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Deficits of Cognitive Executive Functions in Patients With Sleep Apnea Syndrome

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Summary: Impairment of cognitive executive functions previously has been suspected to occur in association with sleep apnea syndrome (SAS), as suggested by some neuropsychological studies. However, such functions have not been assessed directly. In the present study, 17 patients with SAS were evaluated with various focused frontal lobe-related tests in comparison with 17 normal controls. Such tasks explored attention, short-term memory spans, learning abilities, planning and programming capacities, categorizing activities and verbal fluency. Patients were found to have a significantly decreased ability to initiate new mental processes and to inhibit automatic ones, in conjunction with a tendency for perseverative errors. They were also affected with deficits of verbal and visual learning abilities and had reduced memory spans. Such defects were further evaluated via logistic regression against two criteria of the severity of the disease: the number of apneas and hypopneas per hour of sleep and the level of nocturnal hypoxemia. Memory deficits were rather related to the former, whereas typical frontal lobe-related abnormalities seemed rather consistent with the latter. These findings are discussed in light of data from the literature concerning cognitive impairments described for patients with isolated daytime sleepiness versus hypoxemia, as illustrated in other pathological or physiological circumstances. **Key Words:** Sleep apnea syndrome—Neuropsychology—Executive functions.

Sleep apnea syndrome (SAS) is a common disorder affecting more than 4% of the general adult population (1,2) and more than 25% of the elderly (over age 65) (3). The chief clinical consequence of obstructive sleep apnea is excessive daytime sleepiness, thought to be related both to the fragmentation of sleep by recurrent arousals and to the effects of hypoxemia on cerebral function (4–11). Cerebral blood flow changes associated with apneas may also contribute to the impairment of brain activity (12–15).

Besides the common impairment of daytime vigilance, psychological alterations have been reported, such as irritability, impatience or even depressive manifestations (16). Moreover, apneic patients have been found with cognitive impairments, including deficits in attention and visio-motor abilities (17,18), long-term memory (18,19) and intellectual efficiency (18,20–22). In most studies, data have suggested an impairment of the so-called "executive functions", a concept initially introduced by Luria and Lezak (23,24) to define cognitive functions such as planning, programming, regulation and verification of goal-directed behavior. Hence, there is ample evidence, both from animal and human studies, that the prefrontal cortex might be the neuroanatomical substrate for these functions (23,24).

Low intellectual performances of SAS patients have been evaluated by the use of global assessment scales without a priori assumption on the underlying cognitive functions involved. Therefore, the present study was designed to evaluate in patients with SAS some

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limited patterns of daytime intellectual abilities, particularly the executive functions. In light of the results already found using global assessment scales, this experiment focused on different aspects of frontal-related cognitive functions: memory (short- and long-term memory, verbal and visual memory), selective attention (with shift and focus components), verbal fluency, planning abilities and mental flexibility.

METHODS

Subjects

Seventeen male SAS patients, 27–76 years of age [49 ± 3 years (mean ± SEM)], complaining of daytime sleepiness were eligible for inclusion. Their acceptance in the study was based on consecutive choice. Subjects who were taking medications that could interfere with cognitive efficiency, those with depressive manifestations [i.e. with a score above 10 (out of 59) on Beck's evaluation scale (25)], cerebral insult, narcolepsia and daytime impairment of respiratory function were excluded from the study.

Volunteer clinically normal male controls (n = 17), devoid of known or suspected alcohol or drug abuse and without history of learning disabilities, cerebral insult of any etiology or sleep disorder, matched for age (mean ± SEM = 49 ± 3 years), verbal IQ (26) (106 ± 4 for SAS patients and 107 ± 2 for controls) and school education level, were selected from the general population.

Sleep apnea syndrome patients were included after 1 night of polysomnography (27), wherein sleep was recorded and scored according to standard methods, including central and occipital electroencephalogram, chin electromyogram, electrooculogram and electrocardiogram (28). Polysomnography included oxygen saturation (SaO_2) by transcutaneous oxymetry, airflow measurement both at nose and mouth levels with thermistors, and thoracic and abdominal movements monitored by uncalibrated impedance plethysmography (29). All patients studied had a respiratory disturbance index (RDI, defined as the number of apneas and hypopneas per hour of sleep) greater than 10. In absence of universally admitted criteria for objective assessment of the severity of SAS, patients with an RDI below 40 were arbitrarily considered moderately apneic (n = 7), whereas those with an index above 40 were classified as severe (n = 10). Severity of hypoxemia was defined according to the cumulated sleep time spent at SaO_2 levels <85%. SAS patients were arbitrarily considered moderately hypoxemic (n = 10) when the duration of SaO_2 <85% remained below 10 minutes, and were classified as severely hypoxemic (n = 7) for durations exceeding 10 minutes.

Experimental procedure: neuropsychological assessment

All SAS patients were tested between 3:00 and 6:00 p.m. on the day following the night of polysomnography.

Attentional capacity

Trail-making test (30). This test required the subject to draw lines by connecting numbers (part A) or numbers in alternance with letters (part B) as quickly as possible. Both tests were timed, and scoring was based on the test duration in seconds (TMA, TMB).

Digit cancellation task. This test, taken from Pacaud (31), consisted of 20 rows of 15 digits from which all digits "2" placed between two odd numbers and all digits "7" placed between two even numbers had to be crossed out within 1 minute 30 seconds. Scoring (DBL-CANC) was defined as the number of correct crossings from which the number of omissions and errors was subtracted.

Stroop-color test. This test evaluated resistance to interference and measured the ease and rapidity of shifting from a perceptual set to another changing demand. This required the subject to suppress habitual responses in favor of an unusual other one (32). Briefly, it consisted of three white cards, each containing 10 rows of 10 items. After having named the color of dots (blue, red, green), each subject was asked to read the color names (blue, red, green), all printed in black, and then to name the color in which the color names are printed (and not the written names themselves, color names being printed with disparate colors), thus disregarding their verbal content. The time to complete this last task increased significantly and such a speed decrease is called "the interference effect" (STROOP).

Memory efficiency

Short-term and working memory: verbal span (DIGIT). This function was assessed with the WAIS-R digit span procedure (33). The span length for the digits repeated in the same order as presented and that for the digit recalled in inverse order (DIGIT-INV) were both recorded. Visual span was assessed by Corsi's block-tapping tasks described by Milner (34). The span length (CORSI) was the longest sequence the subject could reproduce.

Double-encoding task. This task is supposed to require much more diligent attentional resources than the isolated verbal or visual tasks. It requires the subject to encode both words presented sequentially and their specific locations on a 5 × 5 box matrix. Presentation of the respective words within the empty matrix

was achieved on a computer screen by displaying them one by one in the appropriate box for 1.5 seconds. After a 4-second delay, the subject had to recall the words at their correct locations. The task began at the simplest level of difficulty (only one word presented) followed by increments of one additional word and further, as long as the subject remained successful. The "double-codage" span was calculated as the longest sequence of words at their appropriate locations successfully recalled (DC-SPAN). To evaluate the additional difficulty requested from the subject for such a double-codage performance, the scoring of verbal span alone (VERB-SPAN) and visual span alone (VIS-SPAN) was also performed. This was ensured with two different procedures where the subjects had, in one case, to only recall the words presented without specific location (VERB-SPAN), whereas in the other case they only had to show the recalled location of the appropriate boxes, which were presented by flashing them empty, without any word inside (VIS-SPAN).

Long-term memory

The procedures testing long-term memory were based on serial learning, where the presented lists of items were longer than the common span length. They were chosen because they involve active memory strategies highly sensitive to frontal lobe-related dysfunctions.

Verbal learning test. According to the selective reminding procedure of Buschke (35), subjects were asked to learn a list of 10 names of animals [their frequency of occurrence in French being less than 20 (36)]. The entire list was read aloud once before the first recall trial. In subsequent trials, subjects were selectively reminded only of those items which were not recalled by them on the immediately preceding trial. They had to try to recall in any order all 10 items at each trial. Learning proceeded up to the criterion of two consecutive recalls of the entire list over a maximum of 10 trials. Verbal recall performance (VER-L) was determined from the mean of correct responses from which the mean of errors per trial (i.e. repetitions and additional names) was subtracted. After a 30-minute delay, during which the subjects performed other tasks, participants were asked to recall again the entire list. Verbal forgetting in percent (VER-F) was then calculated (ratio in percent of the difference between the number of names recalled before and after the 30-minute delay to the number of recalled items before this delay).

Visual learning test. Subjects were asked to learn the precise location of 10 black boxes placed on a 5 × 5 white matrix and presented over 30 seconds. The entire pattern was presented at each trial. After each presentation, subjects blackened the 10 remembered locations on a similar but empty matrix. Visual learning proceeded up to the criterion of two consecutive correct recalls of the entire pattern over a maximum of 10 trials. Visual learning performance (VIS-L) was determined as the mean of correct responses to which the mean of errors per trial was subtracted. After a 30-minute delay, during which time the subjects performed other tasks, they had to recall again the same visual pattern. Visual forgetting in percent (VIS-F) was then calculated in the same way as for verbal forgetting.

Frontal lobe functions

Subjects were evaluated with tests classically used for the intellectual assessment of patients with frontal lobe-related lesions.

The Modified Wisconsin card sorting test (37). This test is considered to be a test of "abstract of behavior" and of "shift of set" (38). Briefly, the subjects were asked to sort a set of 48 cards by category (color, form and number) so that they matched one of the four target cards. In addition they had to modify their responses according to the feedback received from the experimenter. Performances were scored in terms of categories achieved (maximum six) (WISC-CAT), total of errors (WISC-ERR) and percentage of perseverative errors (WISC-PER).

Test of verbal fluency. Subjects were told to say as many words as possible, within 1 minute, beginning with a letter of the alphabet provided by the examiner (P, L, F here). Proper names were not allowed. The number of correct words produced per letter in 1 minute was recorded (FLUENCY-P, FLUENCY-L, FLUENCY-F).

Tower of "Toronto" (39). A simplified version of the tower of Hanoï (40) was chosen to assess planning ability of the subjects in a problem-solving situation. The subjects had to move three then four discs from an initial configuration into a goal configuration within a minimum number of moves. Three different trials were allowed in the three-disc experiment and four in the four-disc one. Then a simple tally of the number of moves per trial (without counting illegal moves) was tabulated, and the mean number of moves per disc experiment (TOWER-3, TOWER-4) was recorded.

The twenty questions procedure. This test, as used by Goldstein and Levin (41), was chosen to evaluate subjects' strategies in verbal problem-solving tasks. Subjects had to organize and shift their response sets according to the feedback provided by the examiner and then evaluate their final performance. In this study, only the first five questions asked by the subjects were recorded (QUEST); scoring took into account only the "constraint" ones (i.e. those categorizing at least two or more different pictures among the 42 presented).

Statistical analysis

Graphic analysis of each variable from the various recorded neuropsychological data was performed with the use of SYSTAT 5.2 software, for assessing distribution and continuity. Kurtosis and skewness were also calculated and checked for superior limits set at 1.5 and 1.0, respectively. Because most of these variables appeared as discontinuous, not normally distributed or/and with kurtosis and skewness indexes above the set limits, all further comparisons between the data from control subjects and SAS patients were performed with the use of nonparametric tests (Mann Whitney and Kruskall-Wallis tests from SYSTAT 5.2) with significance limits set at $p < 0.05$.

To evaluate the predictive accuracy of the various neuropsychological tests used here, logistic regression analysis was performed with the help of the SPSS/PC+ 4.0 software package. First, the event of SAS occurrence was tested as the dependent variable (0 = controls, 1 = SAS). Building of the model was facilitated by both forward and backward stepwise methods. Goodness of fit of the model was assessed via the criterion of -2 times the log of likelihood (-2 LL), its chi-square classification table and improvement, followed by the resulting global classification table. The histogram distribution of estimated probabilities for the various cases (class plot) completed the assessment of the model. A "receiver operating characteristics" (ROC) statistical procedure was also checked to evaluate the accuracy of the model for predictive purposes (42). This was ensured by calculating the sensitivity and the specificity of the model over a range of arbitrarily chosen cut-off points of the probability (within 0–1 limits) as predicted by the model (43). Secondly, the same logistic regression procedure followed by ROC analysis was further applied to the neuropsychological data from the SAS patient population, with the dependent variable used for establishing the models either discriminating between severe and moderate hypoxemia or between severe and moderate apneic patients.

RESULTS

The 17 SAS patients had a body mass index (BMI) of 32.4 ± 1.5 kg/m^2 (mean $\pm$ SEM), ranging from 24.0 to 46.8 kg/m^2, an RDI of 41.0 ± 4.5, with a minimum of 14.2 and a maximum of 75.0. They had a diurnal supine SaO_2 of $93.6 \pm 0.5\%$, ranging from 90.0% to 97.0%, PaO_2 of 70.9 ± 2.7 mm Hg, ranging from 57.0 mm Hg to 90.0 mm Hg and $PaCO_2$ of 40.0 ± 0.7 mm Hg, ranging from 35.0 mm Hg to 42.0 mm Hg.

The neuropsychological performances of SAS patients and their matched control subjects are presented in Table 1. When considering the tests that primarily evaluated attention-related processes, only the STROOP test gave significantly different results in SAS patients versus age-matched control subjects ($U = 92.00$; $p < 0.05$). Accordingly, our SAS patients seemed not to have obvious difficulties in performing tasks in which focal attention and even shifting processes are required as evaluated by TMA, TMB and DBL-CANC, at least when these tests remained of short duration (<2 minutes).

In all the tasks where short-term memory (verbal, visual as well as working memory) was evaluated, the performances of SAS patients were significantly worse than those of age-matched control subjects. In the case of working memory evaluation, both VERB-SPAN and VIS-SPAN, tested separately, were significantly impaired ($U = 79.00$; $p = 0.035$ for VERB-SPAN and $U = 70.50$; $p = 0.015$ for VIS-SPAN). These defects could themselves account for the decrease in the performances found in DC-SPAN. To evaluate more precisely whether the additional attention resources typically involved in such double-codage tasks were also reduced in the SAS patients, the differences between VIS-SPAN and DC-SPAN on one hand, VERB-SPAN and DC-SPAN on the other, were also analyzed. No differential effect could be found between SAS patients and their age-matched control subjects.

In SAS patients, long-term memory efficiency was also significantly decreased, both for verbal and visual data. The impairment involved only the learning part of the tasks ($U = 61.50$; $p = 0.004$ for VER-L, $U = 73.50$; $p = 0.024$ for VIS-L), whereas SAS patients did not forget learned data more than control subjects (VER-F, VIS-F). It is worth noting that such a lack of forgetting deficit is not attributable to a too pronounced deficit of learning abilities (see VIS-L and VER-L values in Table 1).

When considering the performances in the tasks commonly sensitive to frontal lobe dysfunction, our SAS patients had significant impairments in the TOWER test with three discs ($U = 118$; $p = 0.05$), but not with four discs. In addition, scores on the Wisconsin card sorting test were only slightly reduced. Effectively, the WISC-CAT criterion is not significantly different in the SAS patients versus age-matched control subjects (only a tendency at $p = 0.069$ could be found). SAS patients also did not produce more errors (WISC-ERR) than age-matched control subjects. However, when they did, they persevered significantly more ($U = 198.50$; $p = 0.05$ for WISC-PER). Finally, their performances in the QUEST and their verbal fluency were not significantly different from age-matched control subjects, no matter which letter was being presented (P, F or L).

In order to evaluate how much these various cognitive tests were able to predict the dysfunctions found

TABLE 1. *Comparisons of neuropsychological tests scores for SAS patients and control subjects*

Variables	Tests	SAS patients Mean	SAS patients SEM	Control subjects Mean	Control subjects SEM	U Mann-Whitney probability
Age		49.06	3.02	49.12	2.95	ns
Verbal IQ	Binois-Pichot	105.82	3.93	107.00	2.27	ns
Attention	TMA (seconds)	38.82	3.67	40.65	3.55	ns
	TMB (seconds)	99.41	10.53	96.47	10.10	ns
	DBL-CANC	15.06	2.06	19.29	1.06	ns
	STROOP	−5.06	1.73	−0.82	0.65	0.05
Short-term memory	DIGIT	5.76	0.33	6.59	0.21	0.05
	DIGIT-INV	4.23	0.30	5.47	0.21	0.003
	CORSI	5.29	0.21	6.53	0.30	0.002
	VERB-SPAN	4.75	0.27	5.62	0.26	0.035
	VIS-SPAN	3.59	0.25	4.44	0.18	0.015
	DC-SPAN	2.78	0.22	3.79	0.19	0.002
Long-term memory	VER-L	7.96	0.19	8.54	0.26	0.004
	VER-F (%)	5.88	1.73	8.65	2.02	ns
	VIS-L	5.51	0.68	7.66	0.39	0.024
	VIS-F (%)	−10.50	5.92	1.47	4.57	ns
Related-frontal function	WISC-CAT	5.53	0.21	5.94	0.06	0.069
	WISC-ERR	7.18	1.25	4.59	0.53	ns
	WISC-PER	34.29	7.06	16.06	3.91	0.05
	FLUENCY-P	12.76	0.99	14.00	1.93	ns
	FLUENCY-F	11.00	0.99	12.29	0.77	ns
	FLUENCY-L	10.06	0.91	11.41	0.82	ns
	TOWER-3	10.75	0.91	8.63	0.33	0.05
	TOWER-4	25.89	1.68	23.76	0.97	ns
	QUEST	9.87	1.09	11.53	0.54	ns

in SAS patients in comparison with control subjects, a logistic regression model was built. For such a purpose, the variables initially introduced were those for which significant differences or tendencies were obtained after bivariate comparisons (Table 1). After performing backward and forward stepwise methods, a final model was found showing an overall 93.94% correct classification. The variables in this model were STROOP, DC-SPAN, VIS-L, TOWER-3 and TOWER-4. As illustrated in Table 2, odds ratios were maximal for TOWER-3, followed by the STROOP-color test, for which the odds ratio remained within the (0–1) limits. In the case of the STROOP test, where scores were higher when performances were better, results were thus inversely related to those of TOWER-3. For the other variables (DC-SPAN, VIS-L and TOWER-4), the confidence limits of exp(B) crossed through the limit value of 1, thus excluding them from any major contribution in predicting cognitive disabilities of our patients. ROC analysis, used as a control, confirmed the quality of the model.

TABLE 2. *Results of the logistic regression model applied to control subjects versus the whole set of patients*

Tests	B	SEM	exp(B)	exp (B − 1.96 SEM)	exp (B + 1.96 SEM)
STROOP	−0.4708	0.2048	0.6245	0.418	0.933
DC-SPAN	−1.1815	0.7964	0.3068	0.0644	1.4614
VIS-L	−0.977	0.5507	0.3764	0.1279	1.1078
TOWER-3	0.9865	0.6132	2.6818	0.8062	8.9209
TOWER-4	−0.4988	0.2835	0.6073	0.3484	1.0585
Constant	12.3353	6.8635	—	—	—

B = calculated coefficients of the best fit model; SEM = standard error of the mean for the calculated coefficients; exp(B) = exponential of B, an index of the odds ratio level for the corresponding item.

To take into account some of the pathological mechanisms likely to contribute to the cognitive disabilities found in the SAS patients, the respective contributions of the number of respiratory events and the time spent overnight in hypoxemia were further evaluated. For such a purpose, SAS patients were arbitrarily subdivided into two subcategories: moderately or severely apneic and moderately or severely hypoxemic. The comparison of the neuropsychological performances from moderately apneic SAS patients and severely apneic ones tested with nonparametric tests revealed that only WISC-CAT scores were significantly different ($U = 52.50$; $p = 0.033$) between both subcategories of SAS patients; WISC-ERR scores were beyond the level of significance ($U = 15.50$; $p = 0.056$). When comparing the performances of moderately hypoxemic SAS patients with those of the severely hypoxemic ones, only WISC-ERR scores were significantly different ($U = 7.00$; $p = 0.006$); WISC-CAT and FLUENCY-F scores were the closest to significance ($U = 49.50$; $p = 0.078$ for WISC-CAT and $U = 53.50$; $p = 0.069$ for FLUENCY-F).

Multivariate analysis performed via logistic regres-

TABLE 3. *Results of the logistic regression model applied to moderately apneic patients versus severely apneic ones*

Tests	B	exp(B)
STROOP	7.6864	2,178.55
DIGIT	65.7994	3.77 E + 28
DIGIT-INV	−78.7325	0
VIS-SPAN	44.7193	2.64 E + 19
VER-L	11.0669	64,014.15
VIS-L	23.0836	1.06 E + 10
WISC-PER	1.4680	4.34
TOWER-3	−21.8049	0
TOWER-4	12.9109	404,697.20
Constant	−536.318	

B = calculated coefficients of the best fit model; exp(B) = exponential of B, an index of the odds ratio level for the corresponding item.

TABLE 4. *Results of the logistic regression model applied to moderately hypoxemic patients versus severely hypoxemic ones*

Tests	B	exp(B)
DIGIT	45.4434	5.44 E + 19
DIGIT-INV	−23.1347	0
CORSI	−25.6633	0
DC-SPAN	−25.7475	0
WISC-CAT	43.2502	6.07 E + 18
WISC-ERR	12.9964	440,811.90
Constant	−301.7560	

B = calculated coefficients of the best fit model; exp(B) = exponential of B, an index of the odds ratio level for the corresponding item.

sion allowed us to build a model that fitted either apneic or hypoxemic subcategories (each being subdivided as moderately and severely affected). Each model could reach an overall 100% correct classification. With the help of backward and forward stepwise methodology and by testing the overall classification obtained, it was possible to select the most important neuropsychological tests that remained necessary in each model to maintain an overall 100% final correct classification. These tests with their respective B factor and exp(B) values (i.e. odds ratios) are presented in Table 3 for the severity of apneas and in Table 4 for the severity of hypoxemia. Performances in the DIGIT, VIS-SPAN and VIS-L tests, followed by those in the TOWER-4 and VER-L tests, appear most predictive of the severity of apneas (Table 3), whereas performances in the DIGIT, WISC-CAT and WISC-ERR seem rather predictive of the severity of hypoxemia (Table 4). Because low scores in the DIGIT test participate in the predictive model of the severity of both severe apneas and severe hypoxemia with a high odds ratio in both cases, one may thus consider that the DIGIT test contributes to the evaluation of the global severity of the disease, at least when considering its consequences on cognitive functions. On the other hand, the Wisconsin card sorting test and particularly the WISC-ERR scores (and perhaps also the related WISC-CAT ones) are likely to be predictive of the deleterious effects of a severe hypoxemia on cognitive performances of SAS patients. It is noteworthy that although SAS patients classified as severely apneic were most often also severely hypoxemic, there still remained others that would be classified as severely apneic without being also severely hypoxemic. Such patients correspond to those with a high number of apneic episodes of short duration without profound desaturations, because they exhibit a normal pulmonary volume and a high initial saturation. This is usually found in younger subjects with normal lung function who are not obese or are only moderately so.

DISCUSSION

Patients with SAS suffer both from night sleep fragmentation, due to repetitive apneic episodes, and intermittent nocturnal oxyhemoglobin desaturation. They have been shown to be affected by cognitive impairments (17–22). The present study sought to evaluate their cognitive functions with more selective tasks than those previously used. Furthermore, it focused mainly on mental processes known to involve frontal networks.

When comparing the SAS patients to their age-matched control subjects, the tests classically sensitive to attention-related disturbances did not show significant abnormalities, except for the STROOP-color test. Although the STROOP test involves focal attention and shifting processes, as do TMA, TMB and DBL-CANC tests, it further takes into account the capacity to resist interferences by inhibiting stereotyped responses. Therefore, such a capacity appears to be impaired in SAS patients. However, Bédard et al. (18) found reduced attentional capacities via TMB, letters cancellation and digit-symbol tests, but this appeared effective only when the most severely affected patients were compared to control subjects. In our population, the resistance to interferences, as shown via the STROOP test, was disturbed even when considering the complete set of patients. This defect, without a concomitant decreased ability to rapidly detect stimuli, at least for a reduced period of time, emphasizes the propensity of these patients for distraction, as is classically found in frontal lobe deficits.

Memory impairment has also been reported to occur, as evidenced from tests like the Wechsler Memory Scale (44) and Rey-Osterrieth Figure (45). However, these studies did not clearly differentiate short-term versus long-term memory processes. In the present study we have shown that performances in short-term memory were altered regardless of the nature of information used, verbal or visual (VERB-SPAN and DIGIT, or VIS-SPAN and CORSI), or the lag between presentation and retrieval (0 second for DIGIT and

CORSI, 4 seconds for VERB-SPAN, VIS-SPAN and DC-SPAN). Likewise, the double-encoding task, which is supposed to involve much higher attentional resources than the isolated verbal or visual ones, was also significantly impaired. However, because of the reduced short-term memory abilities found for isolated verbal and visual information, the defect in the double-encoding task cannot be attributable typically to an additional deficit of working memory. This lack of additional defect is not due to a too low single span, because VERB-SPAN or VIS-SPAN, although decreased, did not decline dramatically.

Decreased retention has been reported in long-term memory of apneic patients (18,19). The weakness of the procedures used in these previous studies for assessing forgetting processes resides on the absence of equalization, at the presentation step, of the amount of learning by the patients to the performances achieved by the control subjects. Effectively, equalization appears necessary for a correct interpretation of the forgetting curve. It is of course obvious that a defect, even moderate, at the immediate recall step might be responsible for a significant worsening of the delayed recall. In the case of Wechsler, Rey auditory learning and Rey-Osterrieth Figure procedures, such methodological conditions are not taken into account. In the present study, the tests used were able to equalize the amount of learning and thus evaluate the amount of forgetting on its own. It then becomes clear that SAS patients, in fact, do not have forgetting disabilities (VER-F and VIS-F), and their long-term memory deficits are related merely to a learning impairment (VER-L and VIS-L). In light of these results, SAS patients appear to have memory disabilities quite different from those found in amnesic patients with temporal lesions, whose forgetting is the core disturbance found (46). Therefore, the long-term memory deficits of SAS patients rather appear in line with the memory impairments encountered in patients with frontal lobe-related disturbances [for review see Shimamura et al. (47)].

Although it has been suggested that SAS patients could be affected by executive intellectual difficulties [in particular planning and sequential thinking, which are reminiscent of frontal dysfunctions (22)], except for the TOWER-3, the tests used here, which are specifically sensitive to frontal lobe-related disabilities, were not significantly impaired. The lack of significant difference for TOWER-4, in contrast to TOWER-3, would mean that SAS patients had difficulties initiating an efficient strategy for performing the tasks, whereas they were still able to achieve and generalize the task, even when more difficult (TOWER-4 vs. TOWER-3), once the solving strategy was found. The absence of impairment in solving problems and in generalizing cognitive strategy is confirmed by the lack of significant difference in the performances on the QUEST test. Likewise, the capacity of SAS patients in categorizing, mental flexibility and shifting, as assessed by the Wisconsin card sorting test, was only slightly reduced: no significant difference for the WISC-CAT or WISC-ERR criteria could be observed, only a significantly higher amount of perseverations (WISC-PER). In addition, verbal fluency (FLUENCY-P, -F or -L) also remained not significantly altered. This surprising absence of impairment on both the Wisconsin card sorting test and in verbal fluency sharply contrasts with what is usually found in patients with frontal lobe damage. However, as observed when considering the results on the whole set of cognitive tasks performed here, many of the significant impairments found, such as in the STROOP-color test, the verbal and visual learning tests, TOWER-3 and the amount of perseverations in the Wisconsin test, correspond to deficits functionally related to frontal lobe disabilities [for review see Crawford et al. (48)]. Therefore, our results consistently confirm the assumption that SAS patients do have deficits in their executive functions, but without the degree seen in patients with frontal lobe lesions or related subcortical abnormalities.

Among the various cognitive tasks carried out in this study, the use of logistic regression for discriminating between the cognitive performances of our SAS patients and their age-matched control subjects allowed us to highlight the importance of the TOWER-3 and STROOP tests, the levels of their corresponding odds ratios being the highest. Hence, such a logistic regression model emphasizes here the importance of difficulties found in SAS patients both to initiate a new mental process (TOWER-3 and STROOP) and to inhibit an automatic one (STROOP). Altogether, these deficits are suggestive of a dysfunction in the Supervisor Attentional System, which is described as a central component in the model of Norman and Shallice. Processing by this system would take place when one needs to suppress an alternative source of stimulation, allowing one then to concentrate on a nonroutine aspect of the stimulus (49).

Apart from all these related defects, the question remains of whether those concerning the impairment of short-term memory might also be attributable to the same altered frontal lobe-related process. Because the various short-term memory tests used here did not also include the tasks specifically devoted to evaluating the involvement of the Supervisor Attentional System, as recommended by Baddeley (50), this question still remains open. It is yet worth noting that we did not find any additional defect in the double-coding span over the single verbal and visual spans taken individually. Hence, we cannot attribute the short-term mem-

ory deficits found here to a typical working memory impairment.

By subdividing the whole set of patients according to their moderate or severe amount of apneas and hypopneas, it was possible, with the help of logistic regression, to point out the cognitive tests most sensitive for categorizing these subsets of patients. DIGIT, VIS-SPAN and VIS-L tests showed maximal odds ratio when testing severity according to the apnea index, with TOWER-4 and VER-L reaching quite lower values. These results thus emphasize the importance of memory difficulties, particularly for visual information. Bédard et al. (18) attributed attentional and memory deficits of SAS patients primarily to a decrease of daytime vigilance. In addition, after suppression of sleep apnea by continuous positive airway pressure, they observed a significant improvement and even a normalization of these attentional and memory deficits, even if there remained some degree of persistent impairment in daytime vigilance (51). Our findings are consistent with these observations. However, it has to be kept in mind that the decrease of memory and attentional abilities has not proven to be solely related to daytime sleepiness. Effectively, after 1 night of sleep deprivation in healthy volunteers, such a deprivation-induced daytime sleepiness has been reported not to elicit any deficit in cognitive performances (52). Likewise, other studies have shown that hypoxemia levels in SAS patients are in fact strongly correlated with the tendency to fall asleep, as measured by the maintenance of wakefulness test, a variant of the multiple sleep latency test (53). In addition, sleep disruption related to respiratory events has been reported to play an important role in the pathogenesis of daytime sleepiness; such a role is probably not exclusive because the reduction in sleep fragmentation after treatment does not restore daytime vigilance to normal (54).

By applying the same type of logistic regression procedure to our SAS patients after categorizing them as moderately or severely hypoxemic, the most prominent predictive cognitive tests were DIGIT and WISC-CAT, followed by WISC-ERR. The DIGIT test appears thus to be more generally impaired in severely affected patients, whichever criterion of severity is considered, the index of sleep apneas or the level of nocturnal hypoxemia. However, performances in the Wisconsin card sorting test, particularly when referring to categorizing abilities and the number of errors produced, appear to be merely sensitive to the severity of nocturnal hypoxemia. This points out the importance of frontal lobe-related disabilities found in SAS patients with some emphasis on the hypoxemia-induced effects.

Deficits of executive functions, such as planning and shifting (24), have also been considered by others (22) as mostly attributable to the severity of nocturnal hypoxemia, with only poor improvement after treatment. This suggests that such deficits might be at least partly, and particularly for the most severe patients, the results of an irreversible anoxic disruption (51). This contrasts with the neuropsychological deficits found in patients with typical anoxic cerebral damage (55), whose cognitive deficits concern merely memory and visio-perceptive capacities. In the latter case the insult primarily affects posterior and infero-temporal cortex and even deep structures such as the cerebellum and the brain stem. One must be aware, however, that such anoxic insults correspond mainly to an acute and massive event and are thus quite different from the moderate but chronic hypoxemic situation that prevails in SAS patients.

In a less extreme situation, such as in climbers reaching very high altitudes (up to 8,840 m) or being placed at artificial comparable altitudes, hypoxemia is less acute but still very important and has been reported to produce declines in visual and verbal long-term memory (56). In the same situation, others have found mild impairments of concentration, short-term memory and cognitive flexibility (57). These reported data resemble those found here in SAS patients, although the magnitude of hypoxemia reached by these patients is lower than that found at over 8,000 m altitude. Interestingly, in patients suffering from continuous obstructive pulmonary disease with chronic hypoxemia (but less acute and probably of lower amplitude than in such climbers), similar neurobehavioral impairments have also been reported (58).

With the help of the cognitive tests used here, it becomes possible to discriminate between those tasks which are more sensitive to the amount of sleep apneic episodes and those which appear more relevant to their hypoxemic consequences. However, such patterns of results need to be confirmed further by testing through prospective studies applied to large sets of SAS patients.

CONCLUSION

The results of the present study performed with focused cognitive tests allow us to conclude that executive functions, including the acquisition of information for memory processing, are impaired in SAS patients and are consistent with frontal dysfunctions. These disabilities remain discrete when referring to typical frontal lobe damage and might be the result of chronic intermittent oxyhemoglobin desaturation rather than daytime sleepiness.

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