Obstructive Sleep Apnea Syndrome Is Associated with Deficits in Verbal but Not Visual Memory

Gillian L. Twigg¹, Ioannis Papaioannou¹, Melinda Jackson², Ramesh Ghiassi³, Zarrin Shaikh¹, Jay Jaye¹, Kim S. Graham⁴, Anita K. Simonds¹, and Mary J. Morrell¹

¹Clinical and Academic Unit of Sleep and Ventilation, National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, United Kingdom; ²Sleep and Performance Research Center, Washington State University, Spokane, Washington; ³Imperial College Healthcare Sleep Centre, Charing Cross Hospital, London; and ⁴School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom

Rationale: Although cognitive deficits are well documented in patients with sleep apnea, the impact on memory remains unclear.

Objectives: To test the hypotheses that (1) patients with obstructive sleep apnea have memory impairment and (2) memory impairment is commensurate with disease severity.

Methods: Patients with obstructive sleep apnea and healthy volunteers (apnea–hypopnea index <5 events/h) completed a test battery specially designed to differentiate between aspects of memory (semantic, episodic, and working) versus attention. Sleepiness was measured on the basis of the Epworth Sleepiness Scale and Oxford Sleep Resistance test. Memory performance in patients versus control subjects was compared (Mann-Whitney *U* test; $P < 0.01$, Bonferroni corrected for multiple comparisons) and relationships between performance and disease severity were analyzed by linear regression.

Measurements and Main Results: Sixty patients and healthy control subjects matched for age (mean $\pm$ SD: patients, 51 ± 9 yr; control subjects, 50 ± 9 yr) and education (patients, 14 ± 3 yr; control subjects, 15 ± 3 yr) participated. Patients demonstrated impaired Logical Memory Test results (immediate recall: patients, median [range], 36 [9–69]; control subjects, 43 [19–64], $P = 0.0004$; and delayed recall: patients, 22 [6–42]; control subjects, 27 [10–46]; $P = 0.0001$). There were minimal differences in attention, visual episodic, semantic, or working memory; patients performed better than control subjects on Spatial Span forward and backward. Regression analysis revealed that Logical Memory Test performance was not significantly related to disease severity after controlling for age, education, and sleepiness.

Conclusions: Obstructive sleep apnea is associated with impairment in verbal, but not visual, memory. The impairment was present across a range of disease severity and was not explained by reduced attention. Such verbal memory impairment may affect daytime functioning and performance.

Keywords: hypoxia; sleepiness; cognitive function; sleep-disordered breathing

There is increasing evidence to suggest that obstructive sleep apnea (OSA) is associated with cognitive dysfunction (1–6). Cognitive function consists of many factors including perception, attention, language, comprehension, planning, problem

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with obstructive sleep apnea are known to have cognitive dysfunction; however, the scope of impairments in different aspects of memory is unclear.

What This Study Adds to the Field

Assessment based on a comprehensive test battery showed that patients with obstructive sleep apnea have specific impairments in verbal episodic memory, whereas visual episodic memory and semantic memory remain unaffected. The verbal memory performance was equivalent to normative data from healthy people 10 years older than our patients and was largely independent of changes in attention. The impact of these impairments on daytime function requires further investigation.

solving, reasoning, learning, and memory. If these factors are impaired they are likely to have major public health implications, particularly memory impairments, which may lead to early cognitive decline (7). Although some studies have included memory as part of a wider cognitive assessment (1, 3, 5, 6, 8), a detailed examination of memory function in OSA is required (2, 9).

The complexity of memory function means that to capture the different aspects of memory that may be affected by OSA, study design needs to be carefully considered. It must control for attention deficits associated with excessive daytime sleepiness. Figure 1 shows different aspects of memory. Episodic memory is the memory of specific events associated with times and places, for example, the first day at school or work. Semantic memory is memory of information, or knowledge that is not linked to a specific time or event; for example, the reader may know that the capital of the United States is Washington DC, but it may not be clear when this information was learned.

Where memory has previously been examined in patients with OSA, the findings are inconsistent. Some studies have reported deficits in verbal (2, 3, 6, 8) and visual (1, 3) episodic memory, whereas others have failed to replicate these findings (1, 5, 10–13). Semantic memory impairment has also been reported (1, 8, 12), but again the findings are not consistent on all tests (1, 3, 11, 14). Reports of working memory impairment include maintenance and manipulation of information (2, 5) but not dual task performance (2). Finally, where procedural memory has been investigated, this too has produced inconsistent results (2, 15). Taken together these studies suggest that patients with OSA may have difficulties learning new information, using semantic cues to aid retrieval, and in using memory to guide behavior, such as when following directions.

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Correspondence and requests for reprints should be addressed to Gillian L. Twigg, Ph.D., Imperial College Healthcare Sleep Centre, Charing Cross Hospital, London W6 8RF, UK. E-mail: gillian.twigg@imperial.nhs.uk

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Figure 1. Diagram showing the composition of the cognitive testing battery examining various aspects of memory and attention.

The aim of the present study was to systematically investigate various aspects of memory and attention in a large group of patients with OSA and healthy volunteers. Specifically, we aimed to test the hypothesis that patients with OSA would show impairment in various aspects of memory compared with healthy volunteers, independent of any changes in attention. Our secondary hypothesis was that memory impairment would be associated with disease severity. Some of the results of these studies have been previously reported in the form of an abstract (16, 17).

METHODS

Participants

Patients, aged 18 to 69 years, were sleep clinic referrals with suspected OSA. Exclusion criteria were as follows: concurrent sleep disorders; a history of neurological or cardiovascular disease; diabetes, or psychiatric illness including clinically diagnosed depression. Lifestyle factors precluding participation were shift work, excessive alcohol consumption (>35 units/wk), or a history of recreational drug use. Healthy volunteers were recruited from local advertising, and through colleagues who were naive to sleep research, and paid for their participation. All volunteers underwent polysomnography to ensure that they did not have undiagnosed OSA (apnea-hypopnea index [AHI] <5 events/h of sleep). Healthy volunteers were matched within 3 years of age of a selected patient from the OSA group. Likewise, volunteers that were within 2 years of education of a selected patient with OSA were recruited. One exception to this rule was a patient with 6 years of education; the closest match we could find was a volunteer with 10 years of education. The study was approved by the Royal Brompton and Harefield Research Ethics Committee and all participants gave written informed consent.

Memory Assessment

Patients and healthy volunteers completed a 3-hour cognitive testing battery (see online supplement) designed to examine various aspects of memory, including the Logical Memory Test, a verbal test assessing memory for a short story. The battery was conducted in a quiet

laboratory between 15:00 and 17:00 in the afternoon before their polysomnography. Several attention tests were also included to account for the potential influence of attention deficit on memory performance (see Figure 1 and the online supplement). Participants were asked to abstain from caffeinated beverages for the duration of their stay. Sleepiness was assessed subjectively using the Epworth Sleepiness Scale (18) and objectively with the Oxford Sleep Resistance (OSLER) Test, which was performed at 09:00 after polysomnography (19). Mood was assessed using the Hospital Anxiety and Depression Scale (HADS) (20).

Sleep Study

OSA was diagnosed polysomnographically ((SleepScreen; Hoechberg, Germany and Somnomedics; Tampa, FL); see the online supplement for details). Sleep and arousals were scored according to standard criteria (20–22). The AHI and 4% Oxygen Desaturation Index (ODI) were calculated as markers of disease severity (see the online supplement for scoring criteria).

Analysis

Statistical analysis was performed with SPSS (Chicago, IL). Summary data are expressed as means $\pm$ the standard deviation (SD) or as median (range) when data were nonnormally distributed. Group comparisons (patients vs. control subjects) were made with one-way analysis of variance or Mann-Whitney *U* test for data that were not normally distributed; the threshold for statistical significance was $P < 0.01$, Bonferroni corrected for multiple comparisons (24 comparisons, $P < 0.0004$). For memory tasks that were found to be significantly impaired, a linear regression model was constructed to examine the relationship between functional impairment and disease severity (AHI), sleepiness (Epworth Sleepiness Scale), while controlling for the confounding factors of age and education (years). When a model was able to significantly predict performance on a test ($P \leq 0.05$), the individual factors within the model were examined to establish which significantly predicted memory impairments.

Sample size calculations were based on data from a previous study that investigated cognitive function, but not the various aspects of memory (1). A minimal number of 58 patients with OSA and healthy control subjects would be needed to detect a significant difference for the Logical Memory Tests at a threshold $P < 0.01$ and 80% power (assuming

a mean difference in scores of 11, SD 17). For the attentional task Digit Span forward, 48 patients with OSA and healthy control subjects would be needed (assuming a mean difference in scores of 0.5, SD 0.7).

RESULTS

A total of 138 participants completed the protocol, comprising 78 sleep clinic referrals and 60 healthy volunteers. Twelve of the sleep clinic referrals were found not to have OSA (AHI <5 events/h) and were excluded from the analysis. A further six patients were excluded for other reasons: regular heavy alcohol consumption undisclosed during recruitment ($n = 4$), consumption of alcohol before completion of the testing battery ($n = 1$), and chronic obstructive pulmonary disease ($n = 1$). Therefore analysis was performed on 60 patients with OSA and 60 healthy volunteers. Ten of the healthy volunteers were unable to perform the memory tests on the same day as the polysomnography because of time constraints (e.g., unable to leave work). Eight of these people underwent the memory tests after polysomnography, and two performed the tests before polysomnography. The duration of time between the tests and the polysomnography was 25 (range, 2–64) days.

Demographic data for the OSA patient and healthy volunteer groups are presented in Table 1. There were no differences in age, years of education, or caffeine or alcohol consumption between the patient and healthy volunteer groups. The patients with OSA were significantly heavier, smoked more, and had higher HADS scores for possible depression and anxiety compared with the healthy volunteers.

Polysomnographic Parameters

Polysomnographic parameters are presented in Table 2. Patients with OSA had higher levels of intermittent hypoxia (ODI) compared with healthy volunteers. Patients with OSA also reported more subjective daytime sleepiness than did the healthy volunteers, although neither group was found to be objectively sleepy, maintaining wakefulness for the maximal time of 40 minutes on the OSLER Test. Patients with OSA and healthy control subjects had similar levels of sleep efficiency, although the patients were found to have more stage 1 NREM sleep, and the arousal index was higher in patients with OSA.

Memory Impairment and Attention in Patients with OSA versus Healthy Volunteers

Group median performances of patients with OSA and healthy volunteers on each of the memory tests are given in Table 3.

Investigation of episodic memory performance revealed a deficit in immediate and delayed recall from the Logical Memory Test, but normal recognition memory and retention of information over time on this test, suggesting that patients with OSA have difficulty assimilating information, but do not forget learned information more readily than healthy volunteers. That is, they have a reduced capacity to acquire new information but no difficulty in retaining previously learned memories.

Examination of the semantic memory performance revealed that patients with OSA tended to perform less well on the two tests of verbal fluency (Semantic Fluency and Phonemic Fluency), but these did not meet our significance threshold adjusted for multiple comparisons. Working memory and attention appeared to be unaffected in patients with OSA, with the patients performing equally as well as the healthy volunteers on four of the five tests of attention, and significantly better than the healthy volunteers on the Spatial Span test backward and forward. Spatial Span forward is an attention task, whereas Spatial Span backward is considered a working memory task as it requires holding information in memory. This involves attention, but the two tests are considered to map onto different frontal lobe circuits. The good performance of the patients with OSA on the spatial tasks is consistent with the patients with OSA achieving similar scores on the Paired Associate Learning test, another spatial task.

Relationship between Severity of OSA and Memory Impairment

We constructed linear regression models to investigate the relationship between verbal episodic memory performance (immediate and delayed recall from Logical Memory, respectively) and measures of disease severity (AHI, Epworth Sleepiness Scale score) in the patients with OSA, while controlling for age and education. The proportion of the overall variance explained by these models was 13% (immediate recall) and 13% (delayed recall). Examination of the individual components of the models revealed that years of education significantly predicted performance on both immediate (β -coefficient, 0.28; $P = 0.002$) and delayed (β -coefficient, 0.23, $P = 0.008$) recall from logical memory. AHI and sleepiness did not contribute significantly to the model.

We also investigated whether the cognitive tests were correlated with one another. Not surprisingly, several tests such as Semantic Fluency and Phonemic Fluency were related, as were Semantic Fluency and Graded Naming, and Spatial Span

TABLE 1. DEMOGRAPHICS

	Patients (AHI ≥ 5 events/h)	Healthy Volunteers (AHI <5 events/h)	P Value
N	60	60	
Females:males	9:51	11:49	0.81
Age, yr	51 $\pm$ 9 (30–69)	50 $\pm$ 9 (33–68)	0.54
Education, yr	14 $\pm$ 3	15 $\pm$ 3	0.07
BMI, kg/m ²	30.7 $\pm$ 6.0	24.8 $\pm$ 4.4	0.0001*
Typical caffeine consumption, mg/d	171 (0–1,155)	170 (0–782)	0.77
Alcohol consumption, units/wk	5 (0–30)	4 (0–42)	0.95
Number of smokers, n	27	22	0.45
Smoking history, pack-years	19 $\pm$ 15	11 $\pm$ 13	0.002*
HADS, anxiety score	7.5 (1–15)	4 (0–13)	0.02*
HADS, depression score	5.5 (0–16)	2 (0–8)	0.000000*

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; HADS = hospital anxiety and depression scale.

Data are presented as means $\pm$ SD and analyzed by one-way analysis of variance (parametric data) or as medians (range) and analyzed by Mann-Whitney U test (nonparametric data). Sex differences and smoking status between groups were compared by Fisher exact test.

* Significant difference ($P \leq 0.05$).

TABLE 2. POLYSOMNOGRAPHIC PARAMETERS

	Patients with OSA (<i>n</i> = 60)	Healthy Volunteers (<i>n</i> = 60)	<i>P</i> Value
AHI, events/h	23.1 (5.3–133.3)	1.3 (0–4.9)	
4% ODI, events/h	15.6 (1.3–125.2)	0.5 (0–5.1)	0.000*
Sleep efficiency, %	85 (55–94)	79 (23–94)	0.02
Arousal Index, events/h	21.5 (4.7–118)	12.5 (2.6–43.8)	0.000*
Stage 1, % sleep time	25.7 (2.3–79.8)	18.4 (4.2–44.2)	0.002*
Stage 2, % sleep time	46.9 (0–72.1)	47.1 (21–68.3)	0.46
Stages 3 + 4, % sleep time	11.1 (0–43.6)	14.0 (1.1–33.3)	0.04
REM, % sleep time	14.0 (0–39.9)	18.1 (0–32.8)	0.01
Epworth Sleepiness Scale score	10.5 (0–24)	5.5 (1–21)	0.000*
OSLER, time (min)	40 (1–40)	40 (1–40)	0.23

Definition of abbreviations: AHI = apnea-hypopnea index; ODI = Oxygen Desaturation Index; OSA = obstructive sleep apnea; OSLE = Oxford Sleep Resistance Test.

Data are presented as medians (range) and analyzed by Mann-Whitney *U* test.

* Significant difference ($P \leq 0.05$).

forward and backward (*see* the online supplement for details of the analysis).

Memory Impairment and Attention in Patients with OSA with Possible Mild Depression

The patients with OSA had higher scores on the HADS. Seven patients (12%) had a score greater than 11, although none reported any depressive symptoms. Therefore, analysis was undertaken to investigate whether the high HADS scores were associated with memory impairment. A cutoff of 8 was used to reorganize the patients with OSA as follows: possibly mildly depressed patients ($n = 18$; mean [SD], 10 [2.0] HADS) and nondepressed patients ($n = 42$; 3.7 [2.2] HADS). The groups were matched for OSA severity (AHI), body mass index, years

of education, and caffeine and alcohol intake. However, the nondepressed group was significantly older than the mildly depressed group. No significant differences were found between any of the memory scores on any of the test battery in the mildly depressed versus nondepressed patients with OSA (*see* the online supplement for details of the analysis).

DISCUSSION

The main finding of our study was that patients with OSA, compared with a matched sample of control subjects, displayed reduced performance on verbal episodic memory tasks, whereas visual episodic, semantic, and working memory remained intact. The absence of any impairment in attention precludes the

TABLE 3. COMPARISON OF MEMORY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HEALTHY CONTROL SUBJECTS

	Patients (<i>n</i> = 60)	Healthy Volunteers (<i>n</i> = 60)	<i>P</i> Value
Semantic memory			
Semantic Fluency, number of words	104.5 (51–181)	113.5 (69–179)	0.02
Phonemic Fluency, number of words	42.5 (17–71)	48 (18–77)	0.02
Graded Naming	23 (7–30)	24 (6–28)	0.21
Episodic memory			
Logical Memory, immediate recall score	36 (9–69)	42.5 (19–64)	0.0004*
Logical Memory, delayed recall score	22 (6–42)	27 (10–46)	0.0001*
Logical Memory, % retention	80.3 (47–119)	88.6 (40–105.7)	0.08
Logical Memory, recognition component	26 (20–30)	27 (22–30)	0.12
Paired Associate Learning, errors, 8 shapes	6 (0–41)	7 (0–45)	0.84
Rey Complex Figure, % retention	50 (5–86)	55.6 (26–89)	0.14
Source (item memory), proportion correct	0.9 (0.53–1.0)	0.9 (0.74–1.0)	0.24
Source Memory, proportion correct	0.66 (0.5–0.9)	0.64 (0.4–0.8)	0.25
Topographical Recognition Memory	26 (13–30)	26 (13–30)	0.62
Working Memory			
Digit Span, backward	4.5 (2–7)	4 (3–7)	0.71
Spatial Span, backward	8 (3–14)	5 (3–11)	0.000000*
Della Sala	0.61 (–5.4 to 8.17)	0.08 (–3.4 to 5.6)	0.07
Telephone Search Task	1.4 (–0.7 to 356.8)	0.87 (–1.9 to 8.1)	0.19
Attention			
Stroop, <i>t</i> score	50 (23–80)	52 (21–69)	0.31
Sustained Attention, errors of commission	3 (0–21)	3 (0–25)	0.08
Trail Making A, time to complete (s)	36.3 (19.1–92.7)	32.5 (16.4–71.8)	0.17
Trail Making B, time to complete (s)	74.9 (35.7–230.3)	71.3 (27.6–160.8)	0.27
Digit Span, forward	7 (4–8)	7 (5–8)	0.94
Spatial Span, forward	8 (3–14)	6 (3–11)	0.000000*
Other			
Raven's Progressive Matrices	45 (26–56)	46.5 (21–60)	0.62
Pyramid and Palm Tree	51 (41–52)	51 (45–52)	0.39

Data are presented as medians (range) and analyzed by Mann-Whitney *U* test.

* Significant difference: $P < 0.01$, Bonferroni corrected for multiple comparisons (24 comparisons, $P < 0.0004$).

notion that these findings were due to a general attention deficit. Further, no relationship between memory impairment and OSA severity was found, indicating that memory impairment may also be observed in patients with mild OSA. We suggest that patients with OSA have specific difficulties assimilating and later recalling information presented to them verbally, but have no problems in recalling visual information, and these deficits do not show further decline with increasing disease severity.

Using a specially designed comprehensive test battery we were able to distinguish between verbal and visual memory impairment as well as between different types of memory, including episodic versus semantic and short-term (working) memory. To our knowledge, only one other study has employed a similar approach (2). However, this study by Naegele and colleagues included just one test of verbal episodic memory; consequently they were unable to conclude whether these impairments were specific to verbal memory, or whether patients also had deficits in visual episodic memory. Consistent with the study by Naegele and colleagues, we found that patients with OSA had specific difficulties in retrieval from verbal episodic memory, without any associated deficits in recognition memory or difficulties in retaining information over a short period of time. Normative data from standardized Z scores provided with the test suggest that the OSA patient group had verbal memory performance equivalent to that of healthy volunteers 10 years older than themselves (23).

Patients with OSA did not show a visual episodic memory deficit, despite having specific verbal episodic memory impairments. To our knowledge, only the Rey-Osterrieth Complex Figure Test has been previously used with patients with OSA to test visual episodic memory (1, 14). Some of these studies have reported deficits in immediate and delayed recall (14), which may be explained by a failure to adequately encode the material to allow a representation to form in memory; reduced performance has also been reported in copying the figure, for example (1, 14). Our study controlled for this encoding issue by expressing the recall score as a percentage of the copy score. Therefore, we suggest that patients with OSA have intact visual episodic memory performance after controlling for encoding.

Our test battery allowed us to examine the two processes considered to be important for working memory: those associated with maintenance of information in short-term memory, and those that allow successful division of attention between two tasks simultaneously. The patients performed similarly, or better than healthy volunteers on both of these processes, indicating that OSA was not associated with working memory deficits in our patient group. Although our findings of normal dual task performance are consistent with Naegele and colleagues (2), our failure to find deficits in maintenance of working memory is in contrast to the work of others (2, 3, 6). We suggest that a basic attention deficit could explain poor performance on this aspect of working memory (24). Indeed, this may explain the discrepancy between our findings and those of others, because our patients did not have any overt attentional deficits.

Relationship between Disease Severity and Memory Function

Our second aim was to examine the relationship between severity of OSA and memory function. Despite the finding of significant verbal episodic memory defects in patients with OSA, we were unable to detect a relationship with disease severity measures (AHI). However, our data are consistent with other studies that have failed to find a significant relationship between AHI and memory dysfunction (13). Importantly, this

means that even mild OSA ($\text{AHI} \geq 5$) may be sufficient to produce the memory deficits.

Mechanisms of Memory Impairment in OSA: Sleep Fragmentation, Intermittent Hypoxia, and the Hippocampus

Verbal episodic memory impairment has been shown to be associated with distinct neural correlates located bilaterally in the prefrontal cortex and in the left hippocampus (25). Both of these areas are vulnerable to the effects of intermittent hypoxia (26, 27) and some (28–30) but not all (31) studies have shown a reduction in brain volume in the hippocampus in patients with OSA compared with healthy volunteers. An alternative suggestion is that the memory impairments observed in patients with OSA are produced by sleep fragmentation, particularly during REM sleep. In support of this idea, one night of sleep deprivation can result in a reduction in hippocampal activity during episodic memory encoding, and subsequent deficits in memory retention (32). Data from a study in rats also suggest that fragmenting sleep every 2 minutes is sufficient to cause a significant reduction in synaptic plasticity, which would affect memory consolidation (33).

Critique of Methods

It is notable that our patient group had significantly greater scores on the depression and anxiety subscales of the HADS than did the healthy volunteers, although in both groups the mean scores were within the normal range for depression (score < 7) (20). Our analysis revealed no differences between patients with high and lower HADS depression scores. However, this analysis needs to be interpreted with caution because the nondepressed group was older than the mildly depressed group. In addition, the HADS score is a crude measurement of depression, and the cutoff for mild depression is not well defined.

It may be argued that our long testing battery was unsuitable for use with patients with OSA. This issue has been previously investigated and no differences were found when memory was investigated with longer and shorter testing batteries (2). When planning the test battery, we also paid particular attention to the order in which the tests were administered. This minimized the risk of interference between tests. We also took care to allow all volunteers and patients to have a restful break halfway through the battery. Therefore, we do not believe that our findings are attributable to a test order effect.

Summary and Conclusions

In the present study we have shown that patients with OSA have specific difficulties in assimilating and recalling information presented verbally, whereas their ability to process visual information remains intact. The memory deficits were present across the spectrum of disease severity, and even patients with mild disease were affected. The impairments were equivalent to a verbal memory performance of healthy volunteers 10 years older than our patients according to normalized scores provided with the test results. We suggest that such memory impairments may have significant detrimental effects on daytime functional performance in patients with OSA.

Conflict of Interest Statement: G.L.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; I.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Z.S. received more than \$100,001 from NMT Medical in industry-sponsored grants as previous employment as a research fellow on a grant sponsored by NMT from May 2007 to February 2009; J.J. was employed by Intus Ltd, reporting on overnight pulse oximetry studies, received

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References

1. Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, Cappa SF. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). *Brain Res Bull* 2003;61:87–92.
2. Naegele B, Launois SH, Mazza S, Feuerstein C, Pepin JL, Levy P. Which memory processes are affected in patients with obstructive sleep apnea? An evaluation of 3 types of memory. *Sleep* 2006;29:533–544.
3. Naegele B, Thouvard V, Pepin JL, Levy P, Bonnet C, Perret JE, Pellat J, Feuerstein C. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep* 1995;18:43–52.
4. Quan SF, Wright R, Baldwin CM, Kaemingk KL, Goodwin JL, Kuo TF, Kaszniak A, Boland LL, Caccappolo E, Bootzin RR. Obstructive sleep apnea-hypopnea and neurocognitive functioning in the Sleep Heart Health Study. *Sleep Med* 2006;7:498–507.
5. Redline S, Strauss ME, Adams N, Winters M, Roebuck T, Spry K, Rosenberg C, Adams K. Neuropsychological function in mild sleep-disordered breathing. *Sleep* 1997;20:160–167.
6. Adams N, Strauss M, Schluchter M, Redline S. Relation of measures of sleep-disordered breathing to neuropsychological functioning. *Am J Respir Crit Care Med* 2001;163:1626–1631.
7. Steffens DC, Otey E, Alexopoulos GS, Butters MA, Cuthbert B, Ganguli M, Geda YE, Hendrie HC, Krishnan RR, Kumar A, *et al.* Perspectives on depression, mild cognitive impairment, and cognitive decline. *Arch Gen Psychiatry* 2006;63:130–138.
8. Salorio CF, White DA, Piccirillo J, Duntley SP, Uhles ML. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. *J Clin Exp Neuropsychol* 2002;24:93–100.
9. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112.
10. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. *Arch Intern Med* 1992;152:538–541.
11. Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. *Sleep* 1987;10:254–262.
12. Lee MM, Strauss ME, Adams N, Redline S. Executive functions in persons with sleep apnea. *Sleep Breath* 1999;3:13–16.
13. Kim HC, Young T, Matthews CG, Weber SM, Woodward AR, Palta M. Sleep-disordered breathing and neuropsychological deficits: a population-based study. *Am J Respir Crit Care Med* 1997;156:1813–1819.
14. Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *J Clin Exp Neuropsychol* 1991;13:950–964.
15. Rouleau I, Decary A, Chicoine AJ, Montplaisir J. Procedural skill learning in obstructive sleep apnea syndrome. *Sleep* 2002;25:401–411.
16. Twigg G, Papaioannou I, Simonds AK, Morrell MJ. Cognitive defects in patients with moderate to severe obstructive sleep apnoea [abstract]. *Thorax* 2006;61:ii2.
17. Twigg G, Papaioannou I, Simonds AK, Morrell MJ. Effect of intermittent hypoxia on cognitive function in patients with obstructive sleep apnoea [abstract]. *J Sleep Res* 2006;15:44.
18. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545.
19. Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. *J Sleep Res* 1997;6:142–145.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–370.
21. Rechtschaffen A, Kales A. A manual of standardised terminology, techniques and scoring system for sleep stages in human subjects. Washington DC: U.S. Public Health Service, U.S. Government Printing Office; 1968.
22. Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173–184.
23. Weschler D. Weschler memory scale. London: The Psychological Corporation; 1998.
24. Verstraeten E, Cluydts R, Pevernagie D, Hoffmann G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. *Sleep* 2004;27:685–693.
25. Bernard FA, Desgranges B, Eustache F, Baron JC. Neural correlates of age-related verbal episodic memory decline: a PET study with combined subtraction/correlation analysis. *Neurobiol Aging* 2007;28:1568–1576.
26. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J Neurosci* 2001;21:2442–2450.
27. Kheirandish L, Gozal D, Pequignot JM, Pequignot J, Row BW. Intermittent hypoxia during development induces long-term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex. *Pediatr Res* 2005;58:594–599.
28. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA, Harper RK, Yan-Go FL, Harper RM. Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;166:1382–1387.
29. Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR. Changes in brain morphology associated with obstructive sleep apnea. *Sleep Med* 2003;4:451–454.
30. Morrell MJ, Twigg G. Neural consequences of sleep disordered breathing: the role of intermittent hypoxia. *Adv Exp Med Biol* 2006;588:75–88.
31. O'Donoghue FJ, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, Tarquinio N, Jackson GD, Pierce RJ. Cerebral structural changes in severe obstructive sleep apnea. *Am J Respir Crit Care Med* 2005;171:1185–1190.
32. Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP. A deficit in the ability to form new human memories without sleep. *Nat Neurosci* 2007;10:385–392.
33. Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, Brown RE, Strecker RE. Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *Eur J Neurosci* 2006;23:2739–2748.