# Which Memory Processes are Affected in Patients With Obstructive Sleep Apnea? An Evaluation of 3 Types of Memory

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**Study Objective:** To investigate which memory processes are affected by obstructive sleep apnea (OSA).

**Design:** Three separate memory systems were investigated in patients with OSA and normal subjects. Verbal episodic memory was tested after forced encoding, in order to control the level of attention during item presentation; procedural memory was tested using a simplified version of a standard test with an interfering task; lastly, working memory was examined with validated paradigms based on a theoretical model.

**Setting:** Sleep laboratory and outpatient sleep clinic in a French tertiary-care university hospital.

**Participants:** Ninety-five patients with OSA and 95 control subjects matched for age and level of education. Group 1 (54 patients, 54 controls) underwent an extensive battery of tasks evaluating verbal episodic, procedural, and working memory. Group 2 (16 patients, 16 controls) underwent procedural memory tests only, and group 3 (25 patients, 25 controls) working memory tests only.

**Interventions:** N/A.

**Measurements and Results:** Compared with matched controls, patients with OSA exhibited a retrieval deficit of episodic memory but intact maintenance, recognition, and forgetfulness; decreased overall performance in procedural memory, although pattern learning did occur; and impairment of specific working memory capabilities despite normal short-term memory. No consistent correlation was found between OSA severity and memory deficit. The long duration of the test session did not negatively impact the patients' performance.

**Conclusions:** Memory impairment in OSA is mild and does not affect all memory processes but, rather, specific aspects, underscoring the need for extensive and specific memory testing in clinical and research settings.

**Keywords:** Sleep apnea, episodic memory, procedural memory, working memory, cognitive function, neuropsychological dysfunction

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## INTRODUCTION

PATIENTS WITH OBSTRUCTIVE SLEEP APNEA (OSA) ARE AFFECTED BY A BROAD RANGE OF NEUROPSYCHOLOGICAL DEFICITS: ATTENTION, EXECUTIVE, and motor functions and memory are significantly impaired,[1] with sleep fragmentation as well as intermittent nocturnal hypoxia likely to contribute to the cognitive dysfunction.[2-4] Although memory is impaired in most patients with OSA and improves, at least partially, with effective treatment,[5-8] a clear understanding of the pathogenesis of memory dysfunction in OSA is still lacking. However, before investigating pathophysiologic mechanisms, the following questions need to be addressed: what memory system and which processes are affected?

No longer considered a single unitary system, memory is now viewed as a network of interrelated subsystems.[9] One of the major functional distinctions in the memory system is the division into short-term and long-term memory, which, in turn, can be separated in different processes. Long-term memory includes, for instance, episodic and procedural components. Episodic memory refers to the recollection of specific experiences, whereas procedural memory refers to learning skills (perceptual-motor or cognitive skills). Episodic (or declarative) memory is assessed by direct or explicit tests evaluating the acquisition, retention, and retrieval of new knowledge that can be consciously and intentionally recalled.[10] Procedural (or nondeclarative) memory is assessed by indirect or implicit tests, evaluating the acquisition, retention, and retrieval of new knowledge through the changes in performance induced by a prior experience. For these tests, no reference is made to the prior learning experience.[10] Similarly, the notion of a unitary short-term storage system has been progressively abandoned in favor of a multicomponent working-memory system.[11] Working memory allows the temporary maintenance of limited information and keeps that information available for immediate access by other cognitive processes. Such active maintenance is essential for a variety of tasks. Beyond simple simultaneous storage and processing, working memory encompasses many cognitive processes, including, for example, transformation of stored stimuli into short-term memory, supervision of multiple simultaneous operations, and coordination of elements and their interrelations into new mental structures.[12] The different memory systems can be affected independently of one another by medical disorders[13,14] and thus need to be assessed separately.

An impairment of verbal and visual episodic memory has been demonstrated in patients with OSA using standard tests of declarative memory.[3,6,8,15-18] However, we still do not understand the nature of the episodic memory impairment in patients with OSA: is the treatment of information (encoding) deficient? Is the retrieval of successfully encoded information altered? Is forgetful-

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ness abnormal? One way to address these questions is to force the encoding stage[19] by manipulating the conditions of encoding and recalling of information,[20] thereby allowing an evaluation of the different episodic-memory processing stages, once encoding is controlled.

To our knowledge, only 1 study has specifically evaluated procedural memory in patients with OSA.[21] The authors were able to demonstrate marked impairment of this memory system in less than half of patients. While this study was methodologically sound, the final number of patients was small, and they were not matched to control subjects. Increasing the number of subjects and closely matching patients and controls 1 by 1 with regard to variables relevant to memory function could reveal a larger percentage of impaired patients. Furthermore, evaluating the impact of an interfering task during a standard test of procedural memory could help determine whether patients may improve their performance merely because of trial repetition masking poor procedural skills.

A working memory deficit has also been demonstrated in patients with OSA,[22-24] though not consistently.[8,25] What reasons might account for these contradictory findings? One source of confusion is the use of overlapping terms, such as "short-term memory," "working memory," and "attentional capacity," to describe the complex concept of working memory. In addition, most neuropsychological studies reporting working-memory deficits in patients with OSA have used standard short-term memory-span tests, such as the auditory span test, which are considered by some authors to measure attentional capacity rather than working memory.[26] Indeed, patients could successfully perform span tests while scoring poorly in other tests of working memory. Another source of heterogeneity in experimental findings stems from the confusion between the type of memory being evaluated (i.e., short-term) and the (short) delay that elapses before the retrieval task. Overall, the lack of consensus with regard to the different concepts of working memory, the terminology used, and the procedures carried out to evaluate working memory makes it difficult, based on the available literature, to ascertain whether working memory is affected in patients with OSA. Recently, Verstraeten and Cluydt[27] have advocated the use of experimental paradigms with validated ability to examine working memory as well as proper sensitivity to assess neuropsychological deficits of various etiologies to evaluate working memory in patients with OSA.

To clarify the characteristics of memory impairment in OSA, we evaluated 3 separate memory systems in a large number of patients and closely matched control subjects. We tested verbal episodic memory after forced encoding, to control the level of attention during item presentation, using otherwise standard testing procedures. We tested procedural memory, using a simplified version of a standard test and adding an interfering task to evaluate the test's robustness, and, lastly, working memory using 2 validated paradigms assessing separate aspects of this complex memory process. To control for the potential confounding factor represented by the test duration in patients whose most common symptom is excessive daytime sleepiness (EDS), we tested either only procedural or only working memory in 2 separate groups of patients with OSA and matched control subjects.

## METHODS

### Subjects

#### Recruitment and Screening

Patients were selected from a group of consecutive subjects referred to a tertiary-level sleep laboratory for evaluation of clinically suspected OSA. Control subjects were recruited by advertisements placed in local newspapers and on the hospital bulletin boards. All subjects were screened during an initial interview to exclude the presence of underlying conditions that could interfere with memory performance or with adherence to the study protocol. These included medical disorders (e.g., diabetes, cardiovascular or respiratory disease, cirrhosis), neurologic diseases (stroke, seizure disorder, head trauma, suspected neurodegenerative disease), alcohol or drug abuse, regular use of medications that could impair memory (e.g., benzodiazepines), score on the Mini-Mental Status Exam < 27, and sleep disorders other than sleep-disordered breathing (SDB), (narcolepsy, insomnia, periodic leg movements, or history of restless leg syndrome).

Ninety-five patients were included after the diagnosis of OSA was confirmed by polysomnography, with a threshold respiratory disturbance index (RDI) $\geq$ 10 per hour. Patients with mostly flow-limitation episodes[34] were excluded from the study. Patients with OSA were matched with control subjects based on age and level of education, assessed by the number of years in school. In order to ascertain the absence of subclinical SDB, each control subject underwent overnight oximetry. In addition, overnight polysomnography was performed in a random subset (25%) of control subjects. One hundred and eleven control subjects were screened for the study. Overnight oximetry was considered normal when mean nocturnal $SaO_2$ was above 93% and no $SaO_2$ dip greater than 3% was recorded. Sixteen subjects had to be excluded because of abnormal (n = 13) or incomplete (n = 3) oximetry data. None of the controls undergoing polysomnography had SDB, as defined by an RDI $\geq$ 10 per hour. Informed consent was obtained from all subjects included in the study at the time of screening or prior to the beginning of the experimental protocol. None of the participants received compensation for participating in the study.

### Overall Assessment

To evaluate daytime vigilance, subjective sleepiness was assessed by the Epworth Sleepiness Scale[28] (ESS) score, which was obtained in all subjects enrolled in the study on the evening preceding the overnight study. In subjects undergoing extensive memory testing (group 1, see below), reaction time was measured using a custom-made computerized test at 9:00 AM and at 11:00 AM to objectively evaluate daytime vigilance. To complete the test, the subject sat in front of a computer screen, in a well-lit room. Two numbers (from 2 to 9) appeared simultaneously on the screen, 1 on each side of the screen. As the targets appeared on the screen, the subject had to decide which of the 2 numbers was the highest and press a key corresponding to the appropriate side of the screen (left or right) as quickly as possible. A mean performance score taking into account both the reaction time and the accuracy of the answer was calculated for each test, with lower scores indicating better performance. Lastly, the Beck Depression Inventory (BDI) and 2 tests of verbal IQ (part B of the Mill Hill test and the verbal automatism test) were administered to all

subjects, using validated versions adapted for French-speaking patients.[29,30]

## Experimental Groups

Patients and their matched controls were included in 3 separate experimental groups. Subjects were included in chronologic order. Group 1 (54 patients with OSA and 54 matched controls) was assessed with an extensive battery of memory tests evaluating episodic, procedural, and working memory. One of the main symptoms of OSA is EDS, which may impact on psychometric performance when multiple tests are performed consecutively.[31,32] To control for the potential effect of prolonged test duration in patients with EDS, 2 additional independent groups were evaluated for only 1 type of memory. Group 2 subjects (16 patients with OSA and 16 matched controls) were only tested for procedural memory and group 3 subjects (25 patients with OSA and 25 matched controls) were only tested for working memory.

## Measurements

### Sleep and Breathing

For in-laboratory polysomnography, electroencephalogram with electrode positions C3/A2-C4/A1-Cz/O1 of the international 10-20 electrode placement system, eye movements, chin electromyogram, and electrocardiogram with modified $V_2$ lead were continuously recorded. Airflow was estimated with nasal pressure, plus the sum of oral and nasal thermistor signals. Respiratory effort was monitored with uncalibrated inductance respiratory plethysmography. Either esophageal pressure or pulse transit time was recorded concurrently. Oxygen saturation was measured using a pulse oximeter (Biox-Ohmeda 3700; Ohmeda; Liberty Corner, NJ). Overnight records were scored manually by trained polysomnography technicians according to standard criteria.[33,34] Respiratory events were classified as obstructive or central based on airflow, pulse transit time, or esophageal pressure-signal analysis.[34,35] The number of inspiratory flow-limitation episodes, obstructive apneas, and hypopneas per hour of sleep was calculated to obtain an RDI (number of events per hour of sleep).[34] Severity of $O_2$ desaturation was assessed by mean $SaO_2$ and by time spent at a $SaO_2$ below 90% during the recording. In control subjects who did not undergo polysomnographic testing, oxygen saturation was monitored overnight at home using the pulse oximetry (Biox-Ohmeda 3700). Analysis of the $O_2$ trend was performed the next morning, yielding mean $SaO_2$ and time spent at a $SaO_2$ below 90% during the recording.

### Memory Tasks

Episodic memory was tested using a serial verbal learning task, with control of encoding and recall, according to the modified procedure of Grober and Buschke.[36] Subjects were asked to learn a list of 16 words. Each item belonged to a different semantic category and was chosen so that it was not the most prototypic item of its category.[37]

#### ENCODING PROCESS AND IMMEDIATE RECALL:

Sixteen words were presented orally by groups of 4. For each word, the subject was asked to identify the semantic category to which the item belonged (ex: harp = musical instrument). When the subject had correctly identified the 4 items in a group, the examiner proceeded to an immediate cued recall in order to verify that the words had been correctly encoded. This first phase finished when the 16 items had been recalled. The number of words correctly recalled on the first trial was recorded ("Immediate Recall", maximum = 16).

#### FREE AND CUED RECALL:

After a 20-second interfering task (counting backward for 20 seconds), the subject had to freely recall as many words as possible from the list (free recall). After 2 minutes, the examiner gave a semantic cue for each forgotten item (cued recall). If the subject was still unable to recall the item, the examiner gave the correct answer. These procedures (free and cued recalls) were repeated 3 times with an interference task between trials. For this test, we recorded the total number of words recalled freely over the 3 trials ("Total Free Recall," maximum = 48); the total number of words recalled freely plus the total number of words recalled with a semantic cue, over the 3 trials ("Total Recall," maximum = 48); and the learning slope between the first and the third trial ("Learning," the difference between the number of words recalled freely on the third trial and on the first trial, expressed as a percentage of the number of words recalled on the first trial).

#### RECOGNITION:

Forty-eight words were presented orally, 1 at a time. The subject had to identify which words belonged to the previous list. The list of 48 words contained the 16 items from the original list, 16 distracting words from the same semantic categories, and 16 other unrelated words. The number of words correctly recognized minus the number of false recognitions was recorded ("Recognition," maximum = 16).

#### DELAYED RECALL:

Twenty minutes after the recognition task, the subject was asked to once again recall the 16 words from the original list, following the initial procedures (free then cued recall). For this test, we recorded the difference between the number of words recalled freely on the third trial and the number of words recalled freely after the delay, expressed as a percentage of the number of words recalled freely on the third trial ("Delayed Free Recall Forgetfulness," a positive score indicating forgetfulness, a negative score indicating an improvement in recall, maximum = 100%); the difference between the number of words recalled on the third trial (free and cued recall); and the number of words recalled after the delay (free and cued recall) ("Delayed Total Recall Forgetfulness," maximum = 100%).

#### PROCEDURAL MEMORY:

A variation of the Mirror Tracing Task (MTT), a visual-motor skill-learning task,[38] was used to test procedural memory. The subject was required to follow a pattern traced on a sheet of paper within set boundaries using a pencil. The subject's hand as well as the pattern were hidden and could only be seen indirectly in a mirror placed in front of him or her. Following a verbal prompt to begin, the subject was given 2 minutes to complete each trial. Each subject completed 6 trials. Whenever the tracing went out of the boundaries, the subject was asked to start again immediately

at the point of exit. The subject continued to be timed throughout, and, consequently, each exit from the pattern penalized the subject on the length of the tracing in the time allotted.

After a practice trial with a simple geometric shape, the subject was asked to trace a 40-cm frieze of successive Ms (frieze 1) during 5 consecutive trials. On the sixth trial, the frieze was inverted (frieze 2) to evaluate the ability to generalize procedural learning to a new shape of equivalent graphic difficulty. Preliminary data from our laboratory have shown that subjects could manage this task regardless of their age or visual motor skills. Lastly, during trial 7, the subject was asked to perform the MTT with frieze 1 while simultaneously repeating a series of digits corresponding to his or her auditory span. The length of the auditory span had been determined prior to the beginning of MTT trials. For procedural memory tasks, we recorded the difference in tracing length between trials 5 and 1 following familiarization ("Pattern Learning"), the difference in tracing length between trials 6 and 1 ("Procedural Learning"), and the difference in tracing length between trials 6 and 7 ("Resistance to Interference," a negative score indicating that a subject continues to learn in spite of interference).

### WORKING MEMORY ASSESSMENT WAS BASED ON 2 PARADIGMS:

1 requiring maintenance and processing of information, the other requiring simultaneous work on 2 types of information.

### Tasks of Maintenance and Process

#### AUDITORY TRANSFORMED SPAN:

Series of digits were presented orally to the subject, at the rate of 1 per second. Immediately after the presentation of the series, a simple arithmetic operation (+1, +2, +3, -1, -2, -3) was indicated to the subject on a card.[39] The subject had to recall each number presented after transforming it using the operation printed on the card. All subjects started with a series of 2 digits. The test procedure was then adapted to the subject's performance. The length of each series presented depended on the success or failure on the previous series (n+1 in case of a success, n-1 in case of a failure). All subjects were asked to complete 10 series of digits. The average digit span, calculated from the 10 series of digits presented, was recorded ("Transformed Auditory Span").

#### MODIFIED PACED AUDITORY SERIAL ADDITION TEST:

A prerecorded tape delivered a random series of 61 numbers from 1 to 9, at a constant rate of 1 number every 4 seconds in the Modified Paced Auditory Serial Addition Test (PASAT).[40,41] The subjects were instructed to add pairs of numbers such that each number was added to the one that immediately preceded it on the recording: the second was added to the first, the third to the second, the fourth to the third, and so on. The response had to be given before the presentation of the next stimulus (4 seconds later). The sum of any given pair never exceeded 15. The number of correct responses was recorded (PASAT maximum = 60).

#### SELF-ORDERED SPATIAL MEMORY TASK:

This computerized test belongs to the Cambridge Neuropsychological Test Automated Battery and is a spatial memory test.[42,43] On a tactile screen, the subject was alternatively presented with series of 4, 6, or 8 boxes that could be opened by touch.

The subject was asked to search for targets hidden in the boxes. Targets were hidden randomly, using all the boxes, one after the other. The trial ended when all targets had been found (i.e., for a series of 4 boxes, the trial ended when the subject had detected all 4 targets). On a given trial, targets were not hidden twice in the same box. Because the subject was instructed to not reopen a box in which a target had already been found, he or she had to remember where previous targets were hidden while searching for a new target. After 2 practice trials with 4 boxes, 4 tests were run with 6 boxes and 4 with 8 boxes (data were collected only for these 8 runs). In addition to spatial-memory performance, this task also evaluates the efficiency of the strategy used to search for boxes. For this task, we recorded the number of between-search errors, i.e. the number of times the subject reopened a wrong box ("Self-ordered Spatial Memory") and the degree of organization to search for boxes, ("Self-ordered Spatial Strategy," with a low score indicating an efficient strategy).

#### DUAL-TASK PARADIGM:

This paradigm evaluates a specific working-memory process, the capacity to allocate attentional resources. Three tests were used: 2 in which the subject was asked to simultaneously complete a visuoconstructive task and an auditory short-term memory task, and a third test in which the subject was asked to simultaneously complete 2 short-term memory tasks involving different processes (i.e., an auditory task and a visual task). Before beginning the dual tasks, the subject was asked to perform a baseline auditory digit span task. The span was measured following a procedure modified from the digit span subtest of the WAIS-III for a francophone population.[44] The auditory digit span was determined as the number of digits that the subject could recall on at least 2 of the 3 trials.

#### DUAL TASK 1: AUDITORY TASK + MTT:

This task was the seventh trial of the MTT, in which the subject was asked to perform a mirror tracing task for 2 minutes, while simultaneously repeating a series of digits equal to the baseline auditory digit span. For this test of working memory, we recorded a dual-task performance, $\mu_1$, calculated as described by Baddeley et al[45] ($\mu_1=[1-((Pm+Pt)/2)]*100$, with Pm and Pt representing the change in performance score from single-to dual-task situations for auditory memory task and MTT, respectively.

#### DUAL TASK 2: AUDITORY TASK + TRACKING TASK:

While verbally repeating a series of digits in the same order as in the previous task, the subject was required to cross out square boxes that were distributed on a sheet of paper and linked to form a specific path, over a period of 2 minutes.[45] Prior to the task, a shorter version of the tracking task and the auditory task were practiced independently. For this task, we recorded $\mu_2$, calculated as described in the previous task, for the auditory-memory task and the tracking task.

#### DUAL TASK 3: DOUBLE SPAN TASK:

Two short-term memory tasks were undertaken simultaneously: an auditory span task and a visual span task. Prior to the dual task, the performance on each test was measured individually. The visual span was assessed with a computerized tapping task

(Corsi block, see reference 46). The auditory span was assessed by the repetition of a series of digits. Again, the procedure of the test was adapted to match the subject's performance, as was done in the auditory transformed span task. The subject completed 10 trials for each task. We recorded mean auditory span calculated over 10 trials ("Auditory Span"); mean visual span calculated over 10 trials ("Visual Span"); mean double span calculated over 10 trials ("Double Span"); and an index of the double-span performance, taking into account both spans undertaken individually ("Double Span Index" = [(Double Span/((Auditory span + Visual span)/2)]*100)

### Experimental Protocols

Patients and control subjects arrived at the sleep laboratory at 6:00 PM and were administered the ESS, the BDI, and a verbal IQ test. In addition, patients and control subjects from group 1 practiced the reaction-time test 3 times in order to familiarize themselves with the task and reduce the procedural learning that could occur when undertaking the task the following day. All patients and 25% of control subjects then underwent overnight polysomnography in the sleep laboratory, as described above. The remaining control subjects underwent overnight oximetry at home, as described above. All testing of memory and reaction time were performed on the following day between 8:30 AM and 12:00 PM.

### Protocol 1

Following the completion of the first reaction-time test at 9:00 AM, patients and controls from group 1 undertook the different memory tasks in the same order: verbal learning task, auditory digit span test, spatial digit span test, double span, and auditory transformed span test. After a 10- to 15-minute break, they undertook the second part of the testing: the verbal learning task (delayed recall), the PASAT; then, at 11:00 AM, a second reaction-time test, followed by the MTT (familiarization and 6 trials); and, lastly, the 3 dual-task paradigms, starting with the repetition of the

series of digits during the seventh trial of the MTT, followed by the last 2 dual tasks. The total duration of the test session, including breaks, was approximately 3 hours.

### Protocol 2

Following determination of the baseline auditory span, patients and controls from group 2 undertook the MTT (familiarization and 7 trials) at 9:00 AM. Total duration of the test session was approximately 30 minutes.

### Protocol 3

Patients and controls from group 3 undertook the following tests, starting at 9:00 AM: PASAT, self-ordered spatial memory task, and a single dual task (auditory short-term memory plus tracking task). Total duration of the test session was approximately 30 minutes.

### Data Analysis

Normality of distribution was tested using Kurtosis and skewness tests. Because most variables of interest were not normally distributed, statistical comparisons were performed with nonparametric tests. Using the Wilcoxon test, results obtained in patients in each experimental group were compared with results obtained in their matched controls. For tests based on multiple trials, a Kruskal-Wallis test was used to compare performance between trials. Results obtained in patients from Group 1 were compared with results obtained in patients from Group 2 and from Group 3, using a Mann and Whitney test. In Group 1, correlation between abnormal findings (compared with controls) and the following parameters were evaluated in patients using the Spearman rank test: BDI, ESS, RDI, time spent at $SaO_2$ < 90%, and mean $SaO_2$. Statistical tests were performed with SPSS® 11.5 for Windows (SPSS, Inc., Chicago, IL). Statistical significance was achieved for p values greater than .05. Data are presented as mean ± SD.

**Table 1**—Characteristics of Patients and Control Subjects

| Characteristic | Group 1 Patients (n=54) | Controls (n=54) | Group 2 Patients (n=16) | Controls (n=16) | Group 3 Patients (n=25) | Controls (n=25) |
|---|---|---|---|---|---|---|
| Sex, M/F | 38/16 | 37/17 | 16/0 | 16/0 | 21/4 | 16/9 |
| Age, y | 50.0±10.7 | 49.5±3.4 | 39.7±10.8 | 39.3±10.9 | 49.2 ±10.7 | 49.4 ±10.2 |
| Education, y schooling | 11±3.0 | 12±3.4 | 10.9±3.6 | 11.1±3.3 | 10.7±3.2 | 11.7±3.8 |
| BMI, kg/m² | 31.5±11.2 | 22.3±4.4[c] | 25.8±5.0 | 22.6±1.7[a] | 30.2±5.3 | 23.3±3.1[c] |
| Verbal IQ, score | 109.5±12.3 | 109.9±11.1 | 99.5±15.8 | 102.5±18.9 | 107.3±16.6 | 107.5±16.8 |
| BDI, score | 9.6±7.4 | 4.8±4.[b] | 10.8±6.7 | 1.1±1.4[b] | 8.3±7.4 | 6.2±6.9 |
| Reaction time, score | | | | | | |
| 9:00 AM | 136.07±17.04 | 117.42±21.09[c] | — | — | — | — |
| 11:00 AM | 138.4±16.52 | 119.33±20.98[c] | — | — | — | — |
| ESS, score | 11.3±4.9 | 5.0±2.4[c] | 9.2±5.5 | 2.2±1.1[b] | 9.2±4.8 | 4.2±2.8[c] |
| RDI, no./h | 44±23.0 | — | 29.5±18.4 | — | 42.1±19.6 | - |
| Mean $SaO_2$, % | 93.4±3.5 | 96.4±1.3[c] | 94.1±1.7 | 98.0±1.6[b] | 92.9±3.8 | 97.4±1.5[c] |
| Time at $SaO_2$ < 90%, min | 11.6±18.7[b] | 0.7±1.2[c] | 8.2±3.7 | 0.5±1.3[b] | 7.3±14.2 | 0.6±0.8[b] |

Data are presented as mean ± SD unless otherwise indicated. Comparison between patients and control subjects within each experimental group. BMI refers to body mass index; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; RDI, respiratory disturbance index.
[a] p < .05
[b] p < .001
[c] p < .0001

**Table 2**—Results of Memory Testing in Group 1

| Task | Patients (n = 54) | Controls (n = 54) | p value |
|---|---|---|---|
| **Episodic Memory** | | | |
| Immediate Recall | 15.05 ± 1.79 | 14.96 ± 1.75 | NS |
| Free Recall | 32.89 ± 5.53 | 35.81 ± 6.17 | < .01 |
| Learning | 51.75 ± 28.23 | 46.54 ± 32.24 | NS |
| Total Recall (Free + Cued) | 47.28 ± 2.0 | 47.63 ± 0.96 | NS |
| Recognition | 15.91 ± 0.35 | 15.76 ± 2.45 | NS |
| Delayed Free Recall Forgetfulness | -7.58 ± 17.7 | -1.92 ± 11.96 | < .05 |
| Delayed Total Recall Forgetfulness | 0 ± 0 | 0 ± 0 | NS |
| **Procedural Memory** | | | |
| Pattern Learning | 57.98 ± 40.81 | 90.79 ± 67.10 | < .01 |
| Procedural Learning | 65.38 ± 47.66 | 90.14 ± 63.73 | < .01 |
| Resistance to Interference | -4.55 ± 39.34 | -11.80 ± 40.28 | NS |
| **Working Memory** | | | |
| *Maintenance and Process* | | | |
| Transformed Auditory Span | 43.9 ± 0.74 | 4.93 ± 0.73 | < .001 |
| PASAT | 49.44 ± 10.71 | 55.20 ± 4.66 | < .001 |
| Self-ordered Spatial Memory | 20.58 ± 15.28 | 4.73 ± 8.45 | < .001 |
| Self-ordered Spatial Strategy | 33.48 ± 7.02 | 26.78 ± 6.68 | < .05 |
| *Dual Tasks* | | | |
| $\mu_1$ (auditory task + MTT) | 106.39 ± 40.39 | 109.18 ± 39.45 | NS |
| $\mu_2$ (auditory task + tracking task) | 96.78 ± 13.82 | 99.33 ± 12.06 | NS |
| Double Span Index | 91.64 ± 9.82 | 92.71 ± 11.32 | NS |
| **Short-Term Memory** | | | |
| Auditory Span | 5.75 ± 0.73 | 6.0 ± 0.68 | NS |
| Spatial Span | 5.39 ± 0.69 | 5.7 ± 0.78 | NS |

Data are presented as mean ± SD. PASAT refers to Paced Auditory Serial Addition Test; MTT, Mirror Tracing Task.



**Figure 1**—Procedural memory testing in Group 1: comparison of Mirror Tracing Task (MTT) learning curves in 54 patients with obstructive sleep apnea (closed circles) and 54 matched control subjects (open squares). Level of significance is shown for paired comparison between patients and controls for each trial. **p < .01. See text for details of tasks and other statistical comparisons.

## RESULTS
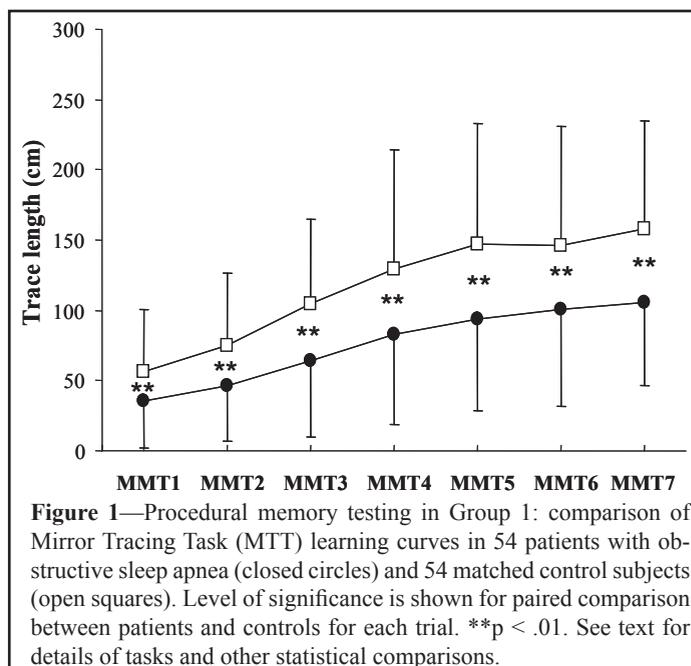
### Subject Characteristics

The main patient and control-subject characteristics are presented in Table 1. Patients and subjects were closely matched for age, education, and verbal IQ. Patients in all 3 groups had moderate to severe OSA, with similar degrees of nocturnal hypoxemia and EDS. None had an abnormal depression score.

### Protocol 1

Results of extensive memory evaluation in group 1 subjects are presented in Table 2.

#### EPISODIC MEMORY:

Several scores were used to evaluate verbal episodic memory. Only 1 of these scores was significantly lower in patients with OSA than in controls: free recall of 16 items on 3 consecutive trials. In contrast, the ability of the patients with OSA to encode and immediately recall the items, to recall these items when prompted by a cue, to recognize them among unrelated items, and to recall them after a delay was not significantly different from that of con-

trols. Moreover, as a percentage of total recall, forgetfulness was lower in patients than in controls.

Free-recall performance in patients correlated with reaction-time scores at 9:00 AM and 11:00 AM (r = -0.63 and -0.55, respectively; p < .01) but not with polysomnography data, BDI, or ESS scores.
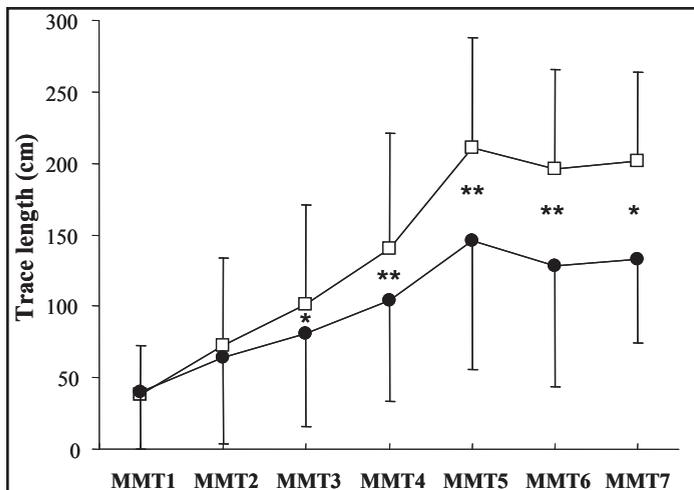
#### PROCEDURAL MEMORY:

Compared with their matched controls, patients with OSA obtained lower scores on all trials of MMT (Figure 1). However, patients significantly improved their performance from one trial to the next, even if this improvement was less than for control subjects. In addition, interference from a simultaneous auditory task had a similar effect on controls and patients. Procedural learning scores in patients correlated weakly but significantly with reaction-time performances at 9:00 AM and 11:00 AM (r = - 0.35 for both; p < .01), as well as with the amount of time spent at $SaO_2 <$ 90% (r = -0.28; p < .05), but not with the BDI, mean $SaO_2$, RDI, or ESS.

#### WORKING MEMORY:

For tasks evaluating information maintenance and processing, performance was lower in patients than in controls. Although baseline auditory spans were similar in both groups, transformed auditory spans were significantly lower in patients. During the spatial memory test (CANTAB), patients did not memorize previously searched boxes as well as controls did, and they demonstrated poorer search strategies. Furthermore, they had lower PASAT performance than did controls. In contrast, the level of performance was similar in patients and controls for all 3 dual tasks.

In patients, PASAT scores were significantly correlated with reaction-time performance at 9:00 AM and 11:00 AM (r = -0.35 and 0.44, respectively; p < .05) and with the BDI (r = -0.27; p < .05). In addition, self-ordered spatial-memory scores, but not strategy scores, correlated with RDI (r = 0.27; p < .05).

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**Figure 2**—Procedural memory testing in Group 2: comparison of Mirror Tracing Task (MTT) learning curves in 16 patients with obstructive sleep apnea (closed circles) and 16 matched control subjects (open squares). Level of significance is shown for paired comparison between patients and controls for each trial. **p < .01; *p < .05. See text for details of tasks and other statistical comparisons.

## Protocol 2

### PROCEDURAL MEMORY:

Mean tracing lengths for each MTT are presented in Figure 2. Although patients and controls performed similarly on the first trial following familiarization, subsequent increments in tracing length were clearly larger in controls than in patients with OSA. The difference was significant as early as the second trial and remained so for all trials. Consequently, the pattern-learning slope (trial 5 minus trial 1) was steeper in controls than in patients. Overall, procedural learning, expressed as the improvement in task performance between the last trial (trial 6, frieze 2) and the first trial (trial 1, frieze 1), was significantly lower in patients, compared with normal controls. However, the difficulty induced by the change of frieze or by a simultaneous auditory task had a similar effect on all subjects, and the expected fall in performance between trials 6 and 5 and trials 7 and 5 was not significantly different between controls and patients.

Compared with patients from group 1, patients from group 2 were significantly younger (p < .004), had a lower BMI (p < .004), and had a higher verbal IQ (p < .03). Furthermore, although subjective sleepiness was similar in both groups, respiratory disturbances in patients from group 2 were less severe than those in patients from group 1 (Table 1). However, in spite of these differences, procedural-learning performances were not significantly different between the 2 groups of subjects (Table 3).

## Protocol 3

### WORKING MEMORY:

Patients obtained significantly lower scores than controls for tasks evaluating maintenance and processing of new information (PASAT and self-ordered spatial tasks) (Figure 3). During the self-ordered spatial-memory task, not only did patients with OSA reopen boxes more often than controls, but they also used poorer search strategies. However, dual-task performance did not differ significantly between patients and controls. No correlation was found between working-memory scores and RDI, $SaO_2$ indexes,

**Table 3**—Results of Procedural and Working Memory Tasks in Patients Undergoing Extensive or Limited Memory Testing

| Tasks | Group 1 (n = 54) | Group 2 (n = 16) | Group 3 (n = 25) | p |
|---|---|---|---|---|
| **Procedural Memory** | | | | |
| MTT trial 1 | 35.96 ±34.24 | 40.09 ±43.07 | — | NS |
| MTT trial 6 | 101.33 ±69.0 | 128.19 ±83.74 | — | NS |
| MTT/Auditory Task | 105.9 ±60.27 | 133.52 ±58.60 | — | NS |
| **Working Memory** | | | | |
| PASAT | 49.44 ±10.71 | — | 45.2 ±9.34 | .03 |
| $\mu_2$ (auditory task + tracking task) | 96.78 ±13.82 | — | 96.40 ±14.98 | NS |
| Self-ordered Spatial Memory | 20.58 ±15.28 | — | 19.64 ±17.31 | NS |
| Self-ordered Spatial Strategy | 33.48 ±7.02 | — | 28.68 ±5.18 | .02 |

Data are presented as mean ± SD. Statistical significance refers to comparison of mean data between group 1 and group 2 patients for Procedural Memory tasks and between group 1 and group 3 patients for Working Memory tasks. See text for details of tasks. MTT refers to Mirror Tracing Task; PASAT, Paced Auditory Serial Addition Test.
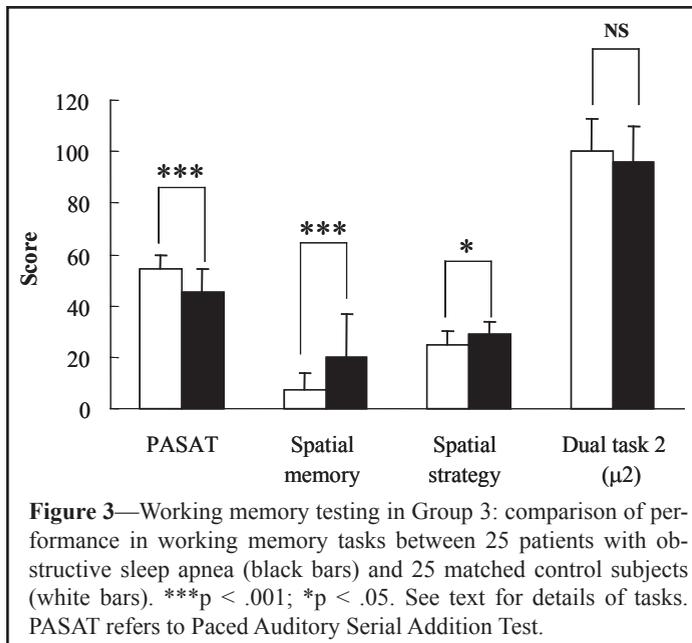
BDI, or ESS.

Patients from groups 1 and 3 were not significantly different in terms of age, BMI, intellectual abilities, depression, or nocturnal respiratory disturbances (Table 1), except that patients in group 3 tended to be slightly less somnolent (p = .07). Compared with patients in group 1, patients in group 3 used a better search strategy during the self-ordered spatial-memory task but obtained lower scores on PASAT (Table 3).

## DISCUSSION

Memory impairment is common in patients with OSA. In this study, we demonstrated that this impairment does not affect all memory processes but, rather, specific components. Extensive memory testing in a large group of patients with moderate to severe OSA and closely matched control subjects revealed (1) a retrieval deficit of episodic memory but intact maintenance, recognition, and forgetfulness; (2) decreased overall performance in procedural memory, although pattern learning did occur; and (3) impairment of working memory, characterized by poor maintenance and processing of new information despite normal attention-resource allocation and short-term memory. The long duration of the test session did not impact negatively on patients' performance, since patients undergoing shorter tasks evaluating either only procedural or only working memory, did not score better than patients subjected to extensive testing.

### OSA and Episodic Memory

Testing of cognitive function in patients with OSA suggests that verbal or visual episodic memory is impaired in these patients: they display poor performances on immediate or delayed recall[3,6,8,15-17,47] and use semantic clustering and semantic cues less efficiently than do normal subjects.[47] Standard global tests of episodic memory measure performance in free recall, delayed recall, and recognition, and the subject is asked to remember as much information as possible. However, the encoding of information, the pathway or pathways through which information is retrieved,

**Figure 3**—Working memory testing in Group 3: comparison of performance in working memory tasks between 25 patients with obstructive sleep apnea (black bars) and 25 matched control subjects (white bars). ***p < .001; *p < .05. See text for details of tasks. PASAT refers to Paced Auditory Serial Addition Test.

as well as the interaction between these 2 procedures, all significantly impact performance.[48] Poor test results could therefore be the consequence of an attention deficit, a failure to use an efficient strategy, or an inability to appropriately process information. Consequently, an important aspect of episodic-memory testing is to ensure that the subject uses an efficient strategy to encode and recall the information. With these results, one cannot conclusively determine whether patients have difficulty memorizing new information because of impaired encoding, impaired retrieval, or impaired maintenance or whether they forget more rapidly than do controls. In the present study, we tested verbal episodic memory in patients with OSA using a forced-encoding technique at the time of word presentation in order to increase the attention paid to the items to memorize.[19,20] In spite of forced item encoding, patients with OSA showed poorer recall than did matched controls. However, they normalized their performance when cued by the examiner, and their learning and recognition scores, as well as their forgetfulness rates, were not different from those of controls. In addition, impaired recall exhibited by patients with OSA was related, at least partially, to mental-process inertia, as recall performances were inversely correlated with reaction time. Overall, the verbal episodic-memory performance pattern observed in our study is consistent with isolated retrieval impairment, with no associated significant storage or consolidation deficit. These findings confirm our previous results[49] as well as those of other authors.[47]

Such retrieval deficit is different from the deficit observed in patients with amnesia secondary to temporomedial cortical or diencephalic lesions, whether the lesions are focal or diffuse. In such patients, the primary memory deficit is characterized by poor storage and consolidation of new information. For instance, in the initial stage of Alzheimer disease, immediate free, as well as cued, recall performances are low, and recognition scores are decreased compared with age-matched control subjects.[50,51] Such a pattern was not seen in our group of patients with OSA. Retrieval deficit of properly encoded and stored information is not specific to OSA and has been demonstrated in patients with a variety of disorders: Parkinson disease,[52] rupture of an anterior communicating artery aneurysm,[53] schizophrenia,[54] amyotrophic lateral sclerosis,[55] and

clinical depression.[54] When verbal episodic memory is tested with the forced-encoding technique, such patients show a performance pattern similar to that of our patients. Overall, the pattern of episodic-memory deficit observed in this study is suggestive of prefrontal, subcortical, or both prefrontal and subcortical dysfunction.[56,57]

## OSA and Procedural Memory

We also examined procedural-memory status in patients with OSA, using a standard, albeit simplified, task, the MTT, which all subjects were able to complete successfully. Few studies have examined procedural memory in patients with OSA. Using a problem-solving task (a simplified version of the Tower of Hanoi), we showed that, although patients with OSA displayed an initial adaptation deficit, their learning and forgetfulness rates were similar to those of control subjects.[49] Nevertheless, such problem-solving tasks may be considered unsuitable to assess procedural memory, as subjects can use episodic-memory abilities to improve performance from one trial to the next. A more relevant way to evaluate procedural memory could be to select skill-learning tasks that do not involve either explicit episodic memory or strategic choices, such as the MTT or the Rotary Pursuit Task. At present, however, data on procedural memory using skill-learning tasks in OSA are scant. Rouleau and coworkers have shown that less than half of patients with OSA display marked difficulty in the initial acquisition of the MTT, without significant differences in learning rates of either the MTT or the Rotary Pursuit Task, as compared with control subjects.[21] All patients in our study exhibited poor MTT performances, which were related to impaired behavior adjustment but not to procedural learning deficit: patients progressed significantly from one trial to the next but remained consistently below the level of performance of matched controls.

We selected only 1 task to measure procedural memory, the MTT, and this is clearly insufficient to fully characterize a process as complex as procedural memory, particularly since the various procedural-memory tests are affected differentially in disorders such as Huntington disease[13] or Alzheimer disease.[21] Yet, in the present study, patients with OSA did show significantly decreased performance in this single task, as compared with controls. Nonetheless, conclusions regarding procedural impairment in OSA should be nuanced, as they cannot be extrapolated to other aspects of procedural memory, such as cognitive procedural learning for instance.

To complete the task chosen for this study, the subject is required to mentally reverse the visual information provided and create new associations between a visual stimulus and a motor response. The automatic behavior prompted by the visual stimulus must therefore be constantly inhibited, and new spatial references must be constantly generated to produce the appropriate response. The handling of such mental representations is not a conscious process but is executed through procedural-memory processes. Our findings suggest that patients with OSA have difficulty creating a new sensorimotor coordination rather than difficulty retaining it. In fact, a global psychomotor deficit has been demonstrated in patients with OSA,[22,58,59] although the pathophysiologic mechanism remains unclear. The role of EDS has been put forward as a potential factor.[2] However, whereas most patients with OSA exhibit poor performances on a test of fine motor skills (Purdue Pegboard Test),[8,22,60,61] they perform as well as controls

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on a test of motor speed only (Finger Tapping).[59,61-63] Their deficit is therefore not characterized by overall slowness but, rather, by impairment in fine motor skills. Neither patients in the initial stage of Alzheimer disease[64] nor patients with amnesia secondary to focal frontal or temporal lesions[65] show such impairment on the standard version of the MTT.

The visual-motor task deficit that we observed was also present in group 2 patients who were younger and tended to have less-severe OSA than group 1 patients. This deficit could therefore constitute a useful indicator of early neuropsychological impairment in OSA.

The association of a deficit in fine motor-skill coordination and MTT impairment, as was seen in our patients, is suggestive of an early dysfunction of subcortical structures,[66] since experimental data in humans and animals have shown that these structures, in particular the striatum, are preferentially involved in the acquisition of motor skills.[67] Interestingly, these regions are particularly sensitive to severe hypoxemia.[68,69]

## OSA and Working Memory

Working memory in patients with OSA is affected inconsistently across experimental studies.[8,22-25] To our knowledge, no experimental study has previously investigated working memory in patients with OSA using validated experimental paradigms based on a theoretical cognitive framework. Verstraeten and Cluydts have recently suggested that executive function in patients with OSA should be examined using the theoretical model proposed by Baddeley in 1986,[27,70] which is currently accepted as the most relevant model of short-term storage of information. Briefly, working memory is a cognitive system of limited capacity, which allows temporary retention and processing of information during various cognitive tasks. This cognitive system includes an amodal central administrator, supported by 2 slave subsystems that are responsible for temporary storage of specific information: the phonologic loop for storage of verbal information and the visuospatial sketch pad for storage of visual, spatial, or visuospatial information. Short-term auditory span tests evaluate the former, whereas short-term spatial tests evaluate the latter. The central administrator controls the allocation of attentional resources and is typically evaluated with dual-task methodology. Working memory includes many capacities: maintenance and processing of information stored in short-term memory, supervision of allocation of attentional resources required to complete simultaneous tasks, and coordination of the mental steps involved in problem solving.[12] As a result, evaluation of working memory is complex, as no single task can assess its multiple aspects. Yet, using a protocol derived from Baddeley's theoretical model allowed us to examine working memory in patients with OSA in a precise manner. The dual-task paradigm proposed by Baddeley[70] and the self-ordering pointing paradigm from the CANTAB battery of tests,[42] for example, have been well validated. Although both paradigms evaluate working memory, they do not test the same mode of information processing: the first paradigm tests the capacity to simultaneously manage 2 separate cognitive activities, whereas the second evaluates the capacity to accumulate and maintain information while simultaneously handling new data. We selected these tests to examine whether working memory is deficient in patients with OSA.

Our findings are 2-fold. First, the capacity for short-term retention of verbal or visual information of patients with OSA was normal with a protocol using a step-by-step assessment technique tailored to the subject's abilities. Second, working memory was impaired but not uniformly: compared with matched controls, patients with OSA had difficulty maintaining auditory and spatial information while simultaneously processing it, whereas they performed similarly while simultaneously completing 2 independent tasks. These results support the theory that patients with OSA do not have a specific dysfunction of the central administrator of Baddeley's model, as has already been suggested by Verstraeten and Cluydt.[4] These authors attributed working-memory impairment to a global decrease in the speed of information treatment, which would partly account for our findings concerning the PASAT. However, these authors evaluated patients using standard tasks of forward and backward digit spans, a method that may be inadequate because it evaluates short-term memory rather than working memory as a whole. Furthermore, the hypothesis of overall slow information treatment does not explain the poor performance of patients with OSA in the transformed auditory span and in the self-ordering spatial task, which are not timed. In addition, unlike auditory span-test performances, transformed span performances were significantly lower in patients than in controls, even though the format was similar: progressive span, span adapted to each subject's capacity, and evaluation based on the same number of trials. Consequently, the slowness of patients with OSA cannot account fully for the working-memory deficit that we observed in this study.

The preserved ability of these patients to allocate attentional resources to 2 simultaneous but unrelated tasks may appear discordant with prior reports. For instance, we recently showed that, compared with control subjects, a group of patients with OSA similar to patients included in this study scored lower when asked to simultaneously carry out a driving-simulation test and a visual-detection test.[71] However, in that particular study, performance was measured and reported separately for each task and, therefore, did not specifically reflect the disruption induced by simultaneously undertaking both tasks. Before concluding that a cognitive ability is impaired, it is necessary to ensure that the subject possesses the proper means to complete each test.[27] The dual-task performance measures used in this study allow the true evaluation of a subject's ability to simultaneously execute 2 tasks.

The dual-task paradigm could lack the proper sensitivity to detect mild working-memory impairment in patients with OSA. In fact, a close examination of studies that have used Baddeley's dual-task paradigm in disorders such as epilepsy, frontal lobe lesion with behavioral problems, or Alzheimer disease suggests that diffuse brain impairment is necessary to manifest a significant deficit.[72,73] In contrast, focal lesions, in particular frontal lesions, are not usually characterized by abnormal dual-task performance.[73] At present, the extent of brain impairment in OSA is not known. Recently, the absence of dorsolateral prefrontal activation on functional magnetic resonance imaging studies during a working-memory task was demonstrated in patients with OSA, while other regions were activated similarly in patients and controls.[24] However, one needs to be cautious when ascribing working-memory dysfunction to specific brain regions, as functional imaging shows that separate components of working memory (manipulation of information, updating of stored information, coordination of attentional resources, and inhibition and shifting ability) activate not only several frontal regions, but also more posterior

areas, such as the parietal cortex.[24,74] In fact, many brain regions are likely to be implicated in a cognitive process as complex as working memory and may be differentially affected by OSA.

## OSA and Memory Impairment: General Considerations

In agreement with other studies, regardless of the type of memory evaluated, the deficit that we observed in patients was mild, in spite of their having moderate to severe OSA, compared with the type of deficit exhibited by patients with dementia, for instance. In group 1 patients, we found no consistent correlation between the severity of OSA, assessed by RDI or $O_2$ saturation data, and the severity of memory deficit. This finding contrasts with the relationship between OSA severity and executive function found in previous reports.[3,17,59,75] However, meta-analysis of the relevant literature is difficult because of the wide dispersion of RDIs among reports, the absence of consensus about OSA-severity criteria, and the lack of focus on memory function in many of these protocols. The present study, however, was not designed primarily to explore this relationship.

Extrapolation of our findings to the general population of patients with SDB may be difficult. Patients included in this study were recruited at a tertiary-care outpatient clinic and, therefore, may not be comparable to individuals who are seen by private sleep practitioners or in community-based hospitals clinics. For instance, a patient with marked mnesic difficulties may be more likely to be referred by his or her family physician to a teaching hospital with an accredited sleep laboratory than would be a patient denying any cognitive dysfunction. Another potential limit is the severity of SDB in our patient sample (mean RDI > 30 per hour and marked oxygen desaturation in all groups, see Table 1). Whether mild SDB, particularly in the absence of moderate to severe intermittent hypoxia, can cause memory dysfunction remains to be examined.

Close examination of the patients' performance shows that there was marked interindividual variability. Variability in disease severity, disease duration. and susceptibility to cognitive consequences of sleep fragmentation and intermittent hypoxia could account, at least partially, for this observation. Nevertheless, similar performance variability was present in control subjects, underlying the need to closely match patients and normal subjects, 1 by 1, for variables relevant to memory function, in order to minimize bias.

EDS is a major symptom of OSA and affects daytime cognitive function.[31,32] Furthermore, selective or total sleep deprivation in normal subjects has a detrimental effect on episodic,[76] procedural,[77] and working[77,78] memory. Therefore, one could argue that a 3-hour test session in patients with moderate and severe OSA could lead to an overestimation of memory impairment, particularly for procedural- and working-memory testing, which took place at the end of the test period. To examine this concern, we tested either procedural memory or working memory alone, in independent groups of patients with OSA and matched controls during test sessions not exceeding 30 minutes. Results obtained during the shorter test session were consistent with those obtained during the long session. In addition, subjective or objective sleepiness evaluation correlated poorly or not at all with memory performance. While these findings do not exonerate sleep fragmentation as a potential cause of neuropsychological dysfunction, they support the validity of extensive testing in patients with OSA.

Both hypoxia and sleep fragmentation affect cognitive function.[32,79,80] However, our findings cannot clarify their relative contribution to the memory deficit observed in patients with OSA. Administering study protocols similar to this one to normal subjects or animals exposed to either intermittent hypoxia or repeated microarousals or to patients with nonhypoxemic SDB could add to our understanding of pathophysiologic mechanisms of memory impairment related to OSA.

Patterns of neuropsychological deficit exhibited by patients with OSA for the various memory processes tested in this study suggest dysfunction in specific brain regions. For instance, as noted above, an isolated retrieval deficit in episodic-memory testing points toward subcortical or prefrontal dysfunction and impairment in visuomotor procedural memory toward striatal dysfunction. So far, however, functional imaging in patients with SDB has yielded inconsistent results. For instance, with similar imaging techniques, one study reported widespread gray-matter loss,[81] whereas another demonstrated unilateral hippocampal lesions.[82] Functional-imaging data collected during specific memory-component evaluation appears promising in patients with OSA.[24]

In conclusion, our study is the first to specifically address which memory processes are impaired in OSA. We have demonstrated that, compared with matched controls, patients with OSA had mild but significant memory impairment affecting episodic, procedural, and working memory, but these impairments were not uniform. Our findings underscore the importance of extensive testing in these patients because a single memory task may not reveal mild impairment. To fully grasp the extent of the mnesic deficit in OSA, additional experimental protocols should be designed to probe specific memory subsystems (for instance, semantic memory, visual and spatial episodic memory, and procedural cognitive learning). Exploring the pattern of poor performance exhibited by patients provides clues about the brain regions that may be affected as a result of OSA and should guide functional brain imaging.

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