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Neuropsychological Dysfunction in Sleep Apnea

Glen D. Greenberg, *Robert K. Watson, and †Dennis Deptula

*University of Health Sciences/Chicago Medical School, North Chicago, Illinois; *Yale University School of Medicine, New Haven, Connecticut; and †University of Connecticut Health Center, Hartford, Connecticut, U.S.A.*

Summary: To evaluate the effect of intermittent hypoxemia on neuropsychological functioning, neuropsychological tests were administered to 14 sleep apnea patients, a control group of 10 patients with other disorders of excessive somnolence, and another control group of 14 healthy volunteers. The sleep disorder groups were matched on two measures of sleepiness. It was found that sleep apnea patients performed significantly worse than both controls on 7 of 14 neuropsychological measures and on a rating of global neuropsychological impairment. The overall level of performance reflected only moderate impairment. Within the sleep apnea group, hypoxemia severity was significantly correlated with deficits on measures of motor and perceptual-organizational ability. **Key Words:** Neuropsychological testing—Sleep apnea—Hypoxemia.

Oxygen deficiency disorders are common. Hypoxemia can occur in chronic obstructive pulmonary disease (COPD) patients, can accompany aging, and can be associated with other environmental and medical conditions (1–4). Since the CNS is particularly sensitive to hypoxemia (5), neuropsychological functioning under these conditions can be impaired. Indeed, studies have consistently revealed neuropsychological deficits in continuously hypoxemic COPD patients (6–10). However, a controlled investigation of the neuropsychological effects of intermittent hypoxemia occurring in medical patients is not currently present in the literature. Sleep apnea represents a good clinical model of intermittent hypoxemia (11). Individuals with sleep apnea can experience hundreds of apneas over the course of the night with repeated episodes of alarming oxygen desaturation.

Investigations of the neuropsychological status in patients with mild to moderate continuous hypoxemia as a result of pulmonary system disease have documented multiple deficits including impairment in abstract reasoning, problem solving, and psychomotor abilities (6–10). These hypoxemia-related deficits are significant since many show a relationship to the degree of psychosocial disruption in these patients' lives (12,13). It is presently unclear if neuropsychological impairment accompanies intermit-

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Address correspondence and reprint requests to Dr. R. K. Watson at New Haven Sleep Disorders Center, 100 York Street, New Haven, CT 06511, U.S.A.

tent hypoxemia. Clinical anecdotes and preliminary reports suggest that changes in cognitive status accompany airway obstructive disorders (14), sleep-related respiratory disturbance in the elderly (15), and even cases of heavy snoring (16), a frequent sign of sleep apnea. However, clinical impressions or uncontrolled research with an adult-onset sleep disorder such as sleep apnea is potentially confounded by the effects of excessive daytime somnolence (17) and aging (18). The former issue makes the use of norm-referenced neuropsychological assessment with this population problematic (19). Therefore, research with sleep apnea patients requires appropriate experimental controls to differentiate hypoxemia-related impairment from the effects of aging and excessive sleepiness.

To investigate the effects of intermittent hypoxemia on neuropsychological functioning, this study compared a group of sleep apnea patients with a heterogeneous group of patients suffering from disorders of excessive somnolence (DOES) without sleep apnea and with a group of healthy matched controls. We compared the sleep apnea group's test performance with that of each control group, and examined the relationship of the sleep apnea group's neuropsychological performance to nocturnal respiratory, hypoxemia, sleep architecture and other measures.

METHOD

Subjects

All patients were physician referrals evaluated at a fully accredited sleep disorders center. Patients were excluded from participation who were concurrently treated for other significant medical disorders (e.g., COPD), who were taking medication that could adversely affect cognitive functioning, who had known or suspected alcohol or drug abuse, and who had reported a history of learning disability or head trauma. For the purpose of this investigation, only sleep apnea patients who demonstrated normal awake S_aO_2 levels were included.

The sleep apnea group consisted of 14 patients who met diagnostic criteria for sleep apnea DOES syndrome according to the *Diagnostic Classification of Sleep and Arousal Disorders* manual (20) after polysomnographic evaluation. No patients with a secondary sleep disorder diagnosis were included. The sleep respiratory features of the sleep apnea group are presented in Table 1.

The DOES control group consisted of 10 patients who demonstrated normal nocturnal respiration upon polysomnographic evaluation. This group was composed of five patients diagnosed as having narcolepsy without cataplexy, four patients with nocturnal myoclonus, and one patient with idiopathic CNS hypersomnolence. A second control group consisted of 14 healthy volunteers without complaints regarding their sleep or daytime alertness. This group was selected to approximately fit the demo-

TABLE 1. *Respiratory features of sleep apnea group*

No. of apneas		Apnea index		Apnea length		Lowest % desaturation		Total time not breathing	
$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
307.8	177.2	48.0	29.3	25.1	8.7	67.71	14.5	146.1	94.6

Apnea index = no. of apneas per hour. Apnea length and total time not breathing are in minutes.

TABLE 2. *Descriptive characteristics*

Variable	Apnea group		DOES group		Healthy group	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Background						
Age (yrs)	43.8	9.1	42.4	6.7	44.2	7.4
Education	12.7	2.3	13.5	2.2	13.7	2.1
Premorbid intelligence						
Vocabulary	10.0	2.1	11.4	2.1	11.2	1.9
Information	10.3	3.5	11.3	2.2	11.2	2.2
Daytime sleepiness rating	3.5	1.4	3.0	1.2		
Sex ratio	13 M	1 F	4 M	6 F	11 M	3 F

DOES, disorders of excessive somnolence.

graphic portrait of the sleep disorder groups. To exclude elderly subjects, an age limit of 55 years was established. The healthy subjects were interviewed as to the presence of sleep pathology or medical problems, and were paid $25 for their participation. All subjects gave their informed consent. Descriptive characteristics of the groups are presented in Table 2.

Procedure

Sleep recordings. All sleep disorder subjects underwent 1 or 2 nights of polysomnographic evaluation. This involved continuous recordings of blood S_aO_2 measured nonintrusively by a BIOX II ear oximeter, pneumographic measurement of respiratory effort, oral and nasal airflow, submental electromyogram (EMG), right and left anterior tibialis EMG, central electroencephalogram, electrooculogram, and single-lead electrocardiogram. All recordings were obtained and scored according to the Association of Sleep Disorder guidelines (21) by registered polysomnographic technicians. In addition to the standard polysomnographic array, two sleep apnea subjects and seven DOES control subjects underwent daytime multiple sleep latency tests (MSLTs). When available, the second recording night was used in the data analysis to minimize "first night effect" sleep difficulties associated with lab adaptation. Polysomnographic summary data for the two sleep disorder groups are presented in Table 3.

Neuropsychological testing. In the morning after the first or second night of lab sleep, the patients were administered a neuropsychological battery by a licensed psychologist blind to diagnosis. The healthy subjects were administered the same battery during working hours.

The choice of neuropsychological tests was guided by several concerns. First, the tests should sample a reasonably diverse number of basic cognitive and motor abilities. Second, the tests should be brief to minimize the possibility of obtaining deficit scores due to intrusions of pathological sleepiness. Third, the tests should be easily administered in one session. Fourth, there should be minimal practice effect associated with the tests to permit posttreatment reevaluation. Descriptions of the neuropsychological tests are given in Table 4 (22–28).

In addition to the neuropsychological tests, the patients were given the self-report Stanford Sleepiness Scale (SSS) (29) to aid in evaluating their home sleepiness. A clinical rating for sleepiness observed during the initial interview, lab evaluation, and patient report was also obtained from the sleep lab director using a six-point scale of

TABLE 3. *Polysomnographic characteristics of sleep disorder groups*

	Sleep latency		Total sleep		Sleep efficiency %		REM %		Delta %	
Group	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Apnea	11.8	21.2	412	79	81.3	21.2	13.7	4.8	3.7	4.0
DOES control	11.6	11.2	378	69	84.8	6.6	20.4	5.5	11.5	8.0

Sleep latency and total sleep are in minutes. DOES, disorders of excessive somnolence.

increasing severity (i.e., 1 = no impairment; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe; 6 = severe). An independent, experienced neuropsychologist provided blind ratings of global neuropsychological impairment with demographic influences such as age and educational background taken into consideration, using the same six-point scale.

RESULTS

Demographic variables

Analysis of variance revealed that the groups were comparable on age and estimated premorbid intelligence using years of education and the Vocabulary and Information subtests from the Wechsler Adult Intelligence Scale—Revised. However, χ^2 analysis of group gender composition revealed significant differences between the groups [X^2 (2, n = 38) = 8.65, $p < 0.025$]. This result was not unexpected since sleep apnea afflicts primarily males. Nevertheless, the relationship of gender to test performance was evaluated since gender is a relevant variable in neuropsychological research (30). Point biserial correlations between gender classification and each neuropsychological measure revealed that gender was not related to adequacy of any test performance within or between the groups. Therefore, the gender ratio difference was judged to have had no effect on the test results in these samples.

TABLE 4. *Neuropsychological tests*

Test	Task demands	Type of score
Wechsler Adult Intelligence Scale—Revised *Subtests* (22):		Age-corrected scaled score
Vocabulary	Word knowledge	
Information	Acquired facts	
Block design	Pattern reproduction	
Digit span	Immediate number recall	
Letter cancellation test (23)	Cancel target letter	Time to completion
Bender visual-motor test (Bender) (24)	Copying designs	Koppitz errors
Trail making B (25)	Connect alternating numbers and letters	Time to completion
Purdue pegboard (26)	Place small pegs into board	Number placed: right (R), left (L), both (B) hands
Controlled oral word association test (fluency) (27)	Verbal fluency	Three-letter total, 60 s/letter
Wechsler memory scale (28)		Russell scoring for immediate and delayed recall and % retained
Logical Memory (L-Mem)	Short-term story recall	
Figural Memory (F-Mem)	Short-term design recall	

Sleep variables

We evaluated the hypersomnolence of the sleep disorder groups by examining two measures, nocturnal sleep latency and the clinical ratings of excessive daytime somnolence provided by the sleep lab director. Both groups were comparable on these measures. The SSSs were not utilized since too few scales were returned or correctly completed by the patients for analysis. The DOES controls with MSLTs were clearly hypersomnolent ($\overline{X}$ sleep latency = 6.9 min across four naps). Since it is unknown if the three DOES patients without MSLTs were truly hypersomnolent, we conducted separate analyses of the neuropsychological results with and without those patients. The results were quite comparable. In fact, those three DOES patients tended to perform somewhat more poorly than the DOES controls with MSLTs. The DOES group mean performance improved slightly on 14 of 17 neuropsychological measures when those three patients were excluded from the analyses. Nevertheless, the following analyses include the entire DOES sample.

A comparison of the quality of the sleep between the sleep disorder groups found that both demonstrated similar total sleep time and sleep efficiency. However, the sleep architecture of the apnea group and DOES control differed. The apnea group had less REM percentage [t (22) = -2.87, $p < 0.02$] and delta percentage [t (22) = -3.20, $p < 0.004$]. However, correlations between REM percentage, delta percentage, and the global neuropsychological impairment ratings revealed neither sleep stage to be related to overall neuropsychological status in the apnea group, suggesting that these altered sleep parameters did not have an effect on cognitive functioning.

Neuropsychological functioning

Test performance was analyzed using the Statistical Package for the Social Sciences (SPSS) analysis of variance subprogram ONEWAY (31) using a priori contrasts (i.e., apnea group versus each control). A posteriori tests for significant F ratios were performed using Scheffé's test, the most conservative method of analysis. Table 5 summarizes the comparisons between the apnea group and each control on the neuropsychological measures as well as the global neuropsychological impairment rating. It can be seen that the apnea group exhibited lower mean scores on 15 of 17 measures compared with the DOES control and on all of the measures compared with the healthy group. Apnea subjects performed significantly worse on seven of the tests compared with the controls.

The contrasting group performances are illustrated in Fig. 1, where T scores derived from the entire sample were plotted for each test to allow intertest comparison within and between the groups. While the apnea group usually performed least adequately, it is noteworthy that the sleepy controls performed more like the healthy controls. The difference between the apnea group and the controls was ~0.5 SD (apnea $\overline{X}$ = 46.62, DOES $\overline{X}$ = 51.68, healthy $\overline{X}$ = 52.25), with higher T scores representing better performance. The apnea group's mean performance was significantly poorer [F (2,14) = 12.05, $p < 0.001$].

The global neuropsychological impairment rating provided further support to the impression of greater cognitive dysfunction in the apnea group. The apnea group was rated as more impaired than both the sleepy controls ($p < 0.01$) and the healthy controls ($p < 0.001$).

To evaluate the relationship between hypoxemia severity and neuropsychological functioning, we examined zero-order correlations between various hypoxemic measures for each patient using the apnea index, mean desaturation level, lowest desatura-

TABLE 5. *Neuropsychological performance with analyses of variance and planned contrasts*

Test	DOES		Apnea		Healthy		*F* ratio	*F* prob.
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD		
Information	11.3	2.2	10.3	3.5	11.2	2.2	0.46	0.60
Vocabulary	11.4	2.1	10.0	2.9	11.2	1.9	1.16	0.32
Digit span	12.7[a]	3.4[a]	9.8	2.5	11.5	2.2	3.35	0.04
Block design	10.8	2.3	10.5	3.0	11.1	2.3	0.16	0.80
Letter cancell.	76.0[b]	9.9	95.6	20.9	84.0	13.5	4.57	0.01
Bender	0.3[b]	0.4	1.2	1.1	0.5	0.7	3.95	0.02
Trails B	79.2	25.5	98.7	28.5	88.8	30.3	1.40	0.25
Pegboard R	14.2[b]	2.0	12.1	1.6[b]	14.0	1.9	4.98	0.01
Pegboard L	13.5[a]	1.7	11.7	2.1[b]	13.7	1.7	4.30	0.02
Pegboard B	10.8	1.6	9.9	1.6[b]	11.7	1.5	4.55	0.01
Fluency	43.4	15.6	35.5	9.0	44.0	10.4	2.25	0.12
L-Mem imm.	19.2	5.7	16.9	6.4	18.0	5.6	0.42	0.60
L-Mem delay	15.3	6.7	12.8	5.1	15.2	5.0	0.81	0.40
L-Mem %	79.8	24.6	79.8	14.5	85.7	12.3	0.51	0.60
F-Mem imm.	10.7	3.0	11.2	2.5	11.6	2.6	0.34	0.70
F-Mem delay	8.1	3.3	8.2	3.6	10.5	2.6	2.22	0.12
F-Mem %	76.2	24.5	74.7	25.4[a]	90.3	9.9	2.31	0.11
Global rating	2.7	1.1[b]	3.9	0.9[c]	1.5	0.9	18.67	0.001

See Table 4 for description of tests. Disorders of excessive somnolence (DOES) versus healthy group comparison revealed two differences; F-Mem % ($p < 0.01$) and global rating ($p < 0.05$).
[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

tion figure, and total minutes not breathing (i.e., number of apneas × average apnea duration) with each neuropsychological measure. Measures of perceptual-organizational ability (block design) and bilateral motor speed (pegboard both hands) showed significant relationships ($p < 0.05$) with both total time not breathing and lowest desaturation (block design $r = -0.51$ and 0.48; pegboard $r = -0.52$ and 0.51, respectively). However, overall neuropsychological status, based on the global impairment ratings, was not correlated with the hypoxemia severity measures within the sleep apnea group. To investigate this further, objective rankings for several neuropsychological measures were summed to obtain overall performance rankings within the group (i.e., 1–14), and with these rankings Spearman rank order correlations with the hypoxemia measures were performed. Again, correlations between overall neuropsychological status and hypoxemia severity were nonsignificant, occurring in the 0.20–0.30 range.

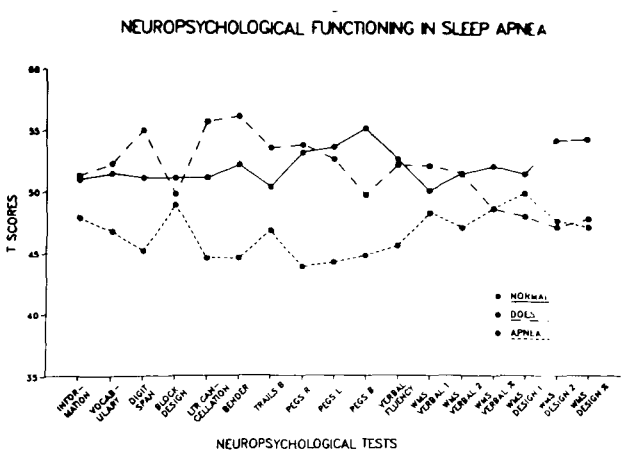

FIG. 1. Contrasting group performances.

Examination of nonhypoxemic illness variables, such as estimated illness duration and self-report measures of depression, revealed a significant correlation between illness duration and global neuropsychological impairment ratings ($r = 0.59$, $p < 0.05$).

DISCUSSION

This study's main finding is that hypoxemic sleep apnea patients experience neuropsychological dysfunction beyond what can be attributed to the effects of either excessive daytime sleepiness or aging. The apnea patients showed deficits on measures of attention, motor efficiency, and graphomotor ability compared with the controls. Motor and perceptual-organizational skills were related to hypoxemia severity, while other test measures and overall neuropsychological status correlated minimally with hypoxemia levels.

The generally low hypoxemia–test score correlations were unanticipated but perhaps not surprising since low correlations between these variables are the rule rather than the exception in hypoxemic COPD research. For example, Fix et al. (6) found that among the 13 neuropsychological test scores obtained from their sample of COPD patients, only 3 were correlated with S_aO_2 values, the median value being $r = 0.15$. Grant et al. (8), using a similar global impairment rating measure, found that only 5% of the variance in these ratings was accounted for by S_aO_2 levels, and the correlation between global ratings and P_aO_2 was only -0.21. It appears, therefore, that it is difficult to establish robust relationships between hypoxemia measures and neuropsychological performance.

Deriving valid relationships between apnea indexes and test scores in apnea research may be additionally problematic because of nightly variability in the respiratory status of mildly apneic patients (32) and the unreliability involved in oximetry measurement of very low S_aO_2 levels in severely ill patients. This study contained both mildly and severely afflicted patients, presumably allowing both factors to suppress correlations. The correlation between illness duration and neuropsychological status suggests that an important factor influencing neuropsychological status may be disorder chronicity, and that needs to be considered in explaining neuropsychological impairment in addition to laboratory assessments of current hypoxemia severity.

The neuropsychological dysfunction appears to be only moderate in degree, but these results might represent a conservative estimate of the severity of the cognitive and motor impairments in a good number of sleep apnea sufferers. Since these patients were relatively young and newly diagnosed, they were unlikely to have been experiencing hypoxemic brain insults as long as might be expected to occur in an older or undiagnosed individual. Owing to the fact that the incidence of sleep apnea rises with age (11) and the disorder in an older patient may frequently interact with a more fragile biologic system and coexisting disease (e.g., hypertension), the neuropsychological compromise in an older sleep apnea sufferer can conceivably be more severe.

The clinical significance of these deficits is presently unclear. The relationship of motor and perceptual-organizational dysfunction to measures of hypoxemia severity suggests that individuals experiencing worsening or untreated sleep apnea and who work in fields requiring nonverbal competence may be most at risk for work-related problems. It is interesting that in the COPD literature the neuropsychological measures most strongly associated with psychosocial impairment are deficits on motor tasks (13). It would be of clinical importance for future research to investigate the relation-

ship of these types of deficits to the sleep apnea patient's work, home, and leisure activities. Since these patients demonstrate average intellectual abilities, as suggested by their vocabulary and information subtest results, sleep apnea patients may appear more cognitively competent than they really are, and that problem may not become apparent until the patient is confronted with a novel task of nonverbal adaptive functioning and problem solving.

The adequate performance of the sleepy control group is in contrast to the deficits noted elsewhere in hypersomnolent patients (33). Valley and Broughton (33) found attention and concentration problems in their sample of patients with narcolepsy with cataplexy. The reasons for the discrepancy may be twofold. First, this DOES sample was composed of only five narcolepsy patients, none of whom had ancillary cataplectic symptoms. It may be that cataplexy is associated with greater cerebral pathology and subsequent neuropsychological impairment. This hypothesis was supported when the neuropsychological test protocols of four narcolepsy with cataplexy patients in our lab were examined. Of those four patients, the two with the most severe cataplexy performed at a level comparable with that of the most impaired sleep apnea patients. These preliminary findings require experimental verification and suggest that a neuropsychological study of narcolepsy subtypes is warranted. The second explanation for the discrepancy is the different nature of the neuropsychological measures in the two studies. This evaluation utilized brief tests to minimize the likelihood of poor performances from individuals experiencing excessive somnolence. Valley and Broughton, on the other hand, used sustained attention measures of significant duration, up to 1 h. It is likely that our DOES control patients would also show deficits on demands of that nature.

In conclusion, this investigation adds to the growing body of literature implicating disease-related hypoxemia as a cause of cognitive dysfunction. In this case, the experience of normal interapnea and awake respiration does not apparently protect the patient from the CNS effects of intermittent oxygen deprivation associated with sleep apnea. With recent advances in the clinical management of sleep apnea, an important research avenue in this lab is in the investigation of the extent to which treatment reverses cognitive dysfunction.

Finally, we are reminded of the 1920 comment by Haldane that "anoxia not only stops the machine but wrecks the machinery" (reported in ref. 1). To this it seems appropriate to add that hypoxia permits the machine to run but ruins its efficiency.

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