Obstructive sleep apnoea syndrome is associated with deficits in verbal but not visual memory

Gillian L Twigg[1], Ioannis Papaioannou[1], Melinda Jackson[3], Ramesh Ghiassi[4], Zarrin Shaikh[1], Jay Jaye[1], Kim S Graham[2], Anita K Simonds[1], and Mary J Morrell[1]

[1]Clinical and Academic Unit of Sleep and Ventilation, National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, UK.

[2]School of Psychology, Cardiff University, Cardiff, Wales, UK.

[3] Sleep and Performance Research Center, Washington State University, Spokane, WA, USA.

[4]Imperial College Healthcare Sleep Centre, Charing Cross Hospital, London, UK

Corresponding Author: Gillian L Twigg

Imperial College Healthcare Sleep Centre

Charing Cross Hospital

London, UK

W6 8RF

Tel: 020 331 17188

Fax: 020 331 17172

Email: gillian.twigg@imperial.nhs.uk

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At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnoea patients 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 using a comprehensive test battery showed that obstructive sleep apnoea patients have specific impairments in verbal episodic memory, while visual episodic memory, semantic memory remain unaffected. The verbal memory performance was equivalent to normative data from healthy people ten years older than our patients, and was largely independent of changes in attention. The impact of these impairments on daytime function requires further investigation. (98 words).

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: While cognitive deficits are well documented in sleep apnoea patients, the impact on memory remains unclear. **Objectives:** To test the hypotheses that i) obstructive sleep apnoea patients have memory impairment and ii) memory impairment is commensurate with disease severity. **Methods**: Obstructive sleep apnoea patients and healthy volunteers (AHI <5 events/ hour) completed a test battery specially designed to differentiate between aspects of memory (semantic, episodic and working) versus attention. Sleepiness was measured using the Epworth Sleepiness Scale and OSLER test. Memory performance in patients versus controls was compared (Mann Whitney U; $p<0.01$ Bonferroni corrected for multiple comparisons) and relationships between performance and disease severity were analysed with linear regression. **Measurements and Results**: 60 patients and healthy controls matched for age (mean± SD: patients 51±9 years, controls 50±9 years) and education (patients 14±3 years, controls 15±3 years) participated. Patients demonstrated impaired Logical Memory (immediate recall, patients median (range) 36 (9-69), controls 43 (19-64), $p=0.0004$; and delayed recall, patients 22 (6-42), controls 27 (10-46), $p=0.0001$). There were minimal differences in attention, visual episodic, semantic or working memory; patients preformed better than controls on Spatial Span forwards and backwards. Regression analysis revealed that Logical Memory performance was not significantly related to disease severity after controlling for age, education and sleepiness. **Conclusions**: Obstructive sleep apnoea 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 in may affect daytime functioning and performance.

Word count: 250

Key words: Hypoxia, sleepiness, cognitive function, sleep disordered breathing

INTRODUCTION

There is increasing evidence to suggest that obstructive sleep apnoea (OSA) is associated with cognitive dysfunction (1-6). Cognitive function consists of many factors including perception, attention, language, comprehension, planning, problem 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). Whilst 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 in order 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 e.g. first day at school or work. Semantic memory is memory of information, or knowledge that is not linked to a specific time or event, e.g. you know the capitol of the USA 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, while 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 OSA patients may have difficulties learning new information, using semantic cues to aid retrieval, and in using memory to guide behaviour, such as when following directions.

The aim of the present study was to systematically investigate different aspects of memory and attention in a large group of patients with OSA and healthy volunteers. Specifically, we aimed to test the hypothesis that OSA patients would show impairment in different aspects of memory compared to 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)

417 WORDS

METHODS

Participants

Patients were sleep clinic referrals with suspected OSA aged 18 to 69 years. Exclusion criteria were concurrent sleep disorders, a history of neurological, cardiovascular disease, diabetes, or psychiatric illness including clinically diagnosed depression. Life-style factors precluding participation were shift work, excessive alcohol consumption (> 35 units per week) or a history of recreational drug use. Healthy volunteers were recruited from colleagues naive to sleep research, and local advertisements and paid for their participation. All volunteers underwent polysomnography to ensure that they did not have undiagnosed OSA (apnoea

hypopnoea index (AHI) < 5 events/hour 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 OSA patient 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 three-hour cognitive testing battery designed to examine different aspects of memory. The battery was conducted in a quiet laboratory between 15:00 and 17:00 in the afternoon prior to their PSG. Several attention tests were also included to account for the potential influence of attention deficit on memory performance (see Figure 1 and 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 following polysomnography (19). Mood was assessed using the Hospital Anxiety and Depression Scale (HADS) (20).

Sleep study

OSA was diagnosed polysomnographically (Somno Medics and Jaeger Sleep Screen; see 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 online supplement for scoring criteria).

Analysis

Statistical analysis was performed using SPSS. Summary data are expressed as mean ± standard deviation (SD) or as median (range) where data were non-normally distributed. Group comparisons (patients versus controls) were made with one-way analysis of variance (ANOVA) or Mann Whitney U for data that was 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). Where a model was able to significantly predict performance on a test ($p\leq0.05$), the individual factors within the model were examined to establish which significantly predicted memory impairments.

Sample size calculations were based upon data from a previous study that investigated cognitive function, but not different aspects of memory (1). A minimum number of 58 OSA patients and healthy controls would be needed to detect a significant difference for the logical memory tests at a threshold $p<0.01$ and 80% power (assumed mean difference in scores 11, sd 17). For the attentional task Digit Span forwards, 48 OSA patients and healthy controls would be needed (assumed mean difference in scores 0.5, sd 0.7).

558 WORDS

RESULTS

A total of 138 participants completed the protocol, comprising of 78 sleep clinic referrals, and 60 healthy volunteers. Twelve of the sleep clinic referrals were found not to have OSA (AHI<5 events/hour) and were excluded from the analysis. A further 6 patients were excluded for other reasons: regular heavy alcohol consumption undisclosed during recruitment (n=4), consumption of alcohol prior to completion of the testing battery (n=1), COPD (n=1). Therefore analysis was carried out on 60 OSA patients and 60 healthy volunteers. Ten of the healthy volunteers were unable to perform the memory tests on the same day as the polysomnography due to time constraints (e.g. unable to leave work). Eight of these people had the memory tests after the polysomnography, and two had the tests before. The duration between the tests and the polysomnography was 25 (range, 2 – 64) days.

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

Polysomnography parameters

Polysomnography parameters are presented in Table 2. OSA patients had higher levels of intermittent hypoxia (ODI) compared to healthy volunteers. OSA patients also reported more subjective daytime sleepiness than the healthy volunteers, although neither group was found to be objectively sleepy, maintaining wakefulness for the maximum time of 40 minutes on the OSLER test. OSA patients and healthy controls 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 OSA patients.

Memory impairment and attention in OSA patients versus healthy volunteers

Group median performances of OSA patients 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 OSA patients 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 OSA patients 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 OSA patients, 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 backwards and forwards. Spatial Span forwards is an attention task, where as backwards is considered a working memory task as it requires holding information. This involves attention, but the two tests are considered to map onto different frontal lobe circuits. The good performance of the OSA patients on the spatial tasks is consistent with the OSA patients achieving similar scores on the topographical 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 score) in the OSA patients, 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 (ß-coeficient, 0.28; p=0.002) and delayed (ß-coeficient, 0.23, p=0.008) recall from Logical Memory. AHI and sleepiness did not contribute significantly to the model.

We also investigated if 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 forwards and backwards (see online supplement for details of the analysis).

Memory impairment and attention in OSA patients with possible mild depression

The OSA patients had higher scores on the HADS depression scale. Seven patients (12%) had a score > 11, although none reported any depressive symptoms. Therefore, analysis was undertaken to investigate whether the high HADS depression scores were associated with memory impairment. A cut off of 8 was used to split the OSA patients into possible mildly depressed patients (n=18, mean (sd): 10 (2.0) HADS) and non-depressed patients (n=42, 3.7

(2.2) HADS). The groups were matched for OSA severity (AHI), BMI, years of education, caffeine and alcohol intake. However the non-depressed group were 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 non-depressed OSA patients (see online supplement for details of the analysis).

DISCUSSION

The main finding of our study was that patients with OSA, compared to a matched sample of control subjects, displayed reduced performance on verbal episodic memory tasks, while visual episodic, semantic and working memory remained intact. The absence of any impairment in attention precludes the 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 OSA patients 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 *et al.,* 2006 included just one test of verbal episodic memory; consequently they were unable to conclude whether these impairment were specific to verbal memory, or whether patients also

had deficits in visual episodic memory. Consistent with the Naegele study 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 standardised Z scores provided with the test suggest that the OSA patient group had verbal memory performance equivalent to healthy volunteers ten years older than themselves (23).

OSA patients 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 OSA patients 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 which 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 *et al*., 2006 (2), our failure to find deficits in maintenance of working memory is in contrast to

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, since our patients did not have any obverse attentional deficits.

The 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 OSA patients, 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 (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 OSA patients compared to healthy volunteers. An alternative suggestion is that the memory impairments observed in OSA patients 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 suggests that fragmenting sleep every

2 minutes is sufficient to cause a significant reduction in synaptic plasticity, which would affects memory consolidation (33).

Critique of methods

It is notable that our patient group had significantly greater scores on the depression and anxiety sub-scales from the HADS than 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 a high and lower HADS depression scores. However, this analysis needs to be interpreted with caution because the non-depressed group was older than the mildly depressed group. Plus the HADS score is a crude measurement of depression, and the cut off for mild depression is not well defined.

It may be argued that our long testing battery was unsuitable for use with OSA patients. This issue has been previously investigated and no differences were found when memory was investigated using a longer and shorter testing battery (2). When planning the test battery, we also paid particular attention to the order in which the tests were administered. This minimised the risk of interference between tests. We also took care to allow all volunteers and patients to have a restful break half way 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, while 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 ten years older than our patients according to normalised scores provided with the test results. We suggest that such memory impairments may have significant detrimental effects on daytime functional performance in OSA patients.

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Figure legends:

Figure 1: Diagram to show the composition of the cognitive testing battery examining different aspects of memory and attention.

Table 1: Demographics

	Patients (AHI ≥5 events/hr)	**Healthy Volunteers (AHI<5 events/hr)**	**P value**
n	60	60	
Females : males	9 : 51	11 : 49	0.81
Age (years)	51±9 (30-69)	50±9 (33-68)	0.54
Education (years)	14±3	15±3	0.07
BMI (kg/m^2)	30.7±6.0	24.8 ±4.4	0.0001*
Typical caffeine consumption (mg/day)	171 (0-1155)	170 (0-782)	0.77
Alcohol consumption (units/wk)	5 (0-30)	4 (0-42)	0.95
Number of smokers (n)	n=27	n=22	0.45
Smoking history (pack years)	19±15	11±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*

Data presented as mean ± SD and analysed with one-way ANOVA (parametric data) or median (range) and analysed with Mann Whitney U (non-parametric data). Gender differences and smoking status between groups and were compared using Fisher's exact test. *denotes statistically significant difference ($p \leq 0.05$).

Table 2: Polysomnography parameters

	OSA Patients (n=60)	Healthy Volunteers (n=60)	p value
AHI (events/hr)	23.1 (5.3-133.3)	1.3 (0-4.9)	
4% ODI (events/hr)	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/hr)	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
Stage 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 Score	10.5 (0-24)	5.5 (1-21)	0.000*
OSLER (time, mins)	40 (1-40)	40 (1-40)	0.23

Data presented as median (range) and analysed with Mann Whitney U.

* denotes statistically significant difference ($p \leq 0.05$).

Table 3: Comparison of memory in OSA patients and healthy controls

	Patients (n=60)	**Healthy Volunteers (n=60)**	**p 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,	6 (0-41)	7 (0-45)	0.84

8 shapes)			
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 (backwards)	4.5 (2-7)	4 (3-7)	0.71
Spatial Span (backwards)	8 (3-14)	5 (3-11)	0.000000*
Della Sala	0.61 (-5.4-8.17)	0.08 (-3.4-5.6)	0.07
Telephone Search Task	1.4 (-0.7-356.8)	0.87 (-1.9-8.1)	0.19
Attention			
Stroop (t 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, secs)	36.3 (19.1-92.7)	32.5 (16.4-71.8)	0.17
Trail Making B (time to complete, secs)	74.9 (35.7-230.3)	71.3 (27.6-160.8)	0.27
Digit Span (forwards)	7 (4-8)	7 (5-8)	0.94
Spatial Span (forwards)	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 presented as median (range) and analysed with Mann Whitney U.

* denotes statistically significant difference $p<0.01$ Bonferroni Corrected for multiple comparisons (24 comparisons $p<0.0004$).