Differential associations of hypoxia, sleep fragmentation and depressive symptoms with cognitive dysfunction in obstructive sleep apnoea

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Abstract

Obstructive sleep apnoea (OSA) is characterized by recurrent episodes of partial or complete cessation of breathing during sleep and increased effort to breathe. This study examined patients who underwent overnight polysomnographic studies in a major sleep laboratory in Saudi Arabia. The study aimed to determine the extent to which intermittent hypoxia, sleep disruption and depression are independently associated with cognitive impairments in OSA. In the sample of 90 participants, 14 had no OSA, 30 mild OSA, 23 moderate OSA and 23 severe OSA. The findings revealed that hypoxia and sleep fragmentation are independently associated with impairments of sustained attention and reaction time. Sleep fragmentation but not hypoxia, was independently associated with impairments in visuospatial deficits. Depressive symptoms were independently associated with impairments in the

domains of sustained attention, reaction time, visuospatial ability, and semantic and episodic autobiographical memories. Since the depressive symptoms are independent of hypoxia and sleep fragmentation, effective reversal of cognitive impairment in OSA may require treatment interventions that target each of these factors.

Keywords: Sustained attention; reaction time; visuospatial ability; autobiographical memory, vitamin D.

Statement of Significance

A high proportion of people with OSA display cognitive impairment. It is widely considered that cognitive impairment is due to the effects of intermittent hypoxia and/or sleep fragmentation. The present study has confirmed that hypoxia and sleep fragmentation contribute independently to impairments in sustained attention and reaction time, while sleep fragmentation independently contributes to visuospatial deficits. The study also showed that depressive symptoms independently contribute to impairments in sustained attention, reaction time, visuospatial ability and autobiographical memory. The contribution of depressive symptoms has been overlooked until now, and the present findings indicate that full recovery of cognition in OSA patients may require interventions that address the depressive symptoms as well as the hypoxia and sleep fragmentation.

Introduction

Obstructive Sleep Apnoea (OSA) is a sleep disorder characterised by repetitive episodes of airway obstruction, which lead to transient hypoxia and sleep fragmentation (Young et al., 1993). According to recent estimates, the global prevalence of OSA ranges from 9% to 38% in middle-aged individuals (Senaratna et al., 2017). Clinical interventions, particularly continuous positive airway pressure (CPAP), can diminish OSA severity (Schwarz et al., 2018). People with untreated OSA frequently exhibit impairment on tests of memory, attention and visuospatial ability (Ayalon, Ancoli-Israel, Aka, et al., 2009; M. Olaithe et al., 2018; Wallace & Bucks, 2013), and are 7.5-20 times more likely to have difficulty with concentration, executing monotonous tasks and learning new tasks (Beebe & Gozal, 2002; Ulfberg et al., 1996). Due to decreased concentration and sleepiness, individuals with

OSA have an increased risk of occupational and motor vehicle accidents (Garbarino et al., 2016; Kales & Czeisler, 2016), which in turn, leads to injuries, death and an increased economic burden on society. Despite widespread agreement that OSA is associated with an increased risk of cognitive impairment, there is no consensus regarding the probable causes of this impairment.

The three favoured causes are hypoxia, sleep fragmentation and depression. For instance, neuroimaging studies have shown that individuals with OSA have structural changes in the brain that are associated with cognitive impairment, and the extent of these changes increases with higher levels of hypoxia, as measured during polysomnography (PSG) (Lal et al., 2012). Hypoxia in OSA patients has been linked to impairments in global cognitive function (Yaffe et al. (2011), and long-term memory and attention (Findley et al., 1986). Some OSA studies have found that hypoxemia is associated with grey matter hypertrophy, presumably due to oedema (Baril et al., 2017).

The arousals associated with apnoea events interrupt sleep (Kimoff, 1996). The restorative processes that occur in the brain during sleep are impaired by sleep disruption and this is thought to contribute to biochemical and cellular stress that leads to poorer cognitive performance (Beebe & Gozal, 2002). Ayalon, Ancoli-Israel and Drummond (2009) found that sleep fragmentation, but not hypoxia, in OSA patients is associated with significantly poorer reaction times during a sustained attention task. Moreover, Thomas et al. (2005) suggested that cognitive dysfunction may not necessarily be caused by hypoxia, but rather by sleep fragmentation. In a review of the literature Bucks et al. (2013) pointed out that sleep fragmentation has a more profound effect than hypoxia on attention and memory, and they concluded that sleep fragmentation may contribute to a slowing of cognitive processing. An experimental study that examined the effects of sleep disturbances on cognition confirmed that sleep fragmentation can impair cognitive functioning, even in young healthy subjects (Ferri et al., 2010). Animal studies have also demonstrated that sleep fragmentation can cause hippocampal memory impairments (Nair et al., 2011).

It is well established that individuals with depressive symptoms, but without any other comorbid condition, exhibit cognitive deficits that can include memory loss, visuospatial deficits, and

an inability to pay attention during routine activities (Faust et al., 2017; Kaser et al., 2017). Depression is frequently observed in patients with moderate-severe OSA (Shoib et al., 2017) and some studies have suggested that it may play a role in cognitive dysfunction (Delhikar et al., 2019a). A neuroimaging study Cross et al. (2008) compared patients with OSA and depressive symptoms to OSA patients without depressive symptoms, and found that OSA patients with depressive symptoms had more extensive areas of brain injury. Research also indicates a connection between autobiographical memory and depression, with lower specificity of autobiographical memory being associated with depressive symptoms (Mackinger & Svaldi, 2004). However, it is not known whether the depressive symptoms observed in OSA are caused by hypoxia or sleep disruption, or whether they have a separate aetiology. Thus, it is possible that depressive symptoms are not an independent contributor to cognitive impairment in OSA.

The primary aim of the present study was to determine the extent to which intermittent hypoxia, sleep disruption and depression are each independently associated with cognitive impairment in OSA.

METHODS

Study participants

The study participants were patients who had been referred for overnight diagnostic PSG studies at the Sleep Medicine and Research Centre, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The following exclusion criteria were applied: (1) aged below 18 years or above 65 years; (2) current use of CPAP therapy; (3) a neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease); and/or (4) regularly sleeping less than two hours per night based on the American Academy of Sleep Medicine (AASM) criteria that recommends the minimum duration of PSG as two hours (Epstein et al., 2009). Ninety out of a sample of 100 patients who presented sequentially to the Sleep Medicine and Research Centre met the study inclusion criteria.

The study was approved by the Royal Melbourne Institute of Technology University Human Research Ethics Committee (ethics number HREC 39518) and the King Abdulaziz University Hospital Human Research Ethics Committee (ethics number HREC 21459). Informed consent was obtained from

all participants after they received an explanation of the nature of the study at the Sleep Medicine and Research Centre.

Procedure and measurements

After consenting to participating in the study and being admitted to the sleep laboratory, the participants' height and weight were measured by a nurse. Participants then completed a series of questionnaires designed to collect demographic information, daytime sleepiness, and mood levels. This was followed by a battery of cognitive assessments and a standard overnight PSG study.

Questionnaires

The Epworth Sleepiness Scale (ESS) Arabic version (Ahmed et al., 2014; Johns, 1991).

This sleepiness scale assesses general level of daytime sleepiness and is frequently used to assess the impact of sleep disorders. The scale consists of eight items, each rated from 0 to 3, with higher numbers indicating a higher chance of dozing. The scores from the eight items are summed to give the overall score. Higher scores reflect greater levels of sleepiness. Scores of less than 11 represent little or no daytime sleepiness; scores between 11 and 14 indicate mild daytime sleepiness; scores between 15 and 17 reflect moderate daytime sleepiness; and scores over 17 indicate severe daytime sleepiness.

Depression, Anxiety, Stress Scale-21 (DASS-21) (*Arabic version) (Ali et al., 2017; Henry & Crawford, 2005).*

This 21-item questionnaire is designed to measure the magnitude of three negative emotional states, including depression. The DASS depression subscale focusses on reports of low mood, motivation and self-esteem. There is convergent validity between the DASS Depression and Anxiety scales and the Beck Depression and Anxiety inventories (Lovibond & Lovibond, 1995).

Polysomnography evaluation

Overnight PSG (SOMNO Medics Plus, SOMNOmedics, Randersacker, Germany) was used to assess OSA. While most of the PSG studies were conducted at the Sleep Medicine and Research Centre, 15 studies were performed in patients' homes for reasons mainly related to patient convenience. The same PSG devices and procedures were used in these home studies as in the Sleep Centre. For all PSG

studies, a sleep technician wired up PSG sensors half an hour before the sleep time. PSG consisted of a ten-channel recording montage (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2), which was used to measure EEG activity. Left and right electrooculography, electrocardiography and submental electromyography (EMG), oronasal airflow (using a thermal sensor and nasal pressure transducer), body position, thoracic and abdominal excursion (inductance plethysmograph), oxygen arterial blood saturation (SaO_2) measured with finger pulse oximetry, left and right leg movement (EMG channel) and a sound recorder were used.

Neurobehavioral evaluation

Psychomotor Vigilance Task - 10 minutes (PVT) (Dinges & Powell, 1985).

This is a computerised visual test that evaluates the ability to sustain attention and respond with a button press in a timely manner to cues that are presented on the screen. The reliability and validity of the 10 minutes version of the test has been confirmed by previous studies (Dinges & Powell, 1985). The test is sensitive to sleep disruption and serves to indicate a sustained attention deficit (Jung et al., 2011). Three PVT outcome measures were used in the present study: (1) mean Reaction Time (RT); (2) mean of the slowest 10% RT; (3) number of lapses with a RT greater than 500 milliseconds. When RT is greater than 100 milliseconds, it is measured as valid. When RT is lower than 100 milliseconds or responses occur without a stimulus being presented, they are recorded as false starts.

Austin Maze-10 trails (AM) (Milner, 1965).

This computerised maze measures visuospatial ability and visuospatial memory (Crowe et al., 1999; Stolwyk et al., 2013). Participants plot a course through a chequerboard maze by pushing buttons and identifying the correct order through trial-and-error. Each time the correct button is pushed, a green light is displayed; when an incorrect button is pushed, a red light is displayed and a buzzer sounds. The current study allowed for a maximum of 10 trials because the literature shows a strong correlation between errors that occur up to the 10th trial of an experiment and errors to criterion (Bowden et al., 1992).

The Autobiographical Memory Interview (AMI) (Kopelman et al., 1989).

This method measures both episodic and semantic memory. Memories were assessed for three stages in the person's lifespan: childhood (before high school); early adulthood (usually including

career, relationships, marriage and children); and recent life (acknowledging present and previous hospital or institution stays over the previous five years as well as last holidays or journeys). Scoring was based on the AMI guidelines (Kopelman et al., 1989). Regarding episodic memory, participants scored 3 for full recall that included specifics in time and place, 2 for recall that was personal but general, 1 for an unclear personal memory, and 0 for no answer or a semantic memory. There was a maximum of nine points for each time period (total score maximum = 27). For semantic memory (i.e., names), responses were weighted on the level of detail retained (i.e., house number, street name and district) with a maximum of 21 points for each time period (total maximum = 63). The AMI has a high level of accuracy, reliability and validity. The first author of the current study (RA) translated the English language version of the AMI results into Arabic. Two other Arabic-speaking researchers reviewed the translation and suggested refinements in expressions, phrasing and concepts. The AMI interviews were then translated into English by an independent bilingual translator with no knowledge of the topic. After the original and the translated interviews were compared, no significant differences in the content were evident.

Analyses

The participants' BMI calculation was based on the international standard of dividing weight, in kilograms, by body height in metres squared (Nuttall, 2015). PSG recordings were scored using an algorithm, then checked by manually scoring all records according to the AASM 2012 scoring protocol (Berry et al., 2012). The description of abnormal breathing events during sleep was based on AASM recommendations (Berry et al., 2012). Breathing abnormalities were defined as follows: a decrease in airflow of 90% or higher from the baseline for at least 10 seconds (apnoea) and a discernible reduction in airflow of at least 30% of the pre-event baseline using nasal pressure, associated with a reduction in oxygen saturation of at least 3% and followed by either oxygen desaturation or an electroencephalographic arousal (hypopnoea), despite persistent effort of the chest and abdominal muscles to overcome the obstruction. The severity of OSA was estimated from the Apnoea-hypopnoea index (AHI). The degree of hypoxia was identified by SaO_2 time duration (in seconds) below 90%. The degree of sleep fragmentation was assessed by the Arousal Index that was calculated by dividing the total number of arousals by the duration of sleep (arousals/h). In addition, the duration of non-rapid eye

movement (NREM) sleep stages N1, N2, and N3; and the duration of the rapid eye movement (REM) sleep stage were analysed. Three PSG technicians verified all PSG scores to ensure the quality of the scoring process. The technicians also randomly selected and scored cases to confirm inter-observer reliability and accuracy.

Test data for the PVT and AM were calculated using software algorithms developed for each task. The AMI scores were based on the AMI guidelines and were consecutively scored and revised by the same researcher who followed the same calculation procedures for all participants. while the degree of sleep fragmentation was assessed by the arousal index that ended apnoeic events

Statistical analyses were performed with IBM SPSS version 26 (IBM Corp., Armonk, NY, USA). Data from continuous variables were reviewed to determine whether any had extremely skewed distributions. Consequently, log transformation was performed to normalize the distribution of the following variables: PVT mean, PVT slowest 10%, AM-time, AM-errors, AMI childhood semantic memory, AMI adult early life memory, AMI recent life memory. The data were expressed as means and standard deviations for continuous variables and as the frequencies and percentages for categorical variables. Analysis of variance (ANOVA) with Bonferroni *post-hoc* analyses were used to determine significant differences between OSA and demographic variables, depressive symptoms, daytime sleepiness, and PSG parameters. Between-group comparisons of categorical data were made using the Pearson's Chi-square. Sample linear regression was used to determine the associations between SaO_2 time <90%, arousal index and depressive symptoms. To examine the associations between depressive symptoms and demographic data multiple linear regression was conducted. Pearson bivariate correlations was also used to demonstrate the relationship between potential confounders and cognitive tests. Thereby, multiple linear regression analysis has been used to reveal the association between hypoxia, sleep fragmentation and depressive symptoms with cognitive dysfunction. All models were corrected for multiple comparisons with the false discovery rate (FDR) (Benjamini & Hochberg, 1995), and multicollinearity was demonstrated using a variance inflation factor (VIF) of <2.0. Accordingly, the statistical significance was reported for models that were at a $p < 0.05$ after having been adjusted for multiple comparisons with the FDR and/or models which showed no multicollinearity, as assumed with a variance inflation factor of < 2.0.

Results

The PSG results showed that 14 of the 90 participants did not have OSA, 30 had mild OSA, 23 had moderate OSA and 23 had severe OSA. The mean patient age was 42.0 (*SD* =12.7) and the mean BMI was 33.4 (*SD*=9.4).

Table 1 shows comparisons of the dependent variables, based on grouping participants according to their AHI score (14 no OSA, 30 mild OSA, 23 moderate OSA, 23 severe OSA). Participants in the severe OSA group were older than those in the non-OSA group. However, ESS score and depression did not increase significantly with OSA severity. BMI was not significantly different between the four groups. Significant differences were found between OSA severity groups for sleep parameters including SaO_2, time spent <90%, and the arousal index. The durations of sleep stages N1, N3 and REM differed significantly and systematically between the OSA severity groups, whereas the duration of N2 did not differ significantly.

(Insert Table 1)

Linear regression analysis revealed moderate significant relationship between SaO2 time <90% and arousal index ($R^2 = 0.31$). Although depressive symptoms were not correlated with any of the PSG factors, the result indicated a significant association between depressive symptoms and daytime sleepiness, as measured by the ESS (Table 2).

(Insert Table 2)

To detect the potential confounding variables, Pearson bivariate correlations were conducted. The results revealed that age was positively associated with performance on all PVT and AM indices, as well as most of the stages of the AMI episodic memories (total episodic memory, episodic early adult life memory and episodic recent life memory), but age was not associated with any stage of semantic memory. Smoking was positively associated with AM-time and AMI episodic recent life memory. Daytime sleepiness was not associated with performance on any of the cognitive tests.

Multiple linear regression analyses were performed to determine whether hypoxia, depressive symptoms and sleep fragmentation independently influence performance on the PVT, AM and AMI. The confounding variables (age and smoking status) that were associated with individual cognitive tests were included in the regression models in addition to the other independent factors.

After FDR adjustments, all models that included PVT and AM variables remained significant at $p<0.05$, whereas models that included four of the AMI variables (childhood semantic memory, early adult life semantic memory, episodic childhood memory, and episodic early adult life memory) were no longer significant at $p<0.05$. Additionally, all models showed no multilinearity according to VIF <2.0.

The results indicated that performance on all three PVT indices was associated with hypoxia and depressive symptoms, while sleep fragmentation was associated with mean PVT and PVT reaction time lapses >500ms but not with PVT slowest 10%. Performance on the AM time and AM errors was associated with depressive symptoms and sleep fragmentation but not with hypoxia (Table 3).

(Insert Table 3)

The AMI, which measures episodic and semantic memory within life stages, did not show any relationships with either hypoxia or sleep fragmentation. However, depressive symptoms were positively associated with deficits in both semantic and episodic total memory (Table 4). In addition, depressive symptoms were positively associated with recent life semantic memory, whereas the other measures of episodic and semantic memories were not significantly associated with any of the independent variables (Table 4).

(Insert Table 4)

Discussion

Ninety participants who had been sequentially admitted to a sleep clinic for an overnight diagnostic PSG, were investigated to determine whether intermittent hypoxia, sleep disruption and/or depressive symptoms are independently associated with cognitive impairments in OSA. Our findings revealed that hypoxia and sleep fragmentation are independently associated with impairments in sustained attention and reaction time. Moreover, sleep fragmentation is independently associated with impairments in visuospatial ability. Depressive symptoms are independently associated with impairments in the domains of sustained attention, reaction time, visuospatial ability, and semantic and episodic memories.

Intermittent hypoxia

Intermittent hypoxia is one of the prominent features of OSA and it has been extensively studied, since it has been linked to brain injury. After controlling for demographic variables, sleep fragmentation and depression, the present study revealed that hypoxia is an independent contributor to impairments on the PVT-10. These findings are consistent with those of a larger study of 912 participants which found that, after adjusting for demographic variables, the severity of intermittent hypoxia was significantly associated with impaired performance on the PVT-10 (Kainulainen et al., 2020). Similarly, a Japanese study reported that sleep-related intermittent hypoxia, as measured by the oxygen desaturation index, was significantly associated with a deterioration of mean RT and number of lapses on the PVT (Tanno et al., 2017). It has also been shown that healthy individuals exposed to experimental hypoxia recorded higher RT's on the PVT-10 task (Fowler et al., 1987). Collectively, these results support the conclusion that the severity of intermittent hypoxia in OSA contributes to a slowing of response times and an impairment of sustained attention. It is noteworthy that neonatal hypoxia in rats leads to a reduction in the size of neurons in the amygdala, which in turn, contributes to a loss of corticotrophin-releasing factor-positive axons that subserve attentional processes (Carty et al., 2010). Although it is not yet known whether similar neuronal losses occur in OSA, brain imaging studies have reported reductions in the volume of the amygdala in patients with severe OSA (Yu et al., 2019). The amygdala has been shown to play an important role in attentional processes (Baxter & Murray, 2002).

Sleep fragmentation

The present study revealed that sleep fragmentation is independently associated with impairments in sustained attention and reaction time and visuospatial ability. These findings are in line with earlier studies. For instance, Bonnet and Arand (2003) found that sleep fragmentation is as effective as sleep deprivation at impairing psychomotor vigilance. Similarly, Ayalon, Ancoli-Israel and Drummond (2009) compared 14 patients with OSA with 14 healthy control individuals and reported that a higher arousal index is associated with slower mean reaction times and decreased brain activation. Furthermore, although there are limited studies that consider the mechanism behind the visuospatial deficits in OSA, a recent meta-analysis review undertaken by Olaithe et al. (2018), concluded that visuospatial deficits are unique to OSA when compared to other sleep disorders such as insomnia, and breathing disorders such as chronic obstructive pulmonary disease, suggesting that the mechanism of

the visuospatial deficits in OSA might not be attributed to hypoxia, hypocapnia or sleep deprivation. However, the present study found for the first time that sleep fragmentation was independently associated with visuospatial deficits. Thus, the current findings support Olaithe and colleagues' statement that *"insomnia may be a poor exemplar of chronic sleep disruption experienced in OSA"* (p. 47).

Depressive symptoms

The present study revealed that depressive symptoms are independently associated with slower response times and impairments in sustained attention, as indicated by poorer performance on the PVT-10 and slower times and errors on the AM-10T. Although previous studies have not examined the influence of depression on sustained attention and reaction time in OSA patients, our results are consistent with findings from studies of depressed patients. For example, a recent study of 1,569 depressive patients found that impaired performance on the PVT-10 was associated with depressive symptomatology (Plante et al. (2020). Similarly, a study of young depressive patients who had not received antidepressant medication revealed that depression is associated with a slower speed of information processing (Tsourtos et al., 2002).

The current study also found that depressive symptoms are independently associated with impairments in visuospatial ability, as indicated by the number of errors and time taken on the AM-10T. This finding is supported by several studies of depressed patients. For example, Schock et al. (2011) demonstrated that significantly depressed patients have impaired visuospatial ability. Amongst depressed patients, there was a strong positive relationship between depressive symptoms and visuospatial deficits (Nelson & Shankman, 2016).

The present study found that depressive symptoms are associated with impairments in semantic memory and to a lesser extent episodic memory, as indicated by poorer performance on the AMI. Interestingly, hypoxia and sleep fragmentation were not independently associated with impairments in autobiographical memory. Previous studies have shown that consolidation of semantic autobiographical memory is dependent on non-REM and REM sleep processes, both of which are attenuated in OSA patients as a result of fragmented sleep architecture (Horton & Malinowski, 2015). The findings of our study are consistent with those of Delhikar et al. (2019b) who reported that depression is strongly

associated with impairments in semantic memory in OSA patients. In contrast, Lee et al. (2016) found that impairment in autobiographical memory impairment are not related to depressive symptoms in OSA. However, Lee et al's study may have been limited by small a sample size and the fact that only older female patients were included.

Our findings support previous research that has shown that deficits in autobiographical memory recall are a psychological marker for depression (Kuyken & Dalgleish, 1995), and individuals who are non-depressed, but vulnerable to depression retrieve less specific autobiographical information than never-depressed individuals (Williams & Dritschel, 1988). Although Lemogne et al. (2006) included small sample size (n = 21) compared to the current study, they found that impairments in episodic memory were linked to depression, which is consistent with our present findings. The hippocampus is involved in episodic memory function (Bird & Burgess, 2008), whereas semantic memory is supported by a distributed network of regions, including the anterior temporal lobes (Rice et al., 2018). Therefore, these two forms of autobiographical memory appear to be associated with different brain regions.

The present study has shown that three factors (intermittent hypoxia, sleep disruption and depressive symptoms) independently account for the cognitive impairments observed in OSA. In particular, the results indicate a major role for depressive symptoms, a factor that has been largely overlooked until now. The fact that depressive symptoms are an independent and primary contributor to impaired performance in a variety of cognitive domains in OSA begs the question as to the cause of these depressive symptoms. In the present study, 15 percent of the variance in depressive symptoms could be accounted for by daytime sleepiness. This finding agrees with those of Ishman et al. (2010) who conducted a case-control study that controlled for race, sex, age and respiratory disturbance index, and found that higher daytime sleepiness was correlated with higher scores on the Beck Depression Inventory. Additionally, Macias et al. (2013) included 345 adult patients with OSA diagnosed by polysomnography in a cross-sectional study. They found that severity of depressive symptoms correlated directly with the severity of daytime sleepiness.

The present study showed that 85% of the depressive symptoms could not be accounted for by excessive daytime sleepiness, and therefore must be due to other causes. Vitamin D deficiency is a possible candidate, since vitamin D deficiency is strongly linked to depression, and supplementation

with vitamin D is associated with a reduction in depressive symptoms and cognitive impairment (Berk et al., 2007; Soni et al., 2012). Furthermore, several studies have shown that vitamin D deficiency is common in obese persons (Walsh et al., 2017) and in OSA (Bouloukaki et al., 2019). Having OSA may also affect people behaviour and lead to less outdoor activity. Given that Saudi Arabia has a high incidence of vitamin D deficiency (Bokhari & Albaik, 2019) due to an indoor lifestyle, it may be fruitful to explore this possibility in a future study.

Although the present study is novel, there are several limitations. First, the sample size of the non-OSA group was smaller than that of the OSA group. Thus, it is possible that the smaller number of participants without OSA decreased the statistical power. Second, the present study recruited participants who had been referred for a sleep study because they were suspected of having a sleep disorder. This selection bias means that the present results may not necessarily be representative of a randomly chosen sample. Third, even though performance on the three chosen cognitive tests was correlated with OSA severity, these tests do not span all cognitive domains, so it is possible that additional aspects of cognitive function are impaired in OSA. Finally, since the present study did not image the brains of the participants, we were unable to correlate the observed cognitive deficits with structural changes. It would be interesting to conduct further studies to address these limitations.

Conclusion

This study investigated the independent roles of hypoxia, sleep fragmentation and depressive symptoms in cognitive dysfunction in OSA. Our data revealed that depressive symptoms are associated with impairments in sustained attention, reaction time, visuospatial ability and autobiographical memory. Hypoxia and sleep fragmentation are associated with deficits in sustained attention and reaction time, while sleep fragmentation but not hypoxia is associated with visuospatial deficits. The current findings suggest that cognitive impairment in OSA has multiple causes, and the reversal of this cognitive impairment may require interventions that simultaneously address all factors.

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Disclosure Statement

None

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Table 1. *Comparisons of demographic variables, depressive symptoms, daytime sleepiness, and PSG parameters stratified by OSA severity groups*

	No OSA	***Mild OSA***	***Moderate OSA***	***Severe OSA)***

	(n=14)	(n=30)	(n=23)	(n=23)	
Variables	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***p-value***
Age (years)	[4,3]33.6 (14.2)	38.7 (11.8)	[1]46.8 (11.8)	[1]46.7 (10.3)	**0.02**
Body mass index	32.3 (12.4)	32.8 (8.3)	31.2 (8.4)	36.7 (9.5)	0.22
Current smoker (%) +	1 (7)	7 (23)	5 (22)	9 (39)	0.16
DASS-21 depression subscale	8.0 (8.1)	13.5 (9.3)	11.6 (11.7)	11.3 (8.9)	0.39
ESS	9.5 (5.2)	9.5 (4.3)	11.1 (7.1)	13.0 (7.1)	0.13
SaO_2 time <90% (mins)	[4]0 (1)	[4]2 (6)	[4]9 (24)	[1,2,3]30 (46)	**0.001**
Arousal Index	[3,4]1.3 (1.1)	[4]5.5 (4.6)	[1,4]10.3 (4.9)	[1,2,3]26.0 (16.8)	**<0.001**
N1 (mins)	[4]20 (8)	[4]29 (16)	[4]30 (15)	[1,2,3]46 (26)	**<0.001**
N2 (mins)	152 (49)	124 (48)	140 (49)	116 (49)	0.11
N3 (mins)	[4]65 (33)	57 (23)	47 (24)	[1]39 (30)	**0.02**
REM (mins)	[4]52 (31)	33 (28)	31 (19)	[1]26 (19)	**0.01**

Note: OSA severity cut off values are: <5 AHI (normal); 5-14 AHI (mild); 15-29 AHI (moderate); ≥30AHI (severe); Significant differences between groups was defined by [1] p <0.05 versus non-OSA; [2] p <0.05 versus mild-OSA; [3] p <0.05 versus moderate-OSA; [4] p <0.05 versus severe-OSA; + Pearson Chi-square. DASS-21, depression, anxiety, and stress scale-21; ESS, excessive daytime sleepiness scale; SaO_2, oxygen arterial blood saturation; N1, stage 1; N2, stage 2; N3, stage 3; REM, rapid eye movement stage.

Table 2. Multiple linear regression analysis for the association between depressive symptoms and demographic variables, and daytime sleepiness.

Variables	***Predictors***	***R^2***	***SE***	***β***	***sr***	***p-value***
Depressive symptoms		*R^2= 0.16*				
	Daytime sleepiness		0.16	0.38	0.38	**<0.001**
	Age (years)		0.08	0.84	0.02	**0.40**
	Body mass index		0.10	0.15	0.08	**0.15**

R^2=models' multiple correlations; SE = standard error; β=standardized regression coefficient; sr=semi-partial correlation.

Table 3. Multiple linear regression analyses for three key measures on the psychomotor vigilance test, showing the strength of association between scores on this test and measures of hypoxia (SaO_2 time <90%), sleep fragmentation (arousal index) and depressive symptoms, after adjusting for confounders.

Cognitive tests	*Predictors*	R^2	*SE*	*β*	*sr*	*p-value*
PVT RT-mean*		*0.26*				
	Hypoxia		0.00	0.35	0.28	**0.003**
	Sleep fragmentation		0.54	0.26	0.21	**0.02**
	Depressive symptoms		0.60	0.32	0.30	**0.002**
	Age (years)		0.47	0.24	0.22	**0.02**
PVT slowest 10%*		*0.17*				
	Hypoxia		0.01	0.37	0.31	**0.003**
	Sleep fragmentation		1.93	0.16	0.13	0.18
	Depressive symptoms		2.04	0.24	0.23	**0.02**
PVT RT-10-lapses >500ms*		*0.29*				
	Hypoxia		0.00	0.42	0.34	**<0.001**
	Sleep fragmentation		0.06	0.24	0.18	**0.03**
	Depressive symptoms		0.07	0.30	0.29	**0.002**
	Age (years)		0.06	0.20	0.19	**0.04**
AM-time*		*0.40*				
	Hypoxia		0.00	0.14	0.12	0.192
	Sleep fragmentation		0.14	0.22	0.18	**0.04**
	Depressive symptoms		0.18	0.26	0.25	**0.006**
	Age (years)		0.13	0.59	56	**<0.001**
AM-errors*		*0.24*				
	Hypoxia		0.08	0.07	0.07	0.48
	Sleep fragmentation		0.28	0.22	0.22	**0.03**
	Depressive symptoms		0.27	0.26	0.26	**0.01**
	Age (years)		0.07	033	0.30	**0.002**
	Smoking		1.81	0.21	0.023	**0.03**

Note:*significant model (p <0.05) after FDR adjustment; *PVT, Psychomotor Vigilance Task; RT, Reaction Time; AM, Austin Maze; R^2=models' multiple correlations; SE= standard error; β=standardized regression coefficient; sr=semi-partial correlation.*

Table 4. Multiple linear regression analyses for measures on the Autobiographical memory interview, showing the strength of association between scores on this test with measures of hypoxia (SaO_2 time <90%), sleep fragmentation (arousal index) and depressive symptoms, after adjusting for confounders.

Cognitive tests	*Predictors*	R^2	*SE*	*β*	*sr*	*p-value*
Total semantic memory*		0.15				
	Hypoxia		0.00	-0.02	0.02	0.84
	Sleep fragmentation		0.04	-0.18	-0.15	0.15
	Depressive symptoms		0.05	-0.37	-0.37	**<0.001**
Childhood semantic memory**		0.09				
	Hypoxia		0.00	-0.13	0.11	0.29
	Sleep fragmentation		0.03	-0.03	0.02	0.81
	Depressive symptoms		0.03	-0.30	-0.29	**0.006**
Early adult life semantic memory**		0.08				
	Hypoxia		0.00	-0.21	-0.18	0.09
	Sleep fragmentation		0.02	-0.23	-0.19	0.06
	Depressive symptoms		0.03	-0.21	-0.21	**0.04**
Recent life semantic memory*		0.12				
	Hypoxia		0.00	-0.04	0.01	0.67
	Sleep fragmentation		0.02	-0.11	0.13	0.38
	Depressive symptoms		0.02	-0.27	-0.22	**0.01**
	Smoking		0.49	-0.25	-0.24	**0.02**
Total episodic memory*		0.14				
	Hypoxia		0.00	-0.02	-0.02	0.87
	Sleep fragmentation		0.06	0.04	0.03	0.77
	Depressive symptoms		0.06	-0.24	-0.24	**0.02**
	Age (years)		0.10	-0.30	-0.29	**0.006**
Episodic childhood memory**		0.04				
	Hypoxia		0.00	0.05	0.04	0.67
	Sleep fragmentation		0.03	0.25	0.02	0.83
	Depressive symptoms		0.28	-0.19	-0.19	0.07
Episodic early adult life memory **		0.06				
	Hypoxia		0.00	-0.10	-0.08	0.43
	Sleep fragmentation		0.02	0.07	0.06	0.57
	Depression		0.26	-0.17	-0.17	0.11
	Age (years)		0.20	-0.25	-0.23	**0.02**
Episodic recent life memory *		0.12				
	Hypoxia		0.00	-0.06	-0.46	0.65
	Sleep fragmentation		0.23	0.02	0.02	0.87
	Depression		0.03	-0.15	-0.17	0.16
	Age (years)		0.20	-0.31	-0.29	**0.006**

Note:*significant model (p <0.05) after FDR adjustment; **none-significant model (p >0.05) after FDR adjustment; R2=models' multiple correlations; SE = standard error; *β=standardized regression coefficient; sr=semi-partial correlation.*