognitive deficits in attention and memory, suggesting that sleep disturbance in OSA may contribute to deficits in these domains. These findings are supported by the well-known role of sleep in consolidation of memory, learning and brain plasticity (Ellenbogen, Hulbert, Stickgold, Dinges & Thompson-Schill, 2006).

Another topic that has received considerable attention in the literature is the effect of CPAP treatment on daytime sleepiness and neurocognitive performance in apneic patients (Henke et al., 2001; Valencia-Flores, Bliwise, Guilleminault, Cilveti & Clerk, 1996). According to Engleman and Douglas (2004), the therapeutic effect sizes for sleepiness after CPAP are frequently moderate to large. Clinical trials have shown that CPAP treatment may improve sleepiness, attention, memory, and executive functioning, however, deficits in learning and psychomotor ability persevere (Otero et al., 2019). These results suggest a potential relationship between sleepiness and certain cognitive deficits, as well as an association between severity of OSA and improvement on cognition (Otero et al., 2019). Early studies as well as current work have nevertheless found that the decrease in sleepiness and improvement in sleep quality do not actually reflect positive changes in neurocognitive performance (Jurádo-Gámez et al., 2015; Kotterba et al., 1998). It has been suggested that although EDS improves with CPAP, hypoxemia produces long-term effects on cognition that are less likely to improve with CPAP treatment (Zhou et al., 2016).

The association between EDS and hypoxemia has been repeatedly discussed in the literature. Due to its correlation with numerous indices of oxygenation, it has been proposed that EDS is a result of hypoxemia (Garbarino et al., 2018). Animal studies have proposed that increased hypoxemia induces neural damage to brain areas responsible for wakefulness through a combination of oxidative and inflammatory events, which eventually causes neuronal cell loss and the manifestation of sleepiness (Mediano et al., 2007). The biological mechanism connecting sleep-related hypoxemia and EDS in humans is nonetheless unknown. Overall, the question of whether EDS is caused by hypoxemia, sleep fragmentation or it is an independent risk factor for neurocognitive dysfunction in OSA remains unclear.

Previous studies on the major determinant in the pathogenesis of EDS indicate that sleep disruption may be one of the main predictors for EDS (Zhou et al., 2016). Recurrent arousals and subsequent poor sleep quality have often been considered the main factor underlying daytime sleepiness as many parameters indicative of changes of sleep architecture including sleep fragmentation (e.g., sleep efficiency, slow wave sleep/SWS, rapid eye movement sleep/REM, arousal index, sleep latency, etc.) and sleep deprivation (total sleep time) are correlated with EDS in apneic patients (Garbarino et al., 2018). That is, sleep fragmentation contributes to abnormal sleep architecture, less restorative sleep and consequently increased EDS (Otero et al., 2019). Animal and human studies have pointed out that poor sleep leads to amyloid-β (Aβ) formation and aggregation, a key component of AD pathology (Shokri-Kojori et al., 2018). EDS has been associated with a 2.75-fold increased risk of Aβ deposition 15 years later (Spira et al., 2018). Lack of sleep decreases neuronal excitability and myelination, generates oxidative stress, misfolding of cellular proteins, and alter molecular signalling pathways that regulate synaptic strength, plasticity-related gene expression and protein translation (Otero et al., 2019). That is, insufficient or poor-quality sleep is known to affect biochemical and cerebrovascular health, which could be a mediator in the causal pathway between EDS and cognitive decline (Gosselin et al., 2018).

While EDS has been considered a common symptom of OSA, population-based studies indicate that EDS may be absent in many apneic patients (Garbarino et al., 2018). Sforza, Pichot, Martins, Barthélémy and Roche (2015) found that the prevalence of EDS was low in healthy older adults with OSA and it affected only severe cases. Findings from a study by Barbe et al.'s (2001) have shown that even severely affected OSA patients may not have EDS and that these individuals do not exhibit deficits in objective measures of sleepiness (MSLT), cognitive function (vigilance, attention, memory, information processing), or quality of life. Comparative studies analysing the differences in domains of neurocognitive deficits between

apneic patients with and without EDS indicate that non-hypersomnolent OSA patients tend to show less deficits than sleepy patients (Zhou et al., 2016). These studies suggest that EDS may play an independent role in cognitive decline in OSA. Research involving patients with OSA and without EDS remains nonetheless limited. Additionally, contrary to numerous studies that have reported a positive correlation between AHI and both subjective and objective daytime sleepiness (Koehler et al., 2011), many researchers highlight the lack of an independent link between disease severity and EDS (Zhou et al., 2016). Vgontzas and colleagues (2008) have shown that the presence of severe OSA was not often associated with significant EDS, yet, interestingly, patients with lower AHI complained of significant EDS. Studies with clinical and general population samples have also revealed that EDS may persist after considerable reduction in apneas, suggesting that the relationship between OSA severity and subjective sleepiness may be weak and other elements may play a more important role (Garbarino et al., 2018).

On the whole, there has been much debate over the extent to which neuropsychological deficits are attributable solely to the sleepiness that is often associated with this disorder rather than to effects more directly related to negative overnight physiological exposures (e.g., hypoxemia). As previously mentioned, several authors have speculated that there is an interaction between EDS, sleep disruption and hypoxemia in contributing to neuropsychological decline, with hypoxemia playing a direct role in executive dysfunction, and sleepiness contributing more to attention and memory domains (Sforza & Roche, 2012). However, many studies were unsuccessful at finding a correlation between EDS and cognitive dysfunction (Sforza et al., 2010; Sharma et al., 2010). It is possible that these conflicting findings are a result of the insufficiently sensitive or specific tests used to detect any impact of OSA on particular cognitive domains. Some studies have failed to use a validated measure of EDS, such as the ESS or the Multiple Sleep Latency Test (MSLT). Besides, other factors that have not been considered in past studies may play a critical role, such as sex, age, obesity, chronic diseases and depressive symptoms (Zhou et al., 2016). It is possible that the pathogenesis of EDS in OSA patients is multifactorial, hence these factors should be taken into account to better understand the contribution of EDS on cognitive decline. In any case, the question of whether daytime sleepiness have a significant impact on cognition and if so, which specific cognitive domains are involved remains unknown.

1.2 Current Study

Much research on the impact of OSA on cognition has been done. There is nevertheless no consensus on how OSA may affect specific neuropsychological functions and the factors that may contribute for this damage. One of the aims of this study was to investigate whether neuropsychological performance varies across patients with different OSA severity as well as from normative data. Since the association between OSA and cognitive dysfunction is complicated by numerous comorbidities, including obesity, hypertension, diabetes and depressive symptoms, this study also included a comparative group similar to the OSA group on these conditions as well as on EDS, but with no OSA diagnosis; so that these variables did not influence the investigation of the effects of OSA on cognition. While normative comparison is useful for establishing the clinical significance of findings, the recruitment of a representative comparison group is useful for controlling demographic and clinical factors.

Whether the mean number of apneic events (AHI, related to both arousal and hypoxemia), the length of time patients remain hypoxemic during sleep or daytime sleepiness can predict particular neuropsychological deficits in these patients is still unclear. Studies have revealed that some patients may have mild AHI, but spend a considerable amount of time with SpO_2<90% throughout the night, whereas others may present high ODI but spend a small percentage of time with SpO_2<90% (Temirbekov, Güneş, Yazıcı & Sayın, 2018). It is therefore important to consider all different sleep/breathing parameters when analysing the impact of OSA on cognition. Moreover, while typical used sleep measures, such as AHI and ODI, were designed to measure the incidence of respiratory episodes, detailed information on the severity of hypoxemia is nevertheless not available. Thus, the current study also included time spent with oxygen saturation under 90% (SpO_2<90%) as a more comprehensive measure of hypoxemia. Moreover, while some studies have attempted to investigate the role of PSG parameters as the mediating factors of the relationship between OSA and cognitive dysfunction, several methodological issues have been observed, such as the lack of a cognitive reserve measure or not controlling the effect of information processing speed/attention capacity.

The purpose of this study was also to investigate whether severity of EDS is associated with different neuropsychological and physiopathologic (i.e., hypoxemia) outcomes in OSA patients.

The following questions were explored (Fig. 1):

1. Do OSA patients exhibit neuropsychological impairment (compared to normative data)?

2. Are there differences in neuropsychological performance between OSA patients with different disease severity (mild, moderate and severe AHI)?

3.Can EDS or hypoxemia indexes (ODI, SpO_2<90%) predict neuropsychological deficits?

4. Do AHI, ODI, SpO_2<90% and EDS significantly correlate?

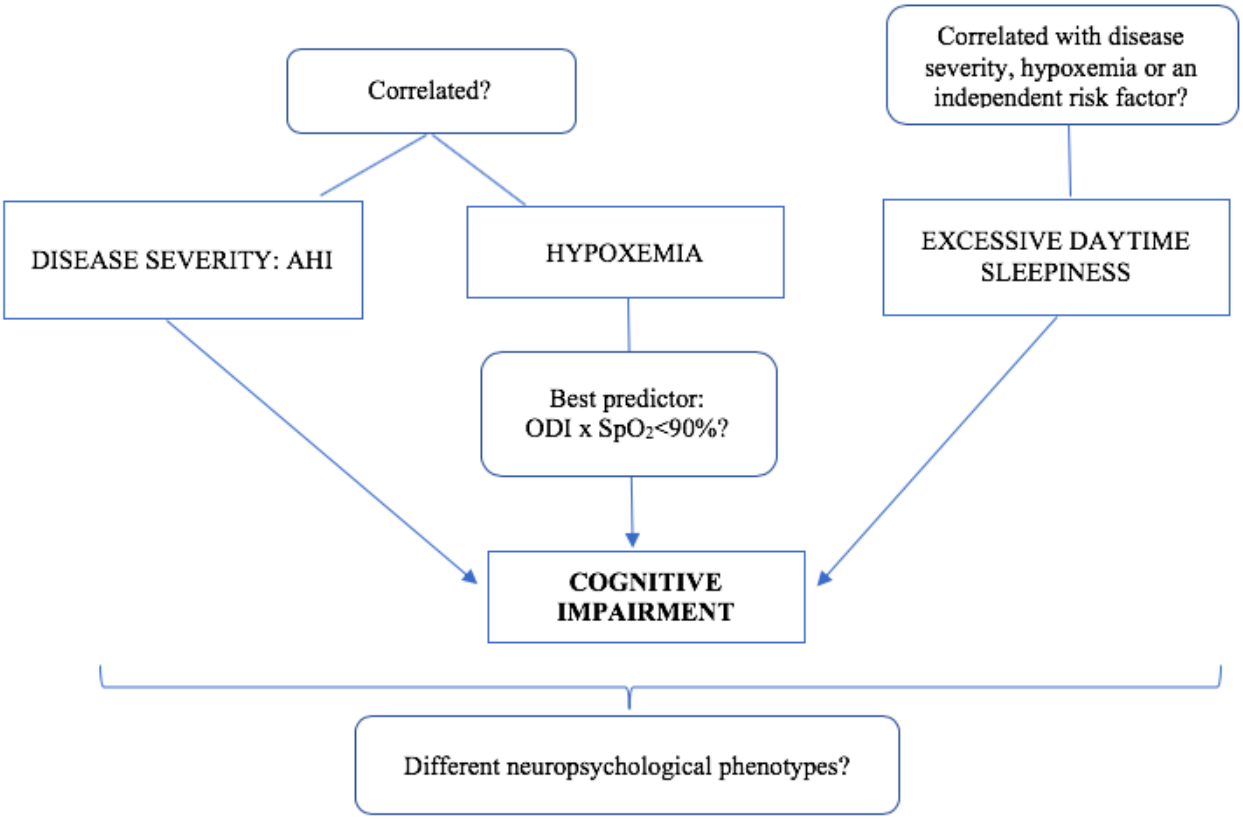

Figure 1. Potential relationships between Apnea-Hypopnea Index, Hypoxemia, Excessive Daytime Sleepiness and Cognitive Impairment.

It is important to characterize what type of deficits OSA patients present in order to identify who requires treatment, who can function better by learning specific compensatory strategies, and under which conditions individuals should be regarded as limited or disabled. Seeing that patients often refuse treatment or have problems with treatment adherence, describing the impact of OSA on cognition and its potential causes is of great importance for treatment adherence and rehabilitation of these patients as well as for the diagnosis of potential neurodegenerative diseases. Besides, learning if the cause of the observed cognitive impairment in apneic patients is reversible is extremely important given that OSA can mimic or exacerbate symptoms of dementia in the elderly. This data may also be relevant for the routine assessment and subsequent treatment of OSA in dementia clinics.

Chapter 2. Methodology

2.1 Design

A one-way multivariate analysis of covariance (MANCOVA) was used to determine whether there were differences in neuropsychological performances (scores: dependent variables) between patients with different OSA severity (groups: independent variable), while controlling for several covariates, namely: hypertension, diabetes, CRIq, BDI and ISI scores. Descriptive analyses were performed to investigate potential decline in standardized neuropsychological scores of OSA patients. Hierarchical linear regression analysis was used to identify independent sleep/breathing variables predicting change in neuropsychological functions in apneic patients. That is, multiple regressions were carried out to understand which among the independent variables (AHI, ODI, SpO_2<90% and ESS) could have been related to the neuropsychological deficits observed.

Another MANCOVA was used to analyse whether there were differences in neuropsychological performance between apneic patients with different EDS severity, while controlling for the same covariates stated above. Pearson correlation coefficient tests were performed to test for associations among OSA parameters, i.e., AHI, ODI, SpO_2<90%, EDS, (only OSA patient groups included).

Comparisons of clinical and demographic data between the four groups (mild, moderate, severe OSA, and controls) were performed using a between-subjects ANOVA, while non-continuous data comparisons between groups (gender, BDI, hypertension, diabetes and AD family history) were analysed using chi-quare test. All neuropsychological test scores were converted into z-scores in order to improve score comparison (apart from D2 scores which were kept as percentiles). The significance threshold was set at $p<.05$. All statistical analyses were done using IBM SPSS Statistics version 24.

Characterising hypoxemia, sleep fragmentation and EDS:

The degree of hypoxemia was operationalised in two ways: (i) the average number of desaturation events per hour of sleep (ODI) and (ii) time spent at a SpO_2 below 90%. (SpO_2<90%) (both desaturation indexes were explored as continuous measures). The degree of disease severity/sleep fragmentation was represented by the apnea-hypopnea index (AHI) and excessive daytime sleepiness (EDS) was characterized by ESS scores.

2.2 Participants

Recruitment and Screening

A total of 54 participants were initially recruited. One participant had to be excluded from the study because of missing neurophysiological data. Thus, 53 participants were included (30 men, 23 women), aged 57.7 ± 10.9 years (range: 39–78 years), of whom 38 were newly diagnosed, untreated OSA patients and 15 were controls.

To avoid research bias, this study was conducted in a double-blind fashion, in which neither the patients nor the researcher knew which study group the patients were in. Participants were recruited from a group of patients referred for an evaluation of clinically suspected OSA, who were referred because of loud snoring, EDS or because of apneas reported by the spouse. Participants were either recruited on the day they came to the hospital to pick up the portable monitor or they were selected from a list of patients from the hospital's system who had recently undergone ambulatory PSG. None had received such a diagnosis nor had undergone CPAP treatment before. All participants underwent an overnight sleep evaluation using level 3 portable monitors, including controls, so that the absence of (sub)clinical SDB could be established. The sample consisted of four groups: Group 1 consisted of 14 patients with mild OSA (AHI 5<15), Group 2 was composed by 10 patients with clinically diagnosed moderate OSA (AHI 15<30); Group 3 was comprised by 14 patients who presented severe OSA (AHI >30) and Group 4 consisted of 15 age and education-matched controls (AHI<5) (Table 1). In addition, patients were subsequently stratified according to their sleepiness symptoms: mild EDS (<10), moderate EDS (≥10-15) and severe EDS (16-24) (Johns, 1991) (Table 2).

Patients underwent extensive neuropsychological evaluation before starting treatment for OSA. All participants were screened during an initial interview to rule out the presence of underlying conditions that could affect cognitive performance. Informed consent was obtained before screening. No monetary compensation was given to the subjects for participating in the study, yet participants were offered a report with the results of the neuropsychological assessment to acknowledge the time and effort they have provided in participating in the research. The study was approved by the Hospital Particular do Algarve Ethics Committee (Appendix A).

Table 1. Sample division according to AHI severity

Apnea-Hypopnea Index (AHI) groups	
Group 1	Mild OSA (AHI: 5<15)
Group 2	Moderate OSA (AHI: 15<30)
Group 3	Severe OSA (AHI: >30)
Group 4	Control (AHI<5)

Note: AHI - number of apneas/hypopneas per hour.

Table 2. Sample division according to EDS severity (only OSA patients)

Excessive Daytime Sleepiness (EDS) groups
Mild EDS (ESS: <10)
Moderate EDS (ESS: ≥10–15)
Severe EDS (ESS: 16-24)

Note: EDS based on Epworth Sleepiness Scale (ESS) scores.

Exclusion Criteria:

The following exclusion criteria was applied:

i. The presence of dementia, alcohol dependence or other substance abuse;
ii. History of cerebrovascular disease or current psychiatric disorder;
iii. Current use of hypnotics or central nervous system active drugs affecting cognitive function, or present illnesses including endocrine disease (e.g., hyperthyroidism), infectious disease (e.g., HIV), chronic renal failure (CRF), chronic obstructive pulmonary disease, cancer, uncontrolled diabetes, and uncontrolled hypertension;
iv. The presence of central sleep apnea or restless legs syndrome;
v. Significant impairment of hearing ability, visual acuity, or language ability, which hampered the completion of neuropsychological tests.

Inclusion Criteria:

i. Patients referred for an evaluation of clinically suspected OSA, who were referred because of loud snoring, excessive daytime sleepiness or because of apneas reported by the spouse.
ii. Only native Portuguese adults aged 35 years and above were included in the current study. This study focused on mid-life and older adults since cognitive decline in sleep apnea is age dependent; that is, older patients are usually more affected than younger patients with the same disease severity. This is explained by the greater brain plasticity presented by younger patients, who are more able to compensate for the cognitive losses of hypoxemia

and sleep fragmentation (Jurádo-Gámez et al., 2015). Moreover, older patients are likely to have been experiencing hypoxemic brain insults longer than younger patients and therefore are more likely to present severer cognitive impairment (Greenberg et al., 1987).

iii. No previous OSA diagnosis or CPAP treatment before.

iv. Only adults with an AHI/ODI below five were included in the control group.

2.3 Materials

2.3.1 Self-report Measures.

Participants answered a brief interview on medical and sociodemographic characteristics, which included questions about participants' age, educational level, medical history, amongst other relevant information (See Appendix B). Family history of dementia was also recorded as it is a well-known risk factor for the development of MCI and sporadic AD (Ten Kate et al., 2016). Moreover, since depression is often associated with OSA and it has a negative impact on cognition, a quantitative measure of depressive symptoms was included in the study (Shi et al., 2017).

The following self-report questionnaires were also used:

- **Beck Depression Inventory-II (BDI-II)** assesses the severity of depressive symptoms. It consists of 21 sets of statements, which express feelings common in depression (e.g., punishment, guilt, suicidal ideas) (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). Individual scale items are scored on a 4-point continuum (0=least, 3=most), with a total summed score range of 0–63. Suggested score ranges for mild depression, moderate depression, and severe depression are 11–20, 21–30, and 31 or higher, respectively. Estimates of internal consistency for this self-report have been acceptable (α=0.82–0.9) in both normal and depressed older adults (Gallagher, 1986; Kim, Pilkonis, Frank, Thase, & Reynolds, 2002).
- **Epworth Sleepiness Scales (ESS)**, the well-validated and most widely used clinical tool to evaluate subjective sleepiness, is a questionnaire in which the individual is asked to rate his or her probability of falling asleep in eight situations (Johns, 1991; Santos, 2001). Scores range from 0 to 24, a score of ≥ 10 reflects daytime sleepiness. The questionnaire presents high level of internal consistency (α=0.88) in OSA patients (Johns, 1992). The use of the ESS to assist in the diagnosis and treatment of sleep apnea is recommended by the *Direção-Geral da Saúde* (2016).

- The **Cognitive Reserve Index Questionnaire (CRIq)** is a measure of cognitive reserve, that is, a person's capacity to cope with or compensate for pathologies (Nucci, Mapelli, & Mondini, 2012). The CRIq consists of questions related to three different domains of a person's entire adult life: education, working activity and leisure time. A score for each domain is calculated as well as a final index score. The assessment of cognitive reserve is central in studies of cognitive impairment as a greater cognitive reserve is considered as a protective factor to cognitive decline, whereas a lower one implies vulnerability (Alchanatis et al., 2005).
- **Insomnia Severity Index (ISI)** is a 7-item scale which was designed to be a brief screening measure of insomnia (Clemente et al., 2017; Morin, 1993). The items include: the severity of sleep onset and maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, appearance of impairment attributed to the sleep problem, and the degree of concern caused by insomnia (Smith & Wegener, 2003). The cut-off point was 14. Good internal consistency has been reported by the authors (α=.88) (Clemente et al., 2017).

2.3.2 Sleep and Breathing Assessment

Due to time constrains and so that as much data as possible was collected, two portable respiratory sleep monitors were used. Nox T3TM and Somnocheck (SC) were used to diagnose OSA and to evaluate sleep-breathing parameters. The NOX T3 is an FDA-approved type 3 portable monitor, which weights 65 g and present dimensions of 79 (W)×63 (H)×21(D) mm. The device records the following signals: airflow via cannula and pressure transducer, thoracic and abdominal respiratory effort via inductance plethysmography, oxygen saturation by wireless pulse oximetry, body position via actigraphy, heart rate and audio (Cairns, Wickwire, Schaefer & Nyanjom, 2014). This portable monitor has been demonstrated to have a high level of sensitivity (92%; 93%) and specificity (85%) for the presence of OSA compared to in-lab PSG, when using an AHI≥15 (Cairns et al., 2014; Xu et al, 2017, respectively).

The SC system (Weinmann) comprises a basic unit measuring approximately 65 (W)×130 (H)× 30 (D) mm and weighing 240 g. It is a type 3 monitor with position sensor, pressure transducer, and pulse oximeter, which records oxygen saturation and heart rate. A combined airflow/snoring sensor is applied to the upper lip of the patient. This sensor picks up the airflow as a summed signal derived from three thermistors, and also picks up the sounds of snoring via an integrated microphone. (Ficker, Wiest, Wilpert, Fuchs, & Hahn, 2001). AHI

provided by the SC system has been shown to correlate closely with that obtained by PSG (r = 0.98); additionally, it has a high level of sensitivity (97%) and specificity (100%) when an AHI≥10 is defined as indicative of OSA and data is analysed manually (Ficker et al., 2001).

Respiratory events were based on airflow, abdominal respiratory effort and oxygen saturation. The number of inspiratory flow-limitation episodes, obstructive apneas, and hypopneas per hour of sleep was calculated to obtain an AHI (number of events per hour of sleep). Severity of oxygen desaturation was assessed by oxygen desaturation index (ODI), which is the average number of desaturation events per hour of sleep and by time spent at a SaO_2 below 90% during the recording. Overnight oximetry was considered normal when mean nocturnal SaO_2 was above 93% and no SaO_2 dip greater than 3% (Naegelé et al., 2006). Patients with an ODI<5 were graded as having no oxygen disturbance (Temirbekov et al., 2018). All sleep parameters were reviewed and interpreted by a qualified physician, as defined in the AASM Accreditation Standards (AASM, 2005).

2.3.3 Neuropsychological Assessment

The choice of neuropsychological tests administered were based on the cognitive functions most affected by OSA according to the literature. The following well-validated neuropsychological tests were administered in the same order to all subjects by the same examiner:

a) General intellectual functioning: The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008) is used to assess several cognitive domains, namely: visuospatial/constructive skills, verbal memory, attention, language, executive functions and orientation (to time and place). This instrument was specifically developed for the detection of mild cognitive impairment (i.e. mild neurocognitive disorder). MoCA was also used to exclude the presence of dementia (two or more standard deviations below the mean). The score is obtained by an item total.

b) Attention:

Selective and Sustained Attention/Vigilance: The **D2 Test of Attention** is a paper-and-pencil measure of concentration, sustained and selective attention (Ferreira & Rocha, 2006). The subject has to identify relevant targets (229) while ignoring irrelevant distractors (429), including orthographically similar stimuli. The subject is asked to scan each row for 20 seconds and cross out all relevant stimuli as fast and as accurate as possible before he or she is asked to

move to the next row. Total test duration is between 8 and 10 minutes. In this study, selective and sustained attention performance were indicated by the Concentration Performance index (CP), which is based on total number of correctly cancelled targets minus the total number of incorrectly cancelled characters. This score was chosen because it cannot be inflated if the respondent skips over many items (Bates & Lemay, 2004).

c) Visuoconstructive/Visuoperceptive Abilities: The **Rey-Osterrieth Complex Figure Test** (RCF) is one of the most widely used instruments to evaluate visual-constructional ability, but it also assesses organizational skills and planning (Rey, 2002). The RCF task involves viewing a complex figure and copying it. Scores were calculated according to the Osterrieth scoring system, which involves splitting the figure in to eighteen identifiable areas, each of which is considered separately and marked on the accuracy of its position and the distortion exhibited (Lezak, Howieson, Bigler & Tranel, 2012).

d) Memory:

- The **Auditory Verbal Learning Test** (AVLT; Cavaco, 2015) assesses verbal learning and memory. The AVLT is a five-trial learning procedure for a list of 15 words. The list is read before each recall trial; words can be recalled in any order. Delayed recalled is tested 25-30 minutes after the trials. This task is followed by a 30-word recognition trial.
- The **Logical Memory Test** (Wechsler Memory Scale – WMS-III, Wechsler, 1997; Machado, Rocha, Barreto, Moreira & Castro, 2008), a measure of prose recall, consists of two short stories that are read to the subject. After the first story is read, the subject is asked to immediately recall as much information as he or she can about it and do the same for the second story. The second story is read twice to evaluate verbal learning ability. Delayed recall is tested 30 minutes later.
- The **RCF recall** is a measure of visuospatial memory. Twenty minutes after the presentation of the RCF, participants are asked to reproduce the drawing from memory.
- The **Digit Span Test (DST) Forward** (Weschler Adult Intelligence Scale – WAIS-III, Wechsler, 1997; Rocha, Ferreira, Barrete, Moreira & Machado, 2008) assesses verbal short-term memory. In this test, the examiner recites a sequence of digits that the subject has to repeat in the correct order. The first set of digits contains two digits and the set size increases by one number every two trials. The test is interrupted when the participant makes two consecutive errors at a particular set size. Span is calculated by the sum of the digits successfully remembered.

e) Executive Functions:

- The **Digit Span Test (DST) Backward** (WAIS-III) same instructions and rules for the DST Forward apply for the DST Backward, however, in this test the sequence of digits has to be recalled in the reverse order. This test evaluates verbal working memory.

- The **Trail Making Test A and B** (Cavaco et al., 2013) evaluates attention and psychomotor speed/visual-scanning (TMT-A), as well as cognitive flexibility (TMT-B). TMT-A involves connecting 25 numbers randomly located in ascending order as fast as possible, without lifting the pen from the paper. Whereas TMT-B consists of connecting alternately numbers and letters in ascending order. Scores are based on task completion time.

- The **Stroop Test** (Golden, 1978; Fernandes, 2013) assesses selective attention and ability to inhibit a response. This test consists of three tasks, each lasting 45 seconds. First, the participant is required to read colour names written in black; second, the participant is asked to name the ink colour of letters "XXXX"; and last, the participant is presented with a card displaying colour names printed in incongruent inks. The participant has to ignore the meaning of the word and to name the ink colour as fast and as accurate as possible. Only the interference score was used, which is based on the correct number of words read in all three tasks.

- The **Fluency Tasks** (Cavaco et al., 2013) evaluates lexical access speed and ability to think flexibly. In the **Phonemic Fluency Task** (PFT) subjects are instructed to generate verbally as many words as possible beginning with the letter P, M, and R in a 1-minute period for each letter. Similarly, for the **Semantic Fluency Task** (SFT) respondents are instructed to name as many animals as possible in one minute. Scores are calculated separately (i.e. total number of words for phonemic fluency and semantic fluency), according to age, sex and educational level. SFT measures conceptual semantic knowledge, while the PFT is more sensible to planning abilities that rely on the activity of cortical and subcortical frontal areas, thereby assisting in the detection of deficits of frontal type.

- The **Similarities Subtest** (WAIS-III) is a measure of abstractive reasoning ability. This test requires participants to explain in what way two concepts are similar (e.g. orange-banana). Nineteen pairs of words are presented to the subject, difficulty ranges progressively from

simple to complex concept formation. A score of two points is assigned for an abstract generalization, and one point if the answer is a specific concrete similarity.

- The **Matrix Subtest** (WAIS-III) explores the ability to conceptualize spatial, design and numerical relationships from a series of visual analogy problems pictured in non-representative designs. Levels of difficulty range from simple to increasingly complex.

Normative data for the Portuguese population based on age, education and/or gender (depending on the instrument and the influence of each factor on the performances) was used in the interpretation of raw scores for each test. Normative data for the Trail Making Test, AVLT and Fluency Tasks was obtained from the NeuroPsi website (*http://neuropsi.up.pt*). All neuropsychological test scores were converted into z-scores, apart from D2 scores which were kept as percentiles.

2.4 Procedure

Participants were invited to participate in the study either face to face (following a neurophysiology consultation) or via telephone (patients who had recently undergone home-based PSG). In the consulting room, participants received both verbal and written information (Appendix C) containing details about the study and signed the hospital's consent form (Appendix D). Since the study may have involved minimal risks (participants could have experienced discomfort/tiredness when performing the neuropsychological tests), it was emphasised that they were free to withdraw from the study at any stage. They were then asked to answer a short interview regarding demographic (age, educational level, etc.) and clinical information (comorbid diseases, habitual medication, etc.) to investigate whether they met the criteria to participate in the study (see Recruitment and Screening section for full list of inclusion and exclusion criteria) and for data collection purpose. Those eligible to participate were then asked to fill out two brief self-reports with regard to daytime sleepiness and sleep quality/insomnia (ESS and ISI, respectively).

After that, a brief general intellectual functioning test (MoCA) was administered, followed by a visuoconstructive measure (RCF copy) and a range of memory tests (Digit Span, AVLT, Logic Memory and RCF recall). Subsequently, participants performed different tasks assessing attention (D2) and several executive functions (TMT, Stroop, Fluency, Similarities and Matrices). They were then asked to complete a questionnaire assessing depressive symptoms

(Beck Depression Inventory). Lastly, participants answered a semi-structure interview regarding their cognitive reserve (CRiQ). This process took around 60 to 85 minutes. Following the administration of the tests, participants were asked to provide their email so that they could receive a short report with the results of the neuropsychological evaluation. The session took place in a quiet consulting room at the Hospital Particular do Algarve. Before the end of the consultation, any remaining questions were clarified.

The researcher was not aware of the participants' diagnoses at the time of the neuropsychological evaluation. After the evaluation, when the researcher received the neurophysiological reports, each participant was assigned to one of the groups (mild, moderate, severe OSA or comparative). Participants with AHI/ODI under five, i.e., did not meet the criteria for OSA according to the American Academy of Sleep Medicine (2005), were allocated to the comparative group. Data collection took place from July to December 2019.

2.5 Consent and Participant Information Arrangements

Participants were informed that any information provided by them would be kept in strict confidentiality. Participants were also made aware that all the data would be anonymized and that they could stop the evaluation at any point and their data would not be used. At the end of the neuropsychological assessment, participants were asked if they had any questions. They were reminded that they could contact the researcher should they have any problems.

Chapter 3. Results

3.1 Demographic and clinical variables

Descriptive data showed no significant age differences between OSA and control groups. Furthermore, groups did not differ on level of education, cognitive reserve index, insomnia index, body mass index, hypertension, diabetes and AD family history. Moderate OSA patients and controls were classified as being overweight whereas mild and severe OSA patients were characterized as obese. Participants CR scores were mostly in the average range. None of the groups met the condition for insomnia (cut-off point of 14), yet, severe OSA patients exhibited the highest insomnia scores. There was a significant difference in the number of males and females between groups, most OSA patients were men whereas the majority of participants in the control group were women. While there were no significant differences between all groups in depressive symptoms, measure of depression was generally high in the severe OSA group, wherein almost one third (four out of 14) of the patients exhibited moderate depressive symptoms. Demographic and clinical variables are presented in Table 3.

3.2 Relationship between OSA Factors

Pearson correlation was run to determine the relationship between different OSA factors (AHI, ODI, SpO_2<90% and EDS) (See Fig. 2). The tests showed that there was a strong, positive correlation between AHI and ODI, which was statistically significant ($r = .90$, $p<.001$). That is, the sum of the number of breathing pauses was highly associated with the average number of desaturation episodes per hour. On the other hand, the length of time spent with saturation below 90% (SpO_2<90%) was moderately, but significantly positively correlated with AHI ($r= .45$, $p= .007$).

The analysis of the two desaturation measures has shown that SpO_2<90% was moderately positively correlated with ODI ($r= .55$, $p= .001$). No significant correlations were found between EDS and OSA factors, apart from a weak to moderate, negative correlation with SpO_2<90% ($r = -.40$, $p=.013$), indicating that patients who remain hypoxemic for prolonged periods of time during sleep tend to present less EDS than less affected patients. Overall, all three OSA groups exhibited moderate EDS symptoms, yet mild OSA patients had the highest EDS scores. Controls exhibited mild to moderate EDS symptoms. For descriptive data of patients' sleep-breathing parameters see Table 4.

Table 3. *Participants' clinical and demographic characteristics.*

	Mild OSA n = 13		Moderate OSA n = 10		Severe OSA n = 14		Controls n = 15			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Age	60.92	10.98	60.00	9.86	54.57	11.42	55.73	11.27	1.05	.378
Years of Education	11.46	4.15	10.50	5.42	12.00	4.33	10.87	4.03	.28	.842
Body Mass Index	30.86	6.99	28.98	2.63	32.69	3.97	28.42	5.62	1.91	.141
CRIq	104.8	9.10	104.3	15.72	103.3	12.46	101.9	10.47	.15	.927
ISI	7.54	4.23	7.50	6.57	10.57	5.90	8.60	6.11	.82	.489
	N		N		N		N		χ^2	*p*
Gender										
Male	9		8		10		3		12.56	.006
Female	5		2		4		12			
BDI										
Normal (0-10)	6		6		6		6		12.05	.160
Mild (11-20)	5		4		4		9			
Moderate (21-30)	1		0		4		0			
Severe (>31)	1		0		0		0			
Hypertension										
Yes	6		7		9		9		2.87	.412
No	8		3		5		6			
Diabetes Mellitus										
Yes	2		0		2		3		2.15	.541
No	12		10		12		12			
AD Family History										
Yes	5		1		4		5		1.89	.596
No	9		9		10		10			

Note: CRIq: Cognitive Reserve Index questionnaire. ISI: Insomnia Severity Index. BDI: Beck Depression Inventory. AD: Alzheimer's Disease.

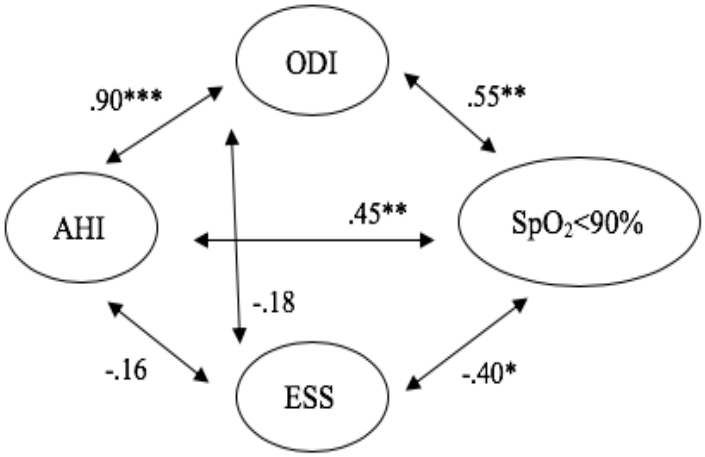

Figure 2. Correlation coefficients values between OSA factors.
Note: * *p*< .05, ** *p*< .01, ***p* <.001. ESS: Epworth Sleepiness Scale.

Table 4. *Comparison of participants' sleep-breathing data using one-way analysis of variance (ANOVA).*

	Mild OSA		Moderate OSA		Severe OSA		Controls		
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
AHI	9.08	2.41	21.43	5.17	45.69	13.73	.	.	<.001
ODI	9.89	2.60	20.88	15.34	44.69	16.39	.	.	<.001
SpO2<90%	3.57	4.52	10.23	10.24	17.89	16.01	.	.	<.001
EDS	13.93	6.07	10.60	3.98	11.21	6.51	9.87	5.29	.262

Note: Oxygen Desaturation Index (ODI) and Apnea-Hypopnea Index (AHI): Mild 5<15, Moderate 15<30, Severe ≥30; SpO2<90%: percentage of sleep time with saturation lower than. 90%; Excessive Daytime Sleepiness (EDS): Mild <10, Moderate ≥10–15, Severe 16-24.

3.3 Neuropsychological Outcome

The neuropsychological characteristics (all measures converted into z-scores, apart from D2 scores) of groups are given in Table 5. Z-scores below 1.0, 1.5 and 2 SD were interpreted as mild, moderate and severe impairment respectively. Deficits of Z-scores of 1.0 to 1.5 have been used in the diagnosis of MCI (Albert et al., 2011). Based on normative data for the Portuguese population, mean neuropsychological scores of patients with mild and

moderate OSA did not indicate impairment. However, controls and severely affected OSA patients were moderately and mildly impaired in a global cognitive measure (MoCA), respectively (z=-1.45 and z= -1.19).

In general, average z-scores for the entire OSA cohort fell within normal range in most neuropsychological tests (Appendix E). However, descriptive analysis has revealed moderate to severe impairment on the D2 performance (10_{th}-1_{st} percentile) in 18.9% of the total OSA sample. Further analysis has shown that 23.7% of the entire OSA cohort were categorized as mildly impaired on the AVLT immediate recall (-1SD), whereas 15.8% were considered moderately to severely impaired (-1.5 to -2SD). In addition, 15.8% of the OSA sample was defined as mildly impaired on the AVLT delayed free recall and 39.5% was categorized as moderately to severely impaired. With regard to visual memory (RCF recall), 18.4% of the sample presented mild to moderate impairment (-1 to -1.5 SD). Results related to executive functions revealed that 15.8% of the total OSA sample exhibited mild impairment on the TMT-B and an accumulative percentage of 15.8 presented moderate to severe impairment on this test. No significant differences in z-scores were found between the entire OSA cohort and the control group (p>.05).

3.3.1 Prediction of Neuropsychological Deficits by OSA factors

Step hierarchical regressions were conducted to determine the proportion of the overall variance in general cognitive ability (MoCA), sustained attention (D2), verbal and visual memory (AVLT and RCF recall), and cognitive flexibility (TMT-B) performances explained by a model composed by hypertension, diabetes, BDI scores and specific OSA factors (ODI, SPO_2<90% and ESS). This was done to determine whether particular OSA factors contributed incrementally to the prediction of the neuropsychological deficits above and beyond that accounted for by clinical variables.

Neuropsychological scores were explored as continuous measures (dependent variable) and OSA factors as nominal measures (independent variable), simultaneously controlling for the clinical variables mentioned. However, due to the high correlation between AHI and ODI (see page 43 for values of correlation coefficient), the AHI was excluded from the model. This variable was chosen to be removed since the influence of this factor was already analysed separately (see Section 3.4).

Although other clinical variables could also have affected neuropsychological performance, such as cognitive reserve (CRIq), insomnia (ISI) and body mass index (BMI), they were not added to the models as this could have resulted in overfitting. Alternatively, the

impact of scale variables was analysed with Pearson correlations. Results have shown no significant correlations between CRIq, ISI, BMI and the neuropsychological scores analysed (see Appendix F for *r* and *p* values).

The first multiple regression investigated the predictive effects of ODI (IV) on MoCA scores (DV). Clinical variables were entered at Step 1 (Model 1) and ODI was added at Step 2 (Model 2). Results found a non-significant model, $F(4,33) = .69$, $p = .607$, $R_2 = .00$. Data reveals that ODI did not significantly predict MoCA performance ($p > .05$).

The second multiple regression explored the predictive effects of SpO_2<90% (IV) on MoCA scores (DV). Clinical variables were entered at Step 1 (Model 1) and SpO_2<90% was added at Step 2 (Model 2). These variables did not statistically significantly predict MoCA performance, $F(4,32) = .89$, $p = .479$, $R_2 = .10$. The analysis shows that SpO_2<90% did not significantly contribute to the prediction of MoCA performance ($p > .05$).

A third multiple regression analysed the predictive effects of EDS (IV) on MoCA scores (DV). Clinical variables were entered at Step 1 (Model 1) and EDS was added at Step 2 (Model 2). Results indicated a non-significant regression model $F(4,33) = 1.20$, $p = .327$, $R_2 = .13$. EDS did not significantly predict MoCA scores ($p > .05$). See Appendix G for all beta values.

This process was repeated for each independent variable mentioned above (D2, AVLT immediate and delayed recall, RCF recall and TMT-B scores). Results have nevertheless revealed no significant contributions by desaturation indexes nor EDS to these neuropsychological performances when clinical factors were controlled ($p > .05$). See Appendices H-L for all F, R_2 change, and beta values.

3.4 Neuropsychological Performance According to Disease Severity (AHI)

A one-way Multivariate Analysis of Covariance (MANCOVA) indicated that there were no statistically significant differences in the performance of neuropsychological tests between OSA groups after controlling for hypertension, diabetes, CRIQ, BDI and ISI scores ($p > .05$), except in the Digit Span Backward performance, $F(2, 28) = 4.76$, $p = .017$, $\eta p_2 = .254$) (Table 5). To adjust for the potential impact of slowed information processing on patients' Digit Span Backward performances, Digit Span Forward scores were controlled using a one-way Univariate Analysis of Covariance (ANCOVA). Results revealed that differences in estimated means between mild and moderate OSA groups in the Digit Span Backward performance have disappeared ($p > .05$) after controlling for Digit Span Forward scores

(information processing) (Table 6). No further significant differences in other neuropsychological scores were found between groups (see Table 5).

Table 5. *Comparison between neuropsychological test means according to OSA severity using multivariate analysis of covariance (MANCOVA).*

Measure	Mild OSA		Moderate OSA		Severe OSA		Controls			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
MoCA	-.99	1.25	-.76	1.84	-1.19	1.09	-1.45	1.24	.54	.656
D2[a]	42.29	34.30	55.80	39.67	53.85	29.45	46.67	29.31	.24	.786
RCF Copy	.12	1.60	.31	.72	.67	.33	.54	.46	1.55	.229
AVLT Immediate	-.52	.82	-.37	.85	-.43	.98	-.44	.87	.06	.945
AVLT Delayed	-.88	1.04	-.96	1.27	-.66	.75	-.80	.70	.32	.731
AVLT Recognition	1.05	2.01	.67	2.16	1.92	1.46	1.62	1.83	1.01	.356
Digit Span Forward	.11	.70	-.16	.68	.15	.57	-.17	.69	.60	.555
RCF Recall	-.21	.86	-.41	.75	-.22	.47	-.44	.77	.05	.953
LM Immediate	-.19	72	-.37	.55	-.26	.58	-.42	.34	.05	.950
LM Delayed	-.31	.62	-.33	.52	-.26	.85	-.35	.68	.05	.756
Digit Span Backward	.38	.68	-.19	.39	.22	.43	-.22	.45	4.76	.017
TMT-A	.09	1.00	.20	1.21	.13	.74	-.13	.73	.46	.64
TMT-B	-.12	1.30	-.40	1.10	.20	1.02	-.15	.59	1.08	.355
Stroop	-.28	.42	.40	.65	-.07	.65	-.27	.75	1.56	.227
Phonemic Fluency	.07	.93	.33	.52	-.16	.97	-.55	.96	.51	.606
Semantic Fluency	-.21	1.06	-.13	.77	-.05	.76	-.02	1.00	.47	.628
Similarities	.81	.58	.67	.65	.41	.95	.35	.53	.85	.436
Matrices	.33	.90	.23	.80	.61	.74	.11	.87	.39	.678

Note: Mean of *z* scores. [a] Percentile. RCF: Rey Complex Figure. AVLT: Auditory Verbal Learning Test- immediate recall, delayed free recall (30 mins.) and recognition scores. LM: Logic Memory. TMT: Trail Making Test.

Table 6. *Estimated Means and Confidence Intervals for Digit Span Backward Performance after controlling for Digit Span Forward Scores*.

			95% Confidence Interval	
Group (AHI)	Mean	SE	Lower Bound	Upper Bound
Mild	.37	.13	10%	64%
Moderate	-.12	.16	-45%	20%
Severe	.16	.13	-12%	43%

Note: Dependent Variable: Digit Span Backward**.** Covariate Variable: Digit Span Forward. SE: Standard Error.

3.5 Neuropsychological Outcome According to EDS Severity

One-way MANCOVA was carried out to determine whether EDS was an independent risk factor for neurocognitive impairment in OSA patients, after controlling for hypertension, diabetes and BDI scores. It was important to control for depressive symptoms (BDI scores) since a prior analysis has revealed that EDS scores significantly positively correlated with BDI scores (r= .32, p = .020), yet, only weakly. Patients were categorized according to EDS severity: Mild EDS (<10), Moderate EDS (10-15) and Severe EDS (16-24) (Johns, 1991). EDS severity was explored as the independent variable, whereas all neuropsychological scores were considered the dependent variables.

First, to investigate whether EDS was an independent risk factor (regardless of OSA) all participants were included in the analysis (OSA patients and controls). A MANCOVA has shown that EDS did not have a significant effect on neuropsychological performance across the whole sample (p > .05) (see Appendix M). However, in another analysis where controls were excluded and only OSA patients were analysed, statistically significant differences between group means as determined by the one-way MANCOVA were observed in the Stroop Test (inhibitory control) (Table 7). Significant differences in performances were found between severe EDS and mild EDS patients, F (2,34) = 5.92, p=.024). Results revealed that the greater the subjective sleepiness in OSA patients the worse the performance on the inhibitory control task (Table 7). To analyse whether this was indeed an executive function deficit and not a result of slowed information processing, performance on the Digit Span Forward Test was also controlled. A one-way ANCOVA revealed that differences in scores persisted after controlling for the effects of hypertension, diabetes, BDI and Digit Span Forward scores, F (2,33) = 4.16, p= .025 (see Table 8 for estimated means).

Table 7. *Comparisons between neuropsychological test means of OSA patients according to EDS severity using multivariate analysis of covariance (MANCOVA).*

Measure	Mild EDS n = 15		Moderate EDS n = 11		Severe EDS n = 11			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
MoCA	-1.23	1.73	-1.33	.84	-.51	1.23	3.21	.055
D2a	59.67	36.90	38.27	25.57	48.55	35.63	2.41	.107
RCF Copy	.13	1.14	.344	1.43	.74	.21	.88	.424
AVLT Immediate	-.55	.88	-.49	.90	-.22	.87	1.29	.289
AVLT Delayed	-.73	1.10	-1.00	1.11	-.80	.76	.19	.825
AVLT Recognition	1.44	1.85	.76	1.94	1.58	1.96	.12	.884
Digit Span Forward	.21	.81	.01	.57	-.04	.62	1.02	.374
RCF Recall	-.34	.73	-.33	.87	-.05	.50	.39	.681
Logic Memory I	-.22	.54	-.51	.64	-.05	.58	1.31	.283
Logic Memory II	-.15	.64	-.64	.80	-.22	.56	1.84	.176
Digit Span Backward	.20	.73	.11	.41	.16	.48	.42	.662
TMT-A	.49	1.20	-.03	.72	-.03	.82	1.61	.216
TMT-B	.07	1.32	-.27	.81	.20	1.26	1.23	.307
Stroop	.20	.52	-.33	.63	-.35	35	4.76	.016
Phonemic Fluency	.00	.87	.06	1.14	.11	.54	.88	.423
Semantic Fluency	-.15	.94	.00	.88	-.17	.82	.10	.906
Similarities	.55	.59	.76	1.02	.58	.65	.38	.688
Matrices	.51	.79	.39	.85	.82	.74	.75	.479

Note: Mild EDS: <10, Moderate EDS: 10-15, Severe EDS: 16-24. Mean of *z* scores. D2a: Percentile. RCF: Rey Complex Figure. AVLT: Auditory Verbal Learning Test- immediate recall, delayed free recall and recognition scores.

Table 8. *Estimated Means and Confidence Intervals for Stroop Test Performance after controlling for Hypertension, Diabetes, BDI and Digit Span Forward scores.*

			95% Confidence Interval	
Group	Mean	SE	Lower Bound	Upper Bound
Mild	.21	.14	-9%	50%
Moderate	-.26	.18	-61%	10%
Severe	-.42	.17	-77%	-7%

Note: Dependent Variable: Stroop Test. Covariate Variables: Hypertension, Diabetes, BDI and Digit Span Forward scores. SE: Standard Error.

3.6 Correlation between hypoxemia indexes (ODI and SpO_2<90%) and neuropsychological performance

Pearson correlation tests were conducted to investigate whether desaturation measures, namely, ODI and SpO_2<90%, correlated with neuropsychological performances of OSA patients. The analysis did not show any significant correlations between the variables explored (p >.05) (see Appendix N).

A complete summary of the relevant results organized by the proposed goals for the present study (please see Figure 1 from Introduction section, subsection Current Study) is reported on Table 9.

Table 9. *Summary of Results.*

Objectives	Results
1. Do OSA patients exhibit neuropsychological impairment (compared to normative data)?	**Performance according to OSA severity** → MoCA (global cognitive function) was the only measure that fell below normative data for some groups. However, OSA factors did not contribute significantly to MoCA performance. All other neuropsychological measures evidenced normative mean z-score values. → Controls and severe OSA patients were moderately and mildly impaired in MoCA, z=-1.4 and z= -1.2, respectively.
	Percentage of patients with cognitive impairment for the entire OSA sample: **Attention: (D2 test)** Moderate to severe impairment: 18.9% **Verbal Memory: (AVLT)** Mild impairment: 23.7% (immediate recall), 15.8% (delayed recall) Moderate to severe impairment: 15.8% (immediate recall), 39.5% (delayed recall) **Visual Memory: (RCF)** Mild to moderate impairment: 18.4% **Cognitive Flexibility: (TMT-B)** Mild impairment: 15.8% Moderate to severe impairment: 15.8% → OSA factors did not contribute significantly to these neuropsychological deficits.
2. Are there differences in neuropsychological performance between OSA patients with different disease severity (AHI)?	Significant differences between groups in: Working memory performance (Digit Span Backward test) - Moderate OSA < Mild OSA → Explained by slowed information processing.
3. Can EDS or hypoxemia indexes (ODI, SpO_2<90%) predict neuropsychological deficits?	**Performance according to EDS severity**
	Significant differences between EDS groups in: Inhibitory control (Stroop test) (only relevant to OSA patients) - Severe EDS < Mild EDS → A true executive function deficit.
	Hypoxemia: ODI and SpO2<90%
	No significant correlations between these desaturation measures and neuropsychological performances.

Objectives	Results
4. Do AHI, ODI, SpO_2<90% and EDS significantly correlate?	AHI x ODI = positive, almost perfect correlation AHI/ODI x SpO_2<90% = positive, moderate correlation ESS x SpO_2<90% = negative, weak to moderate correlation ESS x AHI/ODI = no significant correlation

Chapter 4. Discussion

The broad aim of the current study was to investigate the impact of OSA parameters on neuropsychological functions. A model proposed by Beebe and Gozal (2002) which suggests that sleep fragmentation, sleepiness and intermittent hypoxemia are the main contributors to OSA-related cognitive impairment, by triggering a homeostatic imbalance and consequently affecting neuronal communication, was used as a theoretical framework along with previous work that suggests that neurocognitive deficits worsen with disease severity but not linearly (Bédard et al., 1991; Boland et al., 2002).

While considerable research has been devoted to the effects of OSA on cognition, there still no consensus on the precise cognitive domains affected and the mechanisms involved in this process. Whether the different components of OSA can explain the neurocognitive deficits seen in these patients or whether they coexist independently from SDB remains unknown. Conflicting findings in the OSA literature may be explained by the use of limited cognitive testing. Several studies lack the assessment of various cognitive subdomains and especially attentional processes, which may introduce methodological bias in neuropsychological evaluation (Sforza et al., 2010). Extensive neuropsychological assessment was therefore needed to elucidate the question as to whether OSA may predispose patients to specific alterations or a more general cognitive decline. Apart from considering the use of a broad variety of neuropsychological tests, the present work has considered patients with different OSA severity as heterogenous groups. A systematic review has revealed that while mild apneic patients exhibit poor cognitive performance in 11.9%, this number rises to 44.2% in moderately affected patients and increases to 78.4% in severe OSA patients (Fulda & Schulz, 2001), emphasizing the importance of distinguishing between patients of varying degrees of OSA. Yet, since the literature shows there might be an inconsistency between AHI, desaturation indexes and EDS (Chervin, 2000; Kulkas et al., 2013), this study also explored the potential effects of different desaturation measures and EDS on neuropsychological performance.

Comparisons of performances were carried out amongst OSA patients as well as between OSA patients and normative data, since the study did not include a healthy control group. A limitation of comparing neuropsychological performance of OSA patients to normative data is the inability to control for certain demographic and clinical factors, therefore, so as to take these factors into account, a comparison of performance was carried out between OSA patients and a comparative group who shared similar comorbidities and sleepiness symptoms to OSA patients.

4.1 Neuropsychogical Performance According to Disease Severity

4.1.1 Global Cognitive Function

One of the main findings of this study was that patients with severe OSA (AHI>30) displayed reduced performance on a global cognitive measure compared to normative data (1.2 standard deviation below the mean). Although several studies have failed to report such impairment, many of them did not categorize patients according to disease severity (Olaithe et al., 2018). The impairment observed is broadly consistent with Bédard and colleagues' (1991) and Findley et al.'s (1986) findings, who have revealed that only severely affected OSA patients performed more poorly on measures of global intellectual functioning. Along these lines, another early study has revealed that performance of 11 out of 28 OSA patients on the WAIS (a general intellectual measure) were categorized as impaired (Kales et al., 1985). More recent studies such as the large-scale Sleep Heart Health Study has described OSA patients with greater desaturations as being more cognitively impaired than patients without considerable desaturations (Kushida et al., 2012). General cognitive impairment was also observed in the control group. While controls also presented EDS, they did not differ significantly from OSA patients, therefore deficit in this domain may not be a result of subjective sleepiness. Results have also revealed that none of the comorbidities examined (high BMI, hypertension, diabetes, depression and insomnia) were significantly correlated with MoCA scores. It is difficult to justify the observed general cognitive deficit in this group since the exact diagnosis of these patients is unknown.

Much work on the aetiology of OSA-related deficits have suggested hypoxemia and/or sleep fragmentation as the main potential contributors for neurocognitive impairment, implying a relationship between OSA severity and cognition. (Beebe & Gozal, 2002). Bédard and colleagues (1991) have proposed that reductions in global intellectual measures are attributable to the severity of hypoxemia. This association is explained by the vulnerability of synthesis of cerebral monoamines and acetylcholine to cerebral hypoxic alterations, which are recognized for their importance of regulating neurocognitive functions (Bédard et al., 1991). Other authors propose that sleep disruption may mediate these cognitive deficits via dysfunction in neural networks by reducing the efficacy of restorative processes (Yılmaz, Voyvoda, İnan, Şirinocak & Terzi, 2016).

Although the current study was unsuccessful at finding a relationship between global cognitive function and any of the OSA parameters assessed, these results corroborate findings from a meta-analysis that compared OSA and other pathologies which share specific symptoms

to OSA. Olaithe et al. (2018) found that general cognition was preserved in COPD patients, indicating that perhaps hypoxemia alone does not account for deficits in this domain. Similarly, in the same meta-analysis, most papers reported no impairment in the global cognitive domain in patients suffering from insomnia (non-restorative sleep for more than 1 month), suggesting that chronic sleep disruption may not contribute significantly to this domain. On the other hand, experimental studies of sleep deprivation reported in the same meta-analysis revealed that short-term sleep loss (e.g., less than 48 hours) may lead to general cognitive impairment (Olaithe et al., 2018). While the majority of OSA patients presented EDS and were unsatisfied with their current sleep pattern, none of the three groups (mild, moderate and severe OSA) met the criteria for insomnia. It is therefore possible that not chronic, but short-term sleep disruption may promote cognitive deficits in OSA. Unfortunately, this association cannot be verified since this study did not have access to EEG to analyse sleep-wake states. While sleep fragmentation measured by AHI was not a good predictor of global cognitive impairment, this study did not include a direct measure of the arousal index. Despite the fact that AHI reflects the number of arousals per hour of sleep indirectly, arousals were not directly assessed because only home monitors were used in the diagnosis of OSA. Since cortical arousals are the most common and reliable measure use to assess sleep fragmentation in OSA patients (Zuurbier et al., 2016), the contributions of sleep fragmentation to global cognitive deficits may not be established with precision.

The effect of CPAP treatment is another important factor to consider when analysing the impact of OSA on general cognitive functioning. While some papers have reported preserved global cognition in OSA patients, many of these studies have observed general cognitive improvement after treatment (Aloia et al., 2004). Bédard and co-workers (1993) initially compared untreated OSA patients to controls and then pre–post treatment modifications in the OSA group and found lower general cognitive performance in untreated patients compared to treated patients. Hence, apneic patients may present few deficits in the general cognitive domain relative to healthy individuals, however treatment may generate within-subjects improvements in performance. It is difficult to establish the reason why these improvements would occur, especially given the considerable range of measures that comprised in this domain. Thus, it is possible that the true effect of OSA on global cognitive functioning is underestimated. A follow-up study after CPAP treatment would be able to clarify this matter. Differences in global cognitive performance of patients suffering from different degrees of OSA in prior studies may also be attributed to the use of different instruments used

to assessed this domain (e.g., MoCA, WAIS) or the use of measures that may not be sufficiently sensitive or specific to detect cognitive changes (e.g., Mini-Mental State Examination; MMSE; specific WAIS subtests).

4.1.2 Attention

The mean standardized scores for sustained attention performance were categorized as normal when OSA patients were divided according to disease severity. Moreover, no significant differences in performances between patients suffering from different OSA severity were detected. Descriptive analysis has nevertheless revealed that almost one fifth of the total OSA sample (18.9%) presented moderate to severe impairment (10th-1st percentile) on the D2 performance. The literature shows that although a few studies have been unsuccessful at finding attention impairment in OSA (Olaithe et al., 2018), a large number of OSA papers have reported deficits in the ability to maintain attention and inability to concentrate, and have proposed sleep fragmentation and sleepiness as the underlying factors for these deficits (Daurat et al. 2016; Devita et al., 2016; Fulda & Schulz, 2001; Sforza & Roche, 2012). None of the OSA factors however predicted performance on this test in the current study. The effect of EDS on cognitive decline cannot nevertheless be ruled out as objective sleepiness (e.g., MLST) was not assessed due to lack of equipment availability (EEG/PSG). Moreover, it is possible that the limited normative data for older Portuguese adults, where adults aged over 36 years old are categorized as one group, may have affected the results (Ferreira & Rocha, 2006). Unfortunately, this was the only accessible and valid Portuguese sustained attention test at the time the research was being conducted.

4.1.3 Memory

Despite extensive neuropsychological evidence demonstrating the impact of different levels of disease severity on specific memory processes (Aloia et al., 2004; Naegelé et al., 2006), on average, all three OSA groups exhibited normal performance on the memory tests administered compared to norm-referenced data and no substantial differences in performances were observed between mild, moderate and severe OSA patients. Nevertheless, when analysing the OSA sample as a whole, 23.7% of the patients were considered mildly impaired on immediate recall performance and 15.8% were regarded as moderately to severely impaired. Additionally, 15.8% of the OSA sample was categorized as mildly impaired on the delayed

free recall test and 39.5% were categorized as moderately to severely impaired. Similar results were observed regarding visual memory (RCF recall), in which 18.4% of the sample presented mild to moderate impairment.

Previous studies comparing OSA to COPD and sleep deprivation have associated all three pathologies to memory impairment, suggesting that both sleep disruption and hypoxemia may promote deficits in this cognitive domain (Olaithe et al., 2018). Nonetheless, data analysis has failed to identify significant correlations between desaturation, disease severity, subjective sleepiness and memory performance in the present study. A recent study has suggested that arousal frequency is the best predictor of impairment in sleep dependent memory consolidation in OSA (Malhotra & Jordan, 2016). Research has shown that OSA reduction of REM sleep generates dissociation of REM traits to other sleep stages, impairing memory formation and consolidation (Otero et al., 2018). Since cortical arousals and sleep stage-parameters could not be assessed, their effect on memory performance could not be verified. Future studies should investigate whether frequency of arousal during sleep correlates with specific memory measures.

4.1.4 Visuospatial/Constructional Skills

With regard to visuospatial/constructional skills, numerous studies in the literature show that OSA patients are likely to perform poorly in tests assessing this cognitive domain (Incalzi et al., 2004). Conversely to what has been reported by some researchers, Olaithe and colleagues (2018) found that adults with pathologies involving hypoxemia and sleep disruption did not present deficits in this cognitive area, suggesting that visuospatial/constructional deficits are unique to OSA. This indicates that perhaps another, as yet, undefined factor contributes to visuoconstructional impairment in these patients. The present study has nevertheless failed to detect deficits in visuoconstructional ability. There is a possibility that the absence of impairment observed could have been influenced by the limited normative data available. Although age is known to negatively influence visuoconstructional performance and level of education is positively associated with faster copy time and better scores (Tremblay et al., 2014), normative data for the Portuguese population in this test does not take into account both factors (age and education) simultaneously; it is classified either according to age or education.

4.1.5 Psychomotor Skills

Despite assessed less frequently than most other domains, psychomotor skills are often impaired in apneic patients compared to healthy controls (Aloia et al., 2004). Psychomotor deficits have been repeatedly associated with severity of hypoxemia, especially because of its clear lack of improvement with CPAP treatment (Bédard et al., 1991; Daurat et al., 2016; Stranks & Crowe, 2016). Based on the absence of psychomotor deficits in apneic patients compared to normative data, the current findings do not appear to support this observation. Moreover, no differences between psychomotor performance were observed between patients with different OSA severity. Notwithstanding the lack of agreement, these findings compare well with a study by Kloepfer and colleagues (2009), who found that patients with moderate OSA and healthy subjects did not differ significantly in their performance on the TMT-A, the same psychomotor task used in this study. A meta-analysis has shown that the use of particular instruments to assess this domain may produce different results. When psychomotor abilities were evaluated with the Groove Pegboard, motor coordination was associated with hypoxemia, but not sleep fragmentation measures, whereas when subjects were evaluated with the Finger Tapping Test, psychomotor speed was not associated with hypoxemia nor sleep fragmentation (Aloia et al., 2004). Similarly, no such association was found in the current study. Several previous OSA studies have used the Grooved Pegboard to measure psychomotor speed, the administration of this instrument was not nevertheless possible in this study as there was no published normative data available for the Portuguese population. Future studies should include more than one measure of psychomotor skills so that a more accurate conclusion can be reached.

4.1.6 Executive Function

When comparing patients with different degrees of OSA, it was found that adults with moderate OSA demonstrated significantly inferior performance in a working memory measure (Digit Span Backward Test) compared to patients with mild OSA. Patients with moderate OSA exhibited considerably higher AHI and desaturation indexes than mild OSA patients, but no differences in subjective sleepiness. However, none of these factors were associated with working memory impairment, nor the comorbidities analysed.

As suggested by Verstraeten and co-workers (2004), a methodological bias in the assessment of executive function (particularly working memory) is the lack of control of processing speed and attention performances during the task, which may lead to a false

conception of executive dysfunction in apneic patients. Thus, the effects of slowed information processing (reflected in forward digit recall) were adjusted in the assessment of this higher mental function (i.e., working memory, reflected in digit backwards recall) (Sharma et al., 2010). After controlling for the effect of attentional capacity/slowed processing speed, findings indicated that the reduced score in Digit Span Backward test may not truly reflect working memory deficits in moderately affected OSA patients. It suggests instead a decline in alertness and speed of processing, confirming the results found by Verstraeten et al. (2004) and Sharma and colleagues (2010).

No further significant differences in the Digit Span Backward performance were found between patients suffering from other degrees of OSA. Furthermore, desaturation indexes were not good predictors of working memory performance in OSA. This is in good agreement with one of the most recent OSA meta-analysis which has revealed that neither OSA, COPD, nor insomnia patients presented working memory deficits, confirming that perhaps sleep fragmentation and hypoxemia do not significantly affect this cognitive domain (Olaithe et al., 2018). An alternative explanation for observing the decrease in performance only in moderate OSA and not in severe OSA patients is that the large number of statistical tests performed could have resulted in the effect of chance (random error). Specific tests to rule out the effect of chance as a result of multiple correlations tested were not carried out.

Despite being one of the most affected cognitive domains in OSA patients, especially in severely affected ones (Bédard et al., 1991), no evidence of executive dysfunction was found when patients were analysed according to disease severity. Patients with severe OSA were slightly more educated and younger than the other patients, however these differences were not significant and therefore it is unlikely that these factors accounted for the lack of differences in neuropsychological performance between groups.

An analysis of the entire OSA cohort has nonetheless revealed that 15.8% of patients presented mild deficits on a cognitive flexibility test (as measured by the TMT-B) and an accumulative percentage of 15.8 presented moderate to severe impairment compared to normative data. Bédard et al. (1991) have proposed that severity of hypoxemia is the mechanism responsible for poor performance on this test. Other researchers have found instead a relationship between sleep restriction or deprivation and poorer performance on the TMT-B. (Quan et al., 2011). Surprisingly, AHI, hypoxemia indexes and EDS did not contribute significantly to the prediction of cognitive flexibility performance in the present study.

Unlike many OSA studies (Décary, Rouleau & Montplaisir, 2000; Olaithe et al., 2015), no further impairment was identified in other executive functions. A Single Photon Emission Photography (SPET) study has shown that although abnormalities in the frontal and temporal cortices of severely affected apneic patients were observed (indicative of perfusion or metabolic defects), no neuropsychological deficits (including deficits in executive functions) were detected in these patients (Tainturier, Hausser-Hauw, Rakotonanahry & Fleury, 1998). Neuroimaging studies with contrasting results between evident metabolic or structural deficit and a minor neuropsychological impairment suggest that compensatory mechanisms may play an important role in the absence of OSA-related neurocognitive deficits (Devita et al., 2016). Therefore, despite the widespread neuroanatomical alterations detected in SDB patients, the severity of cognitive deficits observed may be less pronounced (Sforza et al., 2010). While cognitive reserve helps the brain to actively cope with neural damages by using pre-existing cognitive processing and compensatory approaches (Stern, 2002), the results demonstrated that patients' cognitive reserve did not seem to be a relevant contributor to the relationship between OSA severity and neuropsychological deficits. It should be pointed out, however, that no normative reference data for the Portuguese population was available and so interpretation of the Cognitive Reserve Index questionnaire (CRIq) scores were based on the authors' recommendation for the Italian population (Nucci et al., 2012). It is therefore possible that the true contributing effects of patients' cognitive reserve may have not been accurately estimated.

4.2 Comparison of OSA Patients' Performances According to EDS Severity

An early study has demonstrated that while disease severity did not substantially contribute to cognitive performance in OSA patients, EDS was found to be the best predictor of the cognitive deficits observed (Roehrs et al., 1995). To analyse whether EDS has an independent effect on cognitive function, regardless of the presence of OSA, the sample was divided according to severity of subjective sleepiness. The effect of potential confounding variables was controlled, including hypertension, diabetes and depression scores. When the sample was analysed as a whole (controls and apneic patients), results revealed that EDS did not have a substantial effect on neuropsychological scores. Nevertheless, when controls were excluded from the analysis, severity of EDS revealed a significant effect on inhibitory control performance (i.e., the ability to inhibit conflicting response tendencies due to irrelevant information), measured by the Stroop test. The results indicated that the greater the severity of subjective sleepiness the worse the performance in an inhibitory control task. Furthermore, it was found that OSA patients were significantly impaired in the Stoop test even after adjusting

for the effects of generalized slowing. These findings corroborate similar results reported by Sharma and colleagues (2010). Moreover, while previous research has demonstrated that the relationship between subjective sleep complain and cognitive decline may be moderated by depression (Jelicic et al., 2002; Pilcher & Huffcutt, 1996), the present study suggests that subjective sleepiness has a weak correlation with depression and it has a direct negative impact on inhibitory control, regardless of the severity of depressive symptoms. In general, apneic patients have nonetheless presented moderate symptoms of depression, which is consistent with past researches.

Overall, this study suggests that EDS has an impact on executive function, in terms of inhibitory control, regardless of OSA severity. This result shares a number of similarities with Yılmaz et al.'s (2016) findings, who have investigated the possible relationship between the executive functions, sleep parameters and subjective EDS in OSA patients (Yılmaz et al., 2016). They found that OSA patients had more difficulty in inhibiting accustomed behaviour patterns compared to controls, yet, no significant correlation between neuropsychological deficits and respiratory data was detected. Impairment in executive function was instead associated with subjective sleepiness. Similar results were observed in a study comparing neuropsychological, neuroimaging and polygraphic data between OSA patients and controls (Torelli et al., 2011). These findings indicate that the most important factor affecting deficits in executive function is EDS, rather than hypoxemia and disease severity. However, another OSA-related factor may contribute to impairment on this cognitive domain since EDS was only relevant to OSA patients' performance and not the control group, who also suffer from daytime sleepiness.

4.3 EDS Aetiology in OSA

It is still unclear whether neurocognitive decline is related to EDS caused by sleep fragmentation, repeated desaturation events or it is an independent factor. Although some researchers have claimed that disease severity may be a relevant prognostic factor for EDS, since sleepy patients may present worse sleep-related breathing parameters (e.g., longer apneic episodes and lower saturation levels) and lighter and more fragmented sleep patterns compared to non-sleepy patients (Kulkas et al., 2013; Oksenberg et al., 2010; Zhou et al., 2016), this study has failed to find a correlation between sleepiness and disease severity/sleep fragmentation. Although this finding is unexpected, it substantiates a recent study by Laranjeira, Barbosa and Rabahi (2018), in which subjective sleepiness and poorer sleep perception were not correlated with OSA severity (AHI), indicating that EDS may not be a

good parameter for the diagnostic evaluation of OSA. Nam et al. (2016) have suggested that this may occur due to OSA interrupting deep sleep and the reduction of REM sleep which may alter sleep perception. Since arousals are not perceived as sleep interruptions by the cerebral cortex, no association might be observed between complains of poor sleep quality and recurrent awakenings reported by the patients. Although Laranjeira and colleagues (2018) did find that high frequency of arousals correlated with OSA, arousals did not influence sleep perception. The architecture of sleep was not examined in this study and therefore the association between disruption of deep sleep and sleep perception cannot be verified.

Results have also revealed that patients who spent more time hypoxemic (more sleep time with saturation under 90%) presented significantly less EDS than less affected patients. The pattern of which patients with lower desaturation may exhibit more subjective sleepiness has been described in the literature (Wu et al., 2015). This association has been rationalized by some authors on the basis that intermittent hypoxemia may lead to misperception of sleep state (Laranjeira et al., 2018). Perception of sleep is a complex process of cognition, it involves thought control, temporal awareness and awareness of surroundings, which are greatly related to subjective estimation of physiological sleep states (Yang, Han, Yang, Su & Lane, 2010). Several brain areas, such as the hypothalamus, thalamus, cingulate gyrus, frontal, temporal, and inferior parietal lobes are implicated in sleep perception and are also involved in apneic patients (Yang et al., 2010). Loss of grey matter in these areas may account not only for cognitive dysfunction in OSA but also misperception of sleepiness, suggesting that the longer a patient remains hypoxemic the worse his subjective perception of sleepiness (Wu et al., 2015). This may explain why patients with severe desaturation are less likely to complain about daytime sleepiness.

While hypoxemia and disease severity (which may/may not take into account desaturations) do not account for the EDS-related cognitive impairment in apneic patients, studies suggest that the link between EDS and cognitive deficits (more specifically executive function) in OSA may be explained by irregular sleep parameters. A considerable amount of evidence confirms the association between executive function and certain nocturnal parameters, specifically wake time after sleep onset (WASO) (Holanda, Júnior & de Almondes, 2016). WASO is a more reliable measure of sleep fragmentation and lower WASO reflects better sleep continuity through the night. It has been proposed that higher WASO prevents older adults from passing normally through sleep stages and reduces the time spent in slow wave sleep (SWS; phase 3 sleep, which is the deepest phase of non-rapid eye movement) (Holanda et al., 2016). SWS is known to considerably contribute to prefrontal cortex (PFC)

functioning and therefore executive functioning. Researchers have revealed that disruption of SWS may lead to neurocognitive deficits (including executive dysfunction), which confirms the idea that that neural activity during sleep regulates and strengthens connectivity of prefrontal brain network connections (Mander et al., 2013). These findings substantiate the PFC hypothesis which maintains that the PFC is particularly susceptible to the adverse effects of sleep loss (Holanda et al., 2016). Thus, it is possible that higher levels of subjective EDS may be a reflection of sleep discontinuity in specific sleep stages, which consequently negatively affects executive function performance.

Pathophysiological causes of EDS are not entirely understood. The level of EDS complaints can vary in adults who share the same demographic characteristics and the same AHI values (Yılmaz et al., 2016). In clinical practice, even in the presence of severe OSA, some adults may not present with significant EDS. The subjective perception of sleepiness may be affected by comorbidities, rate of development of conditions causing sleepiness, tolerance to challenges causing sleepiness (i.e., OSA) and/or countermeasures (e.g., caffeine) (Chervin, 2000). Thus, the precise mechanisms by which some apneic patients have EDS, while others do not, remain unknown.

Taken together, this study substantiates previous research on the detrimental effects of OSA-related EDS on cognition (Zhou et al., 2016). This is an important finding since EDS is one of the chief complaints and main reason for presenting for OSA evaluation and adhering to treatment (Rosenthal & Dolan, 2008). While excessive sleepiness has been linked to deficits in inhibitory control in apneic patients, it did not explain cognitive impairment in other domains (attention, memory and cognitive flexibility). EDS and poor sleep quality may partly explain cognitive impairment in OSA; however, CPAP studies have reported that cognitive deficits are only partially reversible with CPAP treatment, even after a complete resolution of daytime sleepiness (Kim et al., 2017). This suggests that further unexplored mechanisms may negatively influence cognitive performance in OSA.

4.4 Relationship Between AHI and Hypoxemia Indexes:

To investigate the impact of OSA factors on neuropsychological performance it was also necessary to examine the potential relationships between AHI and hypoxemia indexes (ODI and SpO_2<90%). Results revealed a strong correlation between AHI and ODI, i.e., the total number of breathing episodes was highly related to the mean number of desaturation events per hour. This finding is in good agreement with a recent study which suggests that ODI is as valuable as AHI in diagnosing and grading OSA (Temirbekov et al., 2018). On the other

hand, it was hypothesized that although OSA indexes (AHI and desaturation indexes) would be positively correlated, they would not correlate perfectly as they still measure different aspects of sleep apnea. Length of time spent with saturation below 90% (SpO_2<90%) correlated only moderately with ODI and AHI. According to Kulkas and colleagues (2013) patients with similar AHI may suffer from OSA of very different severity, since the morphology of oxygen desaturation episodes are not taken into account in the AHI and ODI parameters. For this reason, the impact of SpO_2<90% on neuropsychological performance was analysed separately.

Although researchers have suggested that longer and deeper oxygen desaturations are likely to cause more physiological stress and consequently more adverse health outcomes than shorter and shallower episodes (Kulkas et al., 2013), no significant associations were observed between SpO_2<90% and performances on neuropsychological tests. As previously mentioned, compensatory mechanisms have been put forward as an explanation for the weak or lack of significant relationship between oxygen desaturation and cognitive dysfunction in OSA. Neuroimaging studies have suggested that the brain of never-treated OSA patients tries to compensate to avoid decline in cognitive performance (Castronovo et al., 2009; Quan et al., 2011). Castronovo and co-workers (2009) have revealed that untreated patients exhibit an over-recruitment of brain areas compared to healthy individuals during an executive function task, which may reflect a neural compensatory mechanism that partly masks cognitive impairment.

Research suggests that OSA may represent a clinical example of ischemic preconditioning and the development of adaptive responses to chronic hypoxia (Rosenzweig, Williams, & Morrell, 2014). OSA may lead to ischemic preconditioning through the activation of various gene programs, such as the hypoxia inducible factor-1, vascular endothelial growth factor, and brain-derived neurotrophic factor (BDNF) (Rosenzweig et al., 2014). Animal studies have lent support to the adaptive nature of intermittent hypoxia. In a rodent model, researchers revealed that recurrent hypoxia intervention before the ischemic episode increases the expression of BDNF, neurogenesis and synaptogenesis, and also improves spatial learning and long-term memory deficits (Dirnagl, Becker & Meisel, 2009). It is nevertheless important to highlight that these studies indicate that the intensity and duration of the exposure to recurrent hypoxia and related oxidative stress were major determining factors of whether hypoxia was protective or harmful (Rosenzweig et al., 2014).

In contrast to this explanation, some authors have postulated that intermittent hypoxemia may not be a necessary determinant of neurocognitive impairment in OSA, and sleep fragmentation may be sufficient (Thomas, Rosen, Stern, Weiss & Kwong, 2005). A functional magnetic resonance imaging study has reported that lower level of prefrontal cortex

activation during an executive function performance was similar in hypoxic and nonhypoxic individuals, which suggests that hypoxia may not induce cortical dysfunction observed in OSA (Thomas et al., 2005). The sample size of this study was nevertheless too small to draw any definitive conclusions.

As previously mentioned, further research suggests that the sleep stage in which desaturation events or arousals occur may be important to better understand the impact of OSA on cognition (Otero et al., 2019). Changes in sleep architecture and patterns are known to influence cognitive functioning. Song and colleagues (2015), for instance, have reported that increased time in stage N1 sleep and less time in stage REM sleep are related to poorer neuropsychological performance in older men. AHI/ODI cannot detect the sleep cycle when hypoxemia and arousal took place. Thus, new measures that separate sleep fragmentation and desaturations and measures to identify these episodes in each sleep cycle are needed.

Even though some of the most common comorbidities in OSA were controlled in the analysis of the impact of OSA factors on cognition, it is possible that individual characteristics and other comorbidities not included in this study moderated (reinforced or weakened) the association between cognitive deficits and OSA severity. Although the prevalence of high blood pressure in the sample was taken into account, a common comorbidity in OSA and a risk factor for cardiovascular disease (Tkacova et al., 2014), participants with cardiovascular disease history were not included in this study due to its known impact on cognition (Incalzi et al., 2004). Some authors have demonstrated that the negative effects of desaturation indexes on attention and executive functions were only evident in apneic patients with cardiovascular disease history (Yamout et al., 2012). It is possible that desaturation and disease severity play a contributory role in the increased risk of cognitive decline predominantly in adults with concurrent presence of cardiovascular disease.

4.5 Limitations and Future Directions

This study presents a number of limitations and therefore results need to be interpreted with caution. The current study was underpowered due to small sample size and few outliers could have significantly distorted mean test results. The lack of a large enough sample required to model complex interactions between multiple indicators may have jeopardized the ability to detect a statistically significant difference between groups and therefore explains the absence of a clear relationship between OSA severity and neurocognitive decline. Moreover, the majority of OSA patients were men, which represents an important target group for neuropsychological evaluation, yet, the findings cannot be generalized directly to women.

The role of many potential effect moderators was considered; however, it was infeasible to consider every possible factor in this study, such as disease duration and genotype. Although patients were newly diagnosed with OSA at the time of the neuropsychological evaluation, the precise duration of the disease cannot be confirmed. The association between OSA duration and neuropsychological status indicates that a key factor influencing neuropsychological status may be disorder chronicity and it should therefore be taken into account in future studies (Greenberg et al., 1987).

Participants' state factors such as fatigue, effort, and motivation are relevant factors to take into account when interpreting neuropsychological results, especially in individuals with sleep disorders (Verstraeten et al., 2004). The inclusion of a comparative group in the study which also presented sleep complains but no OSA diagnosis was therefore important. However, while the comparison group was useful for controlling the effects of some shared symptoms and comorbidities seen in OSA patients, their precise diagnoses remained unknown as there was no follow-up of these patients, thus it is difficult to determine why they performed more poorly on some neuropsychological tests than OSA patients. Besides the unknown diagnosis, the only relevant difference in demographic and clinical characteristics between OSA patients and controls was the higher number of females in the control group. This was a double-blind study and therefore the researcher was not aware of which group the patients were going to be allocated. Women are known to have more symptoms of anxiety compared to men (Hantsoo & Epperson, 2017) and therefore it is possible that anxiety symptoms may have had a negative impact on controls' performance which may account for the deficits observed. Future studies should include the assessment of these symptoms.

Other external and biological factors could also have had an impact on neuropsychological performance, such as discrepancy of time of the day across

neuropsychological evaluations and circadian rhythm. A study has revealed that reduced accuracy in tasks involving executive functions in the morning was related to objective sleepiness, but not in the afternoon (Lis et al., 2008). Furthermore, different findings across neuropsychological studies may reflect the impact of circadian rhythm on alertness and neuropsychological performance. In the morning or before noon, the circadian process reaches its peak, inducing greater alertness, whereas the timing of the circadian nadir coincides with the late afternoon testing (Achermann, 2004). Harrison, Jones and Waterhouse (2007) have nonetheless revealed that when separated from the effects of wake duration, circadian cycle did not have a significant effect on cognitive performance (inhibitory control), suggesting that circadian influence will vary dependent on the length of prior wakefulness. This study has nevertheless not included participants with sleep disorders; additionally, participants did not experience moderate or high levels of subjective sleepiness. It is recommended that future OSA studies assess patients' nocturnal parameters and attempt to evaluate all participants at the same time of the day in order to reduce these potential effects.

Once again, to learn whether neuropsychological performance of OSA patients is more similar to cognitive decline typically found after sleep loss, future studies should include measures with more reliable normative data. The absence of differences in the variables examined could also, in theory, be a result of the lack of sensitivity of some instruments used (e.g., ESS). This may nevertheless not be the case since numerous randomized clinical trials have demonstrated that these measures detect clinically relevant alterations.

This research has also raised questions in need of further investigation in the neuroscience field, such as whether the presence of OSA and EDS could be seen as combined factors which speeds up brain's ageing process by increasing the susceptibility of specific cerebral structures to clinical and pathological occurrences. Moreover, in addition to AHI, microarousals should be assessed with EEG so that a concrete conclusion can be made regarding the effect of sleep fragmentation on cognitive functions. Functional neuroimaging could help discriminate the effects of sleep fragmentation and hypoxemia. In addition, neuroimaging techniques should be included in future studies in order to learn whether OSA results in structural brain abnormality but cognitive reserve or neural compensatory mechanisms counterbalance this damage, or if neuropsychological testing is not sensitive enough to detect subtle changes in neurocognitive outcomes in apneic patients.

Future work should also focus on whether CPAP treatment improves EDS and sleep parameters and consequently cognitive performance. Answering this question will help us

understand whether cognitive decline in OSA is in fact reversible. This is particularly relevant for older patients since most published studies investigating the effect of CPAP on cognition were performed among young and middle-aged adults. Moreover, older adults present an increased risk of undiagnosed comorbidities, which can contribute to cognitive alterations. It is important that prospective studies investigate whether these identified cognitive alterations may be a result of a pre-existing MCI or even a risk factor for dementia.

While neuropsychological testing revealed that cognition in apneic patients was rather affected, the extent to which OSA may affect performance in tasks of daily living, including a higher vulnerability to car accidents, or to mistakes during work-related or daily tasks, is still unknown. It is recognized that an executive dysfunction, for example, can particularly change the recruitment of other cognitive abilities, potentially causing maladaptive behaviour in daily life (Beebe & Gozal, 2002). Therefore, further work should attempt to establish the degree of functional impairment in OSA patients so that compensatory strategies can be developed to improve patients' life quality.

Chapter 5. Conclusions

This study shows that the relationship between cognition and apnea severity is not completely linear, even in middle-aged and older adults. Neuropsychological assessment revealed mild impairment in the general cognitive performance of severely affected OSA patients, but no significant impairment in less affected patients. The OSA parameters assessed were not, however, relevant contributing factors to impairment on this measure. Based on previous studies, it is possible that this deficit is a result of short-term sleep disruption (Olaithe et al., 2018). While the AHI was not a significant predictor of general cognitive performance, the use of a more valid measure of sleep fragmentation would be able to better clarify this matter. Although no further evidence of profound cognitive impairment was found in OSA patients when they were analysed according to disease severity, an analysis of the whole OSA sample revealed deficits in sustained attention, immediate and delayed recall of verbal material, delayed recall of visual stimulus and cognitive flexibility. This exact pattern of cognitive decline (attention, memory and executive function) has been previously identified in several studies (Aloia et al., 2004; Bédard et al., 1991; Daurat et al., 2016; Olaithe et al., 2018).

In general, disease severity, hypoxemia and subjective sleepiness were not significantly associated with most neuropsychological deficits observed, suggesting that perhaps another unexplored factor may account for cognitive impairment in OSA. Results have nevertheless indicated that increased subjective sleepiness in apneic patients may lead to lower inhibitory control, regardless of the disease severity, presence of depressive symptoms or the impact of slowed information processing. These findings challenge the widely held view that neuropsychological functions are especially vulnerable to the influence of hypoxemia and disease severity in OSA and emphasize the unique effect of EDS on executive function. This study supports the prefrontal cortex vulnerability hypothesis which proposes that poor sleep have detrimental effects on the prefrontal cortex circuitry (Holanda et al., 2016). It should be emphasised that the negative effect of EDS on cognition was only significant in apneic patients, it did not have an impact on performance of patients with daytime sleepiness but no OSA diagnosis, suggesting that another OSA-related factor may be involved in this association.

The present study further revealed that EDS was not associated with disease severity, therefore, perception of sleep reported by the patient may not be useful for grading OSA. EDS severity is nevertheless important from a neuropsychological perspective and consequently for the functional capacity of apneic patients. This highlights the importance of the psychological aspects of the disorder, which should encourage clinicians to look beyond the medical status

of the patient. That is, besides taking into account severity of disease and desaturation indexes, clinicians should also consider the importance of symptoms of EDS and individual differences. Perhaps sleepy apneic patients are more prone to cognitive decline and other factors may be involved in this association. Individual differences in susceptibility to sleepiness or differences in individual compensatory abilities might strength or weaken any dose-response relationship between sleepiness and neurocognitive performance (Holanda et al., 2016).

Conflicting findings from past studies and the limited effect of OSA parameters on cognition observed in this study suggest the existence of a complex OSA-neurocognitive relationship. Although desaturation measures and the comorbidities assessed were not relevant for the detection of neuropsychological deficits in OSA, future studies should include a more comprehensive medical evaluation (assessment of other possible comorbidities) and use more valid measures to determine the direct impact of sleep parameters.

In conclusion, this study substantiates the concept that OSA is a multifaceted disorder which has detrimental effects on specific cognitive domains, however it is possible that these deficits may be reversible. Moreover, EDS should be taken into account when evaluating patients and developing potential compensatory strategies to improve their everyday lives.

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Appendices

Appendix A. Hospital Particular do Algarve Ethics Committee Approval.

Hospital Particular do Algarve
GRUPO HPA SAUDE

COMISSÃO DE ÉTICA PARA A SAÚDE DO HOSPITAL PARTICULAR DO ALGARVE

PARECER Nº 3/2019

Assunto: "Obstructive Sleep Apnea: The Effects of Apnea-Hypopnea Index, Oxygen Desaturation and Daytime Sleepiness on Cognitive Function/ Apneia Obstrutiva do Sono (AOS): Os efeitos do Índice de Apneia-Hipopneia, Dessaturação de Oxigênio e Sonolência Diurna no Funcionamento Cognitivo",

Nos termos e para os efeitos do disposto na alínea a), do nº 1 do artº 9º da Lei nº 21/2014 de 16 de Abril, foi solicitado o parecer desta Comissão, tendo em vista a autorização para a realização do estudo acima identificado.

No âmbito das competência que lhe são conferidas pelo artº 6º do Decreto-Lei nº 97/95 de 10 de Maio e pelo do artº 16º da Lei nº 21/2014 de 16 de Abril, a CES-HPA analisou o processo que lhe foi apresentado para aquele efeito e avaliou todos os aspectos apontados no nº 6 do referido artº 16º.

1. Pertinência do estudo clínico e sua concepção:

De acordo com a informação prestada a esta Comissão a realização deste estudo torna-se pertinente uma vez que pretende clarificar as causas de declínio neurocognitivo em utentes com Apneia Obstrutiva do sono (AOS).

Conhecer o impacto da AOS nas funções cognitivas é de grande importância para o tratamento e reabilitação destes utentes, bem como para a prevenção de possíveis doenças neurodegenerativas.

3. A aptidão do investigador principal e dos restantes membros da equipa.

Cada membro pesquisador está apto a exercer sua tarefa.

Sendo o Investigador Principal: Laura Nedel Duarte, esta investigação é orientada pela equipa: Dr. Miguel Coutinho, Dina Silva e Vinícius Duarte, atendendo ao tipo de estudo, parece adequada as qualificações dos profissionais responsáveis pelo estudo.

Hospital Particular do Algarve

GRUPO HPA SAUDE

4. Procedimento de obtenção do consentimento informado incluindo as informações a prestar aos participantes.

As informações recolhidas serão efetuadas através de uma entrevista clínica, questionários e testes neuropsicológicos.

Concordando com a sua participação no estudo, estará também a consentir o uso dos dados neurofisiológicos recolhidos através do monitor portátil utilizado para o diagnóstico da AOS.

O consentimento informado será explicado ao participante voluntário durante a visita e assume um caráter confidencial e anónimo, sendo que os dados recolhidos serão apenas utilizados no âmbito do estudo referido e a qualquer momento poderá abandonar a sua participação sem qualquer género de prejuízo.

Parece, pois, que neste protocolo de estudo e considerando os documentos entregues para avaliação e sua fundamentação são observados os compromissos éticos, o que permite que esta comissão profira um parecer favorável ao plano de investigação, e por o mesmo respeitar os princípios deontológicos e legais específicos para estas situações.

Portimão, 17 de Julho de 2019

Appendix B. Interview Questions on Clinical and Sociodemographic Information

QUESTIONARIO SOCIODEMOGRÁFICO E CLÍNICO

Código: _____

Sexo: F ☐ M ☐ **Idade:** _____

Reformado? SIM ☐ NÃO ☐

Fumador: NÃO ☐ SIM ☐ → Mensalmente ☐ Semanalmente ☐ Diariamente ☐

Consumo de Álcool: NÃO ☐ SIM ☐ →Mensalmente ☐ Semanalmente ☐ Diariamente ☐

Histórico familiar de demência: SIM ☐ NÃO ☐

Medicação habitual: _____

DIABETES MELLITUS	SIM	NÃO
HTA	SIM	NÃO
ALTURA		
PESO		

Appendix C. Information Sheet

PROTOCOLO DE CONSENTIMENTO DE PARTICIPAÇÃO EM PROJETO DE INVESTIGAÇÃO

Investigação no âmbito do Mestrado em
Neurociências Cognitivas e Neuropsicologia

Autora: Laura Nedel Duarte

O atual trabalho de investigação, intitulado "*Obstructive Sleep Apnea: The Effects of Apnea-Hypopnea Index, Oxygen Desaturation and Daytime Sleepiness on Cognitive Function/ Apneia Obstrutiva do Sono (AOS): Os efeitos do Índice de Apneia-Hipopneia, Dessaturação de Oxigênio e Sonolência Diurna no Funcionamento Cognitivo*", insere-se num estudo que decorre no âmbito do Mestrado em Neurociências Cognitivas e Neuropsicologia, em parceria com o Hospital Particular do Algarve.

O estudo tem como objetivo principal clarificar as causas de declínio neurocognitivo em utentes com AOS. Conhecer o impacto da AOS nas funções cognitivas é de grande importância para o tratamento e reabilitação destes utentes, bem como para a prevenção de possíveis doenças neurodegenerativas. Portanto, a sua colaboração é fundamental.

O resultado da investigação, orientada pela equipa: Dr. Miguel Coutinho, Dina Silva e Vinícius Duarte, será apresentado na Universidade do Algarve no começo de 2020 podendo, se desejar, contactar a autora para se inteirar dos resultados obtidos.

As informações recolhidas serão efetuadas através de uma entrevista clínica, questionários e testes neuropsicológicos. Concordando com a sua participação no estudo, estará também a consentir o uso dos dados neurofisiológicos recolhidos através do monitor portátil utilizado para o diagnóstico da AOS.

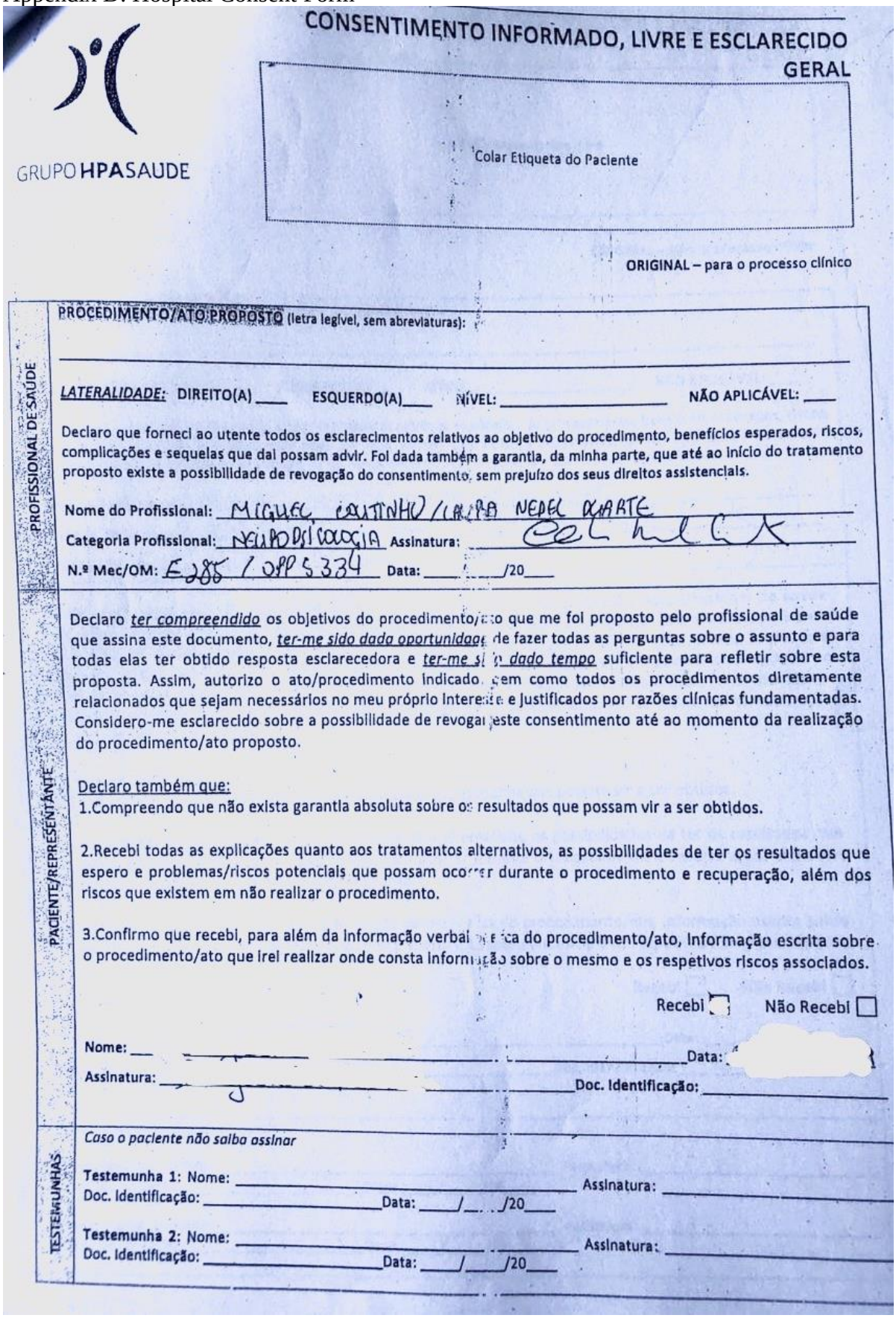
É garantido o anonimato e confidencialidade dos dados. Toda a informação recolhida será mantida em local seguro, o qual apenas os envolvidos na investigação terão acesso.

Este estudo não lhe trará nenhuma despesa ou risco. A sua participação neste estudo é voluntária e pode retirar-se a qualquer altura, ou recusar participar, sem que tal fato tenha consequências para si.

Se tiver qualquer questão ou apreensão com este estudo, poderá contactar as seguintes pessoas:
Autora: Laura Nedel Duarte Email: lauranedeld@hotmail.com
Supervisor: Dr. Miguel Coutinho Email: miguelcoutinho@grupohpa.com

Assinatura: _____Data: _____

Appendix D. Hospital Consent Form



GRUPO HPASAUDE

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO
GERAL

Colar Etiqueta do Paciente

ORIGINAL – para o processo clínico

PROFISSIONAL DE SAÚDE

PROCEDIMENTO/ATO PROPOSTO (letra legível, sem abreviaturas):

LATERALIDADE: DIREITO(A) ___ ESQUERDO(A) ___ NÍVEL: _____ NÃO APLICÁVEL: ___

Declaro que forneci ao utente todos os esclarecimentos relativos ao objetivo do procedimento, benefícios esperados, riscos, complicações e sequelas que daí possam advir. Foi dada também a garantia, da minha parte, que até ao início do tratamento proposto existe a possibilidade de revogação do consentimento, sem prejuízo dos seus direitos assistenciais.

Nome do Profissional: MIGUEL CAETANO / LARA NEDEL QUARTE

Categoria Profissional: NEUROPSICOLOGIA Assinatura:

N.º Mec/OM: E285 / OPP 5334 Data: ___/___/20___

PACIENTE/REPRESENTANTE

Declaro *ter compreendido* os objetivos do procedimento/ato que me foi proposto pelo profissional de saúde que assina este documento, *ter-me sido dada oportunidade* de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora e *ter-me sido dado tempo* suficiente para refletir sobre esta proposta. Assim, autorizo o ato/procedimento indicado, bem como todos os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas. Considero-me esclarecido sobre a possibilidade de revogar este consentimento até ao momento da realização do procedimento/ato proposto.

Declaro também que:

1.Compreendo que não exista garantia absoluta sobre os resultados que possam vir a ser obtidos.

2.Recebi todas as explicações quanto aos tratamentos alternativos, as possibilidades de ter os resultados que espero e problemas/riscos potenciais que possam ocorrer durante o procedimento e recuperação, além dos riscos que existem em não realizar o procedimento.

3.Confirmo que recebi, para além da informação verbal prestada do procedimento/ato, informação escrita sobre o procedimento/ato que irei realizar onde consta informação sobre o mesmo e os respetivos riscos associados.

Recebi ☐ Não Recebi ☐

Nome: _____ Data: [redacted]

Assinatura: _____ Doc. Identificação: _____

TESTEMUNHAS

Caso o paciente não saiba assinar

Testemunha 1: Nome: _____ Assinatura: _____

Doc. Identificação: _____ Data: ___/___/20___

Testemunha 2: Nome: _____ Assinatura: _____

Doc. Identificação: _____ Data: ___/___/20___

Appendix E. Average z-scores for the entire OSA cohort.

Measure	OSA sample N = 38			
	M	*SD*	Minimum	Maximum
MoCA	-1.00	1.27	-4.95	2.28
D2[a]	50.00	33.84	1	99
RCF Copy	.38	1.06	-3.77	1.41
AVLT Immediate	-.43	.87	-2.33	1.33
AVLT Delayed	-.83	.99	-2.33	1.33
AVLT Recognition	1.29	1.89	-1.67	2.67
Digit Span Forward	.07	.69	-1.15	2.00
RCF Recall	-.24	.70	-1.54	1.27
Logic Memory I	-.26	.61	-1.67	.67
Logic Memory II	-.31	.67	-1.67	1.33
Digit Span Backward	.16	.57	-.92	1.90
TMT-A	.17	.98	-2.33	2.33
TMT-B	-.11	1.15	-2.33	2.33
Stroop	-.13	.56	-1.32	1.10
Phonemic Fluency	.05	.85	-2.33	1.67
Semantic Fluency	-.11	.87	-2.33	1.67
Similarities	.62	.74	-1.67	2.00
Matrix	.43	.82	-1.00	2.00

Appendix F. Correlation coefficients values between clinical variables and neuropsychological performances of OSA patients.

		CRIq	ISI	BMI
MoCA	*r*	-.05	.03	-.17
	p	.758	.835	.294
D2	*r*	.06	-.06	.24
	p	.728	.714	.143
RCF Copy	*r*	.27	.12	-.12
	p	.099	.455	.478
AVLT Immediate	*r*	-.05	-.11	.00
	p	.745	.508	.990
AVLT Delayed	*r*	.12	.21	-.12
	p	.489	.205	.474
AVLT Recognition	*r*	-.07	.06	.20
	p	.677	.707	.234
Digit Span Forward	*r*	.37	.06	.10
	p	.020	.719	.529
RCF Recall	*r*	.01	.30	-.17
	p	.944	.068	.308
LM Immediate	*r*	.29	.07	.18
	p	.076	.695	.281
LM Delayed	*r*	.20	-.01	.20
	p	.242	.948	.232
Digit Span Backward	*r*	.23	.02	-.05
	p	.155	.906	.756
TMT-A	*r*	-.02	-.16	-.21
	p	.913	.344	.205
TMT-B	*r*	.20	.04	-.01
	p	.232	.802	.951
Stroop	*r*	.22	-.09	-.09
	p	.183	.571	.602
Phonemic Fluency	*r*	-.23	-.18	-.12
	p	.160	.265	.471
Semantic Fluency	*r*	-.19	-.31	.06
	p	.250	.060	.699
Similarities	*r*	.40	-.16	.04
	p	.013	.351	.831
Matrices	*r*	.32	.34	.08
	p	.053	.035	.645

Note: CRIq: Cognitive Reserve Index. ISI: Insomnia Sleep Index. BMI: Body Mass Index. RCF: Rey Complex Figure. AVLT: Auditory Verbal Learning Test- immediate recall, delayed free recall and recognition scores. LM: Logic Memory. TMT: Trail Making Test.

Appendix G. Regression Analysis Summary for OSA factors and clinical factors predicting MoCA Performance.

Regression analysis summary for ODI and clinical factors predicting MoCA performance.

Model		B	SE b	β
1	(Constant)	-.11	1.80	
	BDI	-.43	.30	-.26
	HTA	.53	.46	.20
	DM	-.51	.77	-.12
2	(Constant)	-.01	1.88	
	BDI	-.43	.31	-.26
	HTA	.53	.47	.20
	DM	-.52	.79	-.12
	ODI	.00	.01	.00

Note. BDI: Beck Depression Inventory; HTA: Hypertension; DM: Diabetes Mellitus; ODI: Oxygen Desaturation Index.

Regression analysis summary for SpO_2<90% and clinical factors predicting MoCA performance.

Model		B	SE b	β
1	(Constant)	-.01	1.81	
	BDI	-.46	.31	-.27
	HTA	.49	.47	.18
	DM	-.51	.78	-.12
2	(Constant)	-.01	1.81	
	BDI	-.48	.31	-.28
	HTA	.60	.48	.22
	DM	-.66	.80	-.15
	SpO_2<90%	.02	.02	.16

Regression analysis summary for EDS and clinical factors predicting MoCA performance.

Model		B	SE b	β
1	(Constant)	-.11	1.79	
	BDI	-.43	.30	-.26
	HTA	.53	.46	.20
	DM	-.52	.77	-.12
2	(Constant)	-.81	1.84	
	BDI	-.55	.31	-.33
	HTA	.59	.46	.22
	DM	-.44	.77	-.10
	EDS	.06	.04	.24

Appendix H. Regression Analysis Summary for OSA factors and clinical factors predicting D2 Performance.

Regression analysis summary for ODI and clinical factors predicting D2 performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	46.05	48.19		.346	1.18	.097	.097
	BDI	-6.32	7.57	-.15	.410			
	HTA	-11.26	11.65	-.17	.341			
	DM	15.81	21.06	.13	.458			
2	(Constant)	44.83	49.24		.369	.873	.098	.001
	BDI	-6.22	7.70	-.15	.425			
	HTA	-11.08	11.85	-.16	.356			
	DM	15.41	21.45	.13	.478			
	ODI	.06	.30	.04	.833			

Regression analysis summary for SpO2<90% and clinical factors predicting D2 performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	50.59	47.94		.299	1.44	.119	.119
	BDI	-7.18	7.54	-.17	.348			
	HTA	-12.88	11.63	-.19	.276			
	DM	15.98	20.89	.13	.450			
2	(Constant)	50.50	48.57		.307	1.09	.124	.005
	BDI	-7.46	7.67	-.17	.339			
	HTA	-11.70	12.12	-.17	.342			
	DM	14.28	21.55	.12	.512			
	SpO_2<90%	.20	.47	.07	.679			

Regression analysis summary for EDS and clinical factors predicting D2 performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	46.05	48.18		.346	1.18	.097	.097
	BDI	-6.32	7.57	-.15	.410			
	HTA	-11.26	11.65	-.18	.341			
	DM	15.81	21.06	.13	.458			
2	(Constant)	46.94	50.51		.360	.862	.097	.000
	BDI	-6.17	7.99	-.14	.446			
	HTA	-11.33	11.87	-.17	.347			
	DM	15.72	21.42	.13	.468			
	EDS	-.07	1.02	-.01	.943			

Appendix I. Regression Analysis Summary for OSA factors and clinical factors predicting AVLT immediate recall (AVLT I) performance.

Regression analysis summary for ODI and clinical factors predicting AVLT I performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.34	1.16		.774	.53	.045	.045
	BDI	-.17	.20	-.16	.389			
	HTA	-.20	.30	-.12	.500			
	DM	-.10	.50	-.04	.842			
2	(Constant)	.314	1.217		.307	.39	.045	.000
	BDI	-.172	.200	-.161	.339			
	HTA	-.201	.307	-.116	.342			
	DM	-.099	.510	-.036	.512			
	ODI	.001	.008	.013	.679			

Regression analysis summary for SpO2<90% and clinical factors predicting AVLT I performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.45	1.15		.697	.73	.062	.062
	BDI	-.20	.20	-.18	.325			
	HTA	-.25	.30	-.14	.413			
	DM	-.09	.50	-.03	.852			
2	(Constant)	.45	1.12		.692	1.27	.137	.075
	BDI	-.17	.19	-.16	.385			
	HTA	-.37	.30	-.21	.231			
	DM	.08	.50	.03	.867			
	SpO_2<90%	-.02	.01	-.29	.106			

Regression analysis summary for EDS and clinical factors predicting AVLT I performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.34	1.16		.774	.53	.045	.045
	BDI	-.17	.20	-.16	.389			
	HTA	-.20	.30	-.13	.500			
	DM	-.10	.50	-.04	.842			
2	(Constant)	-.08	1.20		.944	.81	.090	.045
	BDI	-.24	.20	-.23	.238			
	HTA	-.17	.30	-.10	.575			
	DM	-.05	.50	-.02	.912			
	EDS	.03	.03	.22	.211			

Appendix J. Regression Analysis Summary for OSA factors and clinical factors predicting AVLT delayed recall (AVLT II) performance.

Regression analysis summary for ODI and clinical factors predicting AVLT II performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	-1.32	1.30		.317	.84	.069	.069
	BDI	-.22	.22	-.18	.333			
	HTA	.44	.34	.22	.194			
	DM	.11	.56	.04	.840			
2	(Constant)	-1.25	1.37		.367	.62	.071	.001
	BDI	-.22	.22	-.18	.339			
	HTA	.43	.34	.22	.215			
	DM	.11	.57	.03	.851			
	ODI	.00	.01	-.04	.831			

Regression analysis summary for SpO2<90% and clinical factors predicting AVLT II performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	-1.27	1.32		.342	.81	.069	.069
	BDI	-.23	.22	-.19	.319			
	HTA	.43	.34	.21	.221			
	DM	.12	.57	.04	.837			
2	(Constant)	-1.27	1.33		.346	.77	.088	.019
	BDI	-.24	.23	-.20	.292			
	HTA	.49	.35	.25	.172			
	DM	.02	.59	.00	.979			
	SpO_2<90%	.01	.01	.14	.423			

Regression analysis summary for EDS and clinical factors predicting AVLT II performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	-1.32	1.30		.317	.84	.069	.069
	BDI	-.22	.22	-.18	.333			
	HTA	.44	.34	.22	.194			
	DM	.11	.56	.04	.840			
2	(Constant)	-1.30	1.38		.351	.61	.069	.000
	BDI	-.21	.23	-.18	.367			
	HTA	.44	.34	.22	.205			
	DM	.11	.57	.03	.846			
	EDS	.00	.03	-.01	.957			

Appendix K. Regression Analysis Summary for OSA factors and clinical factors predicting RCF recall performance.

Regression analysis summary for ODI and clinical factors predicting RCF recall performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.11	.87		.899	.25	.183	.183
	BDI	-.01	.15	-.01	.970			
	HTA	.48	.22	.34	.038			
	DM	-.55	.38	-.24	.156			
2	(Constant)	.12	.91		.900	1.85	.183	.000
	BDI	-.01	.15	-.01	.971			
	HTA	.48	.23	.34	.044			
	DM	-.55	.38	-.24	.163			
	ODI	.00	.01	.00	.984			

Regression analysis summary for SpO2<90% and clinical factors predicting RCF recall performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.17	.88		.850	2.26	.170	.170
	BDI	-.02	.15	-.02	.910			
	HTA	.46	.23	.33	.050			
	DM	-.54	.38	-.24	.161			
2	(Constant)	.17	.89		.851	1.71	.176	.006
	BDI	-.02	.15	-.03	.881			
	HTA	.49	.24	.35	.047			
	DM	-.58	.39	-.26	.148			
	SpO_2<90%	.00	.01	.08	.646			

Regression analysis summary for EDS and clinical factors predicting RCF recall performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.11	.87		.899	2.54	.183	.183
	BDI	-.01	.15	-.01	.970			
	HTA	.48	.22	.34	.038			
	DM	-.55	.38	-.24	.156			
2	(Constant)	-.22	.89		.810	2.39	.225	.045
	BDI	-.06	.15	-.07	.687			
	HTA	.51	.22	.36	.028			
	DM	-.51	.37	-.22	.181			
	EDS	.03	.02	.22	.192			

Appendix L. Regression Analysis Summary for OSA factors and clinical factors predicting TMT-B performance.

Regression analysis summary for ODI and clinical factors predicting TMT-B performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.85	1.50		.573	1.19	.095	.095
	BDI	-.47	.25	-.33	.074			
	HTA	.11	.39	.05	.769			
	DM	-.19	.65	-.05	.776			
2	(Constant)	.92	1.57		.560	.88	.096	.001
	BDI	-.47	.26	-.33	.078			
	HTA	.10	.40	.04	.794			
	DM	-.19	.66	-.05	.772			
	ODI	.00	.01	-.03	.855			

Regression analysis summary for SpO2<90% and clinical factors predicting TMT-B performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.87	1.52		.574	1.61	.095	.095
	BDI	-.47	.26	-.33	.078			
	HTA	.11	.39	.05	.783			
	DM	-.18	.66	-.05	.780			
2	(Constant)	.87	1.55		.579	.86	.098	.002
	BDI	-.48	.26	-.33	.079			
	HTA	.14	.41	.06	.744			
	DM	-.22	.68	-.06	.744			
	SpO_2<90%	.00	.02	.05	.788			

Regression analysis summary for EDS and clinical factors predicting TMT-B performance.

Model		B	SE b	β	*p*	*F*	R_2	ΔR_2
1	(Constant)	.85	1.50		.573	1.19	.095	.095
	BDI	-.47	.25	-.33	.074			
	HTA	.11	.39	.05	.769			
	DM	-.19	.65	-.05	.776			
2	(Constant)	1.11	1.57		.484	.97	.105	.010
	BDI	-.42	.27	-.30	.122			
	HTA	.09	.39	.04	.814			
	DM	-.21	.66	-.06	.746			
	EDS	-.02	.03	-.10	.551			

Appendix M. Comparisons between neuropsychological test means according to EDS severity using multivariate analysis of covariance (MANCOVA) – entire sample.

Measure	Mild EDS n = 22		Moderate EDS n = 18		Severe EDS n = 12			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
MoCA	-1.39	1.69	-1.27	.76	-.59	1.34	2.62	.083
D2[a]	59.59	34.98	39.50	26.53	49.50	34.12	1.99	.147
RCF Copy	.26	.99	.44	1.13	.63	.33	.60	.552
AVLT Immediate	-.63	.93	-.63	.91	-.35	.79	1.93	.157
AVLT Delayed	-.75	.94	-.92	1.01	-.77	.75	.34	.713
AVLT Recognition	1.83	1.62	.62	1.97	1.58	1.96	1.83	.171
Digit Span Forward	-.02	.78	.05	.64	-.10	57	.57	.570
RCF Recall	-.46	.67	-.24	.87	-.17	.49	1.13	.331
Logic Memory I	-.27	.46	-.48	.56	-.11	.55	1.13	.290
Logic Memory II	-.13	.55	-.64	.78	-.13	.50	2.95	.062
Digit Span Backward	.20	.69	.03	.43	.16	.48	1.12	.335
TMT-A	.18	1.11	-.05	.58	.00	.88	.66	.523
TMT-B	-.06	1.14	-.20	.68	-.03	1.22	1.11	.339
Stroop	-.03	.61	-.16	.73	-.40	.40	1.31	.278
Phonemic Fluency	-.30	.93	-.03	1.10	.11	.54	2.09	.135
Semantic Fluency	-.12	.80	.12	1.07	-.24	.77	.60	.553
Similarities	.45	.54	.64	.88	.58	.65	.91	.411
Matrices	.36	.84	.29	.87	.27	.82	.11	898

Appendix N. Correlations between hypoxemia indexes and neuropsychological test performances.

Correlation coefficient values between ODI and neuropsychological test performances.

Measure	ODI		Measure	ODI	
	R	*p*		*R*	*p*
MoCA	.06	.655	Logic Memory II	.00	.984
D2	.09	.535	Digit Span Backward	.22	.119
RCF Copy	.04	.760	TMT-A	.21	.132
AVLT Immediate	.03	.843	TMT-B	-.01	.935
AVLT Delayed	-.06	.676	Stroop	.02	.862
AVLT Recognition	.03	.816	Phonemic Fluency	.15	.274
Digit Span Forward	.11	.432	Semantic Fluency	.03	.826
RCF Recall	.04	.749	Similarities	-.07	.595
Logic Memory I	-.01	.943	Matrices	.17	.212

Correlation coefficient values between SpO_2<90% and neuropsychological test performances.

Measure	SpO_2<90%		Measure	SpO_2<90%	
	R	*p*		*R*	*p*
MoCA	.09	.607	Logic Memory II	.07	.671
D2[a]	.16	.36	Digit Span Backward	.15	.363
RCF Copy	.03	.88	TMT-A	.03	.877
AVLT Immediate	-.22	.18	TMT-B	.04	.831
AVLT Delayed	-.09	.570	Stroop	-.01	.968
AVLT Recognition	.08	.623	Phonemic Fluency	-.20	.226
Digit Span Forward	.23	.164	Semantic Fluency	.01	.951
RCF Recall	.03	.879	Similarities	.03	.849
Logic Memory I	-.10	.572	Matrices	.13	.425