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Neuropsychological Function in Mild Sleep-Disordered Breathing

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Summary: Although a broad range of neuropsychological deficits has been reported in patients with severe sleep disordered breathing (SDB), little is known about the impact of mild SDB on neuropsychological performance. In this study, we compared neuropsychological test performance in two groups of carefully screened volunteers who differed clearly according to the respiratory disturbance index (RDI). Controls (n = 20) were identified on the basis of an RDI < 5; cases (n = 32) had an RDI in the range of 10–30. Cases and controls were well matched with regard to IQ, age, and sex. Cases had significantly more self-reported snorting and apneas and a higher body mass index than controls but did not differ according to sleepiness as measured by either the multiple sleep latency test or the Epworth sleepiness scale. An extensive battery of neuropsychological and performance tests was administered after an overnight sleep study. Cases performed significantly more poorly on a visual vigilance task (perceptual sensitivity, d′: 2.24 ± 0.64 vs. 2.70 ± 0.53, p = 0.01, for cases and controls, respectively) and a test of working memory, the Wechsler adult intelligence scale–revised digits backwards test (6.12 ± 2.20 vs. 7.55 ± 2.22, p = 0.02), than controls. The groups did not differ in their performance on other tests of memory, information processing, and executive functioning. In summary, subjects with mild SDB may manifest a vigilance deficit in the absence of substantial sleepiness. Subjects with a mildly elevated RDI (10–30) without sleepiness do not appear to suffer appreciable deficits in more complex neuropsychological processes (e.g. executive functions). **Key Words:** Sleep-disordered breathing—Attention—Cognition.

Accumulating data suggest that sleep-related respiratory disturbances occur commonly in individuals from both clinical and community samples (1–3). However, despite the increasing recognition of the high prevalence of sleep-disordered breathing (SDB) in the population, there remains considerable controversy over the health sequelae of SDB of various degrees of severity. This, in turn, has contributed to disparate approaches for defining "abnormal" levels of SDB, i.e. levels that contribute to morbidity or functional impairment.

Previous studies have suggested that severe SDB, associated with a respiratory disturbance index (RDI) of >40, is associated with a broad range of neuropsychological deficits (4–6), some of which may be reversed with treatment (7,8). The impact of milder degrees of SDB on neuropsychological functions is less clear. In a community-based sample of twins, no differences were demonstrated between snorers and nonsnorers on tests of memory, attention, spatial skills, and executive functions (9). This study suggested few functional differences between subjects who also differed little according to level of apnea (indices of SDB were 8 and 5, respectively, for snorers and nonsnorers). In a group of older subjects (>54 years), the majority of whom had an RDI of <15 and who were unselected according to sleepiness or other symptoms, no relationship was demonstrated between level of SDB and vigilance as tested by the steer clear test (10). No study, however, has yet examined the impact on neuropsychological functioning of somewhat higher but commonly observed levels of SDB in subjects unselected according to levels of sleepiness.

Establishing the association, if any, between mild SDB and cognitive functions may help clarify the role of early identification and treatment of mild SDB. In this study, we examined whether deficits in attention, memory, and executive functions, previously described in a clinic sample with severe SDB (4), also occur in individuals with milder SDB as defined by an

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RDI between 10 and 30. Additionally, we examined the extent to which neuropsychological functions relate to measures of sleepiness in subjects with relatively modest numbers of respiratory disturbances and little hypoxemia.

METHODS

Subjects

The thrust of this analysis was to establish whether deficits in neuropsychological test performance, described previously in a clinic sample of severe SDB (mean apnea index 48) (4), also occur in subjects with milder SDB unselected according to level of sleepiness or functional impairment. Extensive screening of a volunteer population was undertaken to recruit and establish two groups (mild SDB and controls), with subjects assigned as a case or control only on the basis of the subjects' frequency of respiratory disturbances and snoring history. Controls were defined as subjects with an RDI (number of hypopneas plus apneas per hour of sleep) of <5 and without a history of frequent snoring or observed apneas. Cases were defined as subjects with an RDI between 10 and 30. All subjects were screened by orally administered and written questionnaires to exclude the presence of underlying conditions that could interfere with neuropsychological test performance or with adherence to the study protocol. These include severe or unstable medical problems (myocardial infarction or congestive heart failure documented within the previous 2 months, uncontrolled diabetes or thyroid disorder, cirrhosis, recently diagnosed cancer), neurological disease (a history of stroke, seizure disorder, head trauma with loss of consciousness), alcohol abuse (a history of ≥5 alcoholic drinks per day for >6 years) or drug abuse (current use, heavy past use leading to tolerance or dependency, or any use of cocaine for >2 months), regular use of medications that impair sensorium (e.g. benzodiazepines), and extremes of educational status (i.e. <8 years of schooling or education yielding a doctorate degree). Hypertension was not a basis for exclusion into the study. Subjects were ineligible for study participation if screening revealed a sleep disorder other than SDB (narcolepsy; insomnia, defined as regularly sleeping <6 hours per night; regular use of hypnotics; sleep insufficiency, defined as sleeping ≥3 hours more on nonwork days in comparison with work days; or a history of periodic leg movements). Volunteers for this study were identified through fliers distributed at local work sites and physician offices eliciting participation of "nonsnorers and snorers", from rosters of participants in other research studies that included sleep apnea screening, and from physician referrals of snorers (n = 3). To achieve group comparability for age, analyses of a larger data set were restricted to subjects aged 40–65 years. The study was approved by the Institutional Review Board and written consent was obtained from subjects.

Evaluation of neuropsychological performance

An extensive neuropsychological battery was administered by a trained technician to all participants on the same day as the multiple sleep latency test (MSLT). The same battery was used for both cases and controls. Attempts were made to keep this technician unaware of each subject's apnea status (e.g. recruitment and scheduling and the handling of all the sleep data were performed by a different technician). However, the testing technician was often made aware of the subject's group status by comments made by the subject. Most tests were administered between the first and second and between the third and fourth naps. There were two testing sequences to minimize time-of-day effects. Because the protocol required retesting after an intervention period (data not presented), alternative forms of tests were used where feasible to minimize practice effects. The alternative forms were randomly ordered. Testing (including the MSLT, a lunch break, and rests between tests) was completed, on average, between 0900 and 1630 hours.

General intelligence was assessed with four subtests of the Wechsler adult intelligence scale–revised (WAIS-R) (11) that have the highest correlation with full-scale IQ (12) (referred to in this paper as "estimated IQ"). The neuropsychological tasks were selected to tap four areas of function—attention, memory, general information processing efficiency, and executive function—shown to be impaired in previous studies of patients with more severe SDB (4–6). Unless otherwise indicated, information about all tests may be found in Lezak (13). Attention was assessed with the WAIS-R digit-symbol substitution test (age-adjusted number correct) and the Talland letter cancellation test (LCT) (number of errors), as well as a visual vigilance task involving a continuous performance test (CPT) (14). This last procedure required the participant to monitor a computer screen for 10 minutes, responding whenever two successive, briefly presented (50 milliseconds), rapidly replaced (1/second) complex shapes were identical. Attention was assessed by perceptual sensitivity (d') during the first 2 minutes and during the last 2 minutes. Memory was assessed with the California verbal learning test (words learned over five trials and long-delay free recall) (15). Procedural memory was tested with a pursuit-rotor task that required the subject to trace a moving target light with a pursuit wand over three sessions during

the day, each session consisting of eight 20-second trials (16). In this test, the percentage change of time "on target" was computed for the third session in comparison with the first session. The speed of target rotation [rotation per minute (rpm)] was constant for all three sessions after an initial determination of the speed of target rotation that produced a 25% on target response during practice runs. General information processing efficiency was assessed using the Gilmore-Royer symbol-digit test. Executive functions were assessed with the WAIS-R digits backwards test (age-corrected scale score), the Wisconsin card sorting test (WCST) (number of perseverative errors) (17), the trail making test—part B (seconds to completion; trails A was used to assess baseline function), and accuracy on a serial digit subtraction task modified from Dinges (18).

Missing data occurred for the letter cancellation test (n = 3), the WAIS-R estimate (n = 1), the pursuit rotor test (n = 8), the continuous performance test (n = 4), the digit symbol substitution test (n = 1), and the digits backwards test (n = 2) because of administrative or technical errors or because of the later addition of several tests to the battery. Three subjects refused to perform the digit subtraction test.

Evaluation of sleep-disordered breathing

Subjects were screened for enrollment (to determine an initial RDI classification) with in-home sleep monitoring, with measurement of nasal and oral thermistry, chest wall impedance, finger pulse oximetry, body position, and heart rate with a portable monitor (Edentec Model 2, Eden Prairie, MN), as previously described (19). An additional in-laboratory polysomnogram was performed on subjects with an RDI of >5 to additionally characterize sleep architecture. This consisted of measurement of the above as well as C4/A1, C3/A2, and O1/A2 electroencephalogram, submental and tibialis electromyograms, and right and left electrooculograph with a Nihon Koden 4400 Polygraph or a SensorMedics Somno Star 4100. When possible, this in-laboratory polysommogram was performed the night prior to the neuropsychological battery. However, if an in-laboratory study could not be scheduled the night immediately preceding the battery, then an additional in-home sleep study was performed that night to expose the subject to a preceding monitoring night and to document adequacy of sleep time. The mean difference between the RDI between the first inhome sleep study and the in-laboratory polysomnogram was 3.3 ± 9.8 standard deviation (SD) events/hour.

Evaluation of sleepiness

Objective sleepiness level was determined with the multiple sleep latency test (MSLT) (20). Subjective sleepiness was assessed with the Epworth sleepiness scale (ESS) (21). On the day of neuropsychological testing, subjects underwent an MSLT consisting of four naps at 2-hour intervals, starting at 0900–0930 hours, allowing the subjects 20 minutes to fall asleep per nap, according to a standard protocol (20).

Subjects completed the ESS on the day of the testing battery, during either the morning or the afternoon session, according to the subject's random test sequence. The ESS is a self-administered questionnaire that requires subjects to rate their chances of falling asleep in eight different situations, referring to their "usual way of life in recent times". Scores vary from 0 to 24, with higher scores indicating greater sleepiness (21).

Sleep symptoms

Symptoms of SDB were assessed with a modified version of the Sleep and Health Questionnaire of the Specialized Center of Organized Research in Cardiopulmonary Disorders of Sleep (SCOR) (22), which was self-completed by each subject. Snoring, breathing pauses (snorting, gasping, or stop breathing), and excessive daytime sleepiness were each considered present if the subject reported these symptoms as occurring "frequently" or "at least 3–4 times per week".

Data analysis

Scoring of respiratory disturbances and quantifying hypoxemia

The RDI used for classification of case vs. control was based either on the average of the RDIs calculated from the screening in-home sleep study and the in-home sleep study performed immediately prior to the testing battery (n = 29) or on the RDI from only one in-home sleep study (n = 23) (because the prebattery sleep study was performed in-laboratory or one of the two in-home sleep studies was technically unsatisfactory). A respiratory disturbance (apnea or hypopnea) was defined as a discernible change in airflow or chest wall movement, lasting >10 seconds, occurring in association with at least a 2.5% drop in oxygen saturation. Use of similar criteria have been previously shown to produce comparable RDI estimates for in-home in comparison with laboratory-based polysomnography (19). For these in-home sleep studies, sleep time was estimated from a patient diary in conjunction with visual inspection of the sleep record. Sleep onset

was identified as the time of occurrence of a reduction in heart rate or movement; wakefulness was noted when movement of signal artifacts occurred for >30 seconds. The RDI was calculated as the total number of respiratory disturbances divided by estimated sleep time in hours.

Summary measures of oxygen saturation, or the percentages of time with a saturation <90% and <85%, were produced by computer-based analysis of the digitized oxygen saturation records from the in-home sleep studies.

Overnight sleep variables

From the in-laboratory polysomnograms (available for "cases" only), electroencephalogram arousals were scored according to criteria set by the American Sleep Disorders Association (23). The number of upward sleep stage shifts was defined as the number of times during in-laboratory polysomnography that sleep shifted from a deeper to lighter stage (e.g. stage I to wakefulness, stage II to I, etc.).

Data from the MSLT

The average sleep latency over four naps was computed. Any nap period during which the subject did not sleep was coded as a latency of 20 minutes (20).

Statistical analysis

All variables were examined for skewness and kurtosis. To achieve approximate normality, the following variables were transformed: percentage of time <90% and <85% (natural logarithm of the reciprocal), number of perseverative errors (reciprocal), number of errors during the LCT (natural logarithm), and number of upward sleep shifts (natural logarithm). Group differences were examined initially with unpaired *t* tests and contingency table analysis. Adjusted analyses were performed with analyses of covariance (ANCOVA), with consideration of the neuropsychological variables as dependent variables and group status (case or control) as the independent variable, and age, race/ethnicity (European American vs. other), and estimated IQ as covariates. In additional analyses, sleepiness (as measured by the MSLT) and an interaction term between MSLT and group status were also considered as covariates. In exploratory analyses, the relationship of the neuropsychological test scores and measures of sleep apnea severity (e.g. RDI, percentage of time at an oxygen saturation <90%, arousal index, etc.) were examined with simple and multiple linear regression. All statistical procedures were performed with Statistical Analysis Systems, version PC 6.1. Using the hypothesis that subjects with SDB should not perform better than normal controls, only one-sided p values are reported for group comparisons of neuropsychological tests.

TABLE 1. *Subject characteristics*

	SDB cases (n = 32)	Controls (n = 20)
Age (years)[a]	51.4 ± 7.2	48.9 ± 7.5
Male (%)	47	40
European American (%)[b]	72	35
Education (years)[a]	13.8 ± 2.4	13.5 ± 2.6
Estimated WAIS-R IQ[a]	102.4 ± 8.9	100.2 ± 10.6
Body mass index (kg/m^2)[ab]	34.9 ± 8.4	27.5 ± 5.6

SDB, sleep-disordered breathing; WAIS-R, Wechsler adult intelligence scale–revised.
[a] Mean ± SD.
[b] $p < 0.01$ (two-tailed).

RESULTS

As shown in Table 1, the subjects with mild sleep apnea and the comparison group were of comparable age and education. Both apnea and control groups were of average intelligence. The groups did not differ by gender distribution. A greater proportion of controls were African American than were cases. Those with SDB had a substantially higher body mass index (BMI; kg/m^2) ($p < 0.001$).

The distributions of measures of SDB and sleepiness are shown in Table 2. The mean RDI among cases was 17, a level approximately two-thirds to one-half lower than that reported in previous studies of neuropsychological function in sleep apnea (4,5). Little hypoxemia was noted in either the SDB or the control group, although the percentage of time spent at <90% saturation and oxygen nadir were significantly different. Measures of sleep fragmentation (time in stage I, arousal index, upward shifts), available for only the SDB group, were less abnormal than reported in more severe sleep apnea (4). Subjects with SDB were significantly more likely to report snoring, breathing pauses, and daytime sleepiness (on a 5-point Likert scale) than were the controls. However, measures of both objective (MSLT) and subjective (ESS) sleepiness were consistent with values reported in more general samples and were no different between cases and controls.

Not surprisingly, most neuropsychological variables were correlated with age and estimated IQ. The correlations with IQ ranged from 0.05 to 0.51 (median 0.47) and with age from 0 to 0.38 (median 0.13). Interactions between group status and age or IQ, however, were not suggested. Table 3 presents the age, race, and IQ adjusted values for the neuropsycholog-

TABLE 2. *Sleep, sleep-disordered breathing, and sleepiness in subjects with SDB and control subjects*

	SDB subjects			Control subjects			
	Mean ± SD	Range	n	Mean ± SD	Range	n	p
Physiological measures							
Respiratory disturbance index (events/hour)[a]	17.01 ± 4.95	9.38–27.06	32	2.22 ± 1.37	0.11–4.53	20	0.00005
Percentage of time with O_2 saturation <90%[a]	4.00 ± 6.98	0.0–35.58	31	0.25 ± 0.33	0.0–1.23	20	0.00005
Percentage of time with O_2 saturation <85%	1.19 ± 3.24	0.0–17.66	31	0.08 ± 0.12	0.0–0.52	20	0.07
Nadir O_2 saturation	81.92 ± 6.04	70.0–91.0	32	91.18 ± 4.75	78.0–97.0	20	0.00005
Percentage of time in sleep stage 1	5.67 ± 5.31	0.0–19.0	30				
Arousal index (no./hour)	16.15 ± 10.06	1.05–39.38	29				
Shifts to lighter sleep stage (no./hour)[a]	3.77 ± 1.49	1.49–8.29	29				
MSLT (minutes)	10.48 ± 4.38	21.7–20.0	29	10.52 ± 4.90	2.75–18.33	20	0.49
Self-report measures							
Epworth sleepiness scale	9.84 ± 4.55	2.0–22.0	32	8.95 ± 4.14	3.0–18.0	19	0.26
Habitual snoring[b]	62.5%		32	5.3%		19	0.0005
Snorting, gasping, or stop breathing[b]	48.4%		31	5.3%		19	0.001
Excessively sleepy during day[b]	25%		32	0%		18	0.01

SDB = sleep-disordered breathing.
[a] Values of p based on transformed values (see Methods).
[b] Affirmative answers based on having reported more than three occurrences per week.

ical test scores. There was a significant difference between SDB cases and controls for one of the four attention measures: Cases were less accurate in discriminating target trials from nontarget trials in the 9th and 10th minutes of the vigilance test (CPT d′, last 2 minutes). The groups did not differ in the first 2 minutes. Comparison of the means between the early and later parts of the vigilance test in each group suggests that cases became less efficient (decline of 0.25 SD units), whereas controls improved slightly (0.07 SD units), over time. Cases recalled fewer digits in reverse order than did controls (WAIS-R digits backward). They also tended to perform more poorly on a second executive function measure, the Wisconsin card sort test perseverative errors ($p < 0.10$). A perseverative error identifies a failure to change one's response after being informed that it is incorrect. There were no significant differences in the other neuropsychological measures.

Because the groups differed by race, analyses also were repeated for each racial/ethnic group separately. These analyses revealed similar differences between cases and controls as suggested (above) by the age,

TABLE 3. *Neuropsychological test performance in subjects with SDB and control subjects*

	SDB subjects			Control subjects			
	Mean[a] ± SD	Range	n	Mean[a] ± SD	Range	n	p
Attention							
Digit symbol: WAIS-R	10.66 ± 2.22	7.0–15.0	32	10.73 ± 2.24	6.0–16.0	19	0.46
Letter cancellation errors[b]	11.89 ± 12.49	0.0–77.0	30	9.54 ± 12.60	0.0–32.0	19	0.16
CPT d′(first 2 minutes)	2.49 ± 0.64	1.31–4.18	25	2.63 ± 0.64	1.64–3.61	12	0.27
CPT d′(last 2 minutes)	2.24 ± 0.64	1.34–3.79	25	2.70 ± 0.53	1.64–3.79	12	0.01
Memory							
CVLT: list learning	47.07 ± 8.98	27.0–69.0	32	46.23 ± 9.11	27.0–63.0	20	0.38
CVLT: long-delay free recall	10.11 ± 2.73	4.0–16.0	32	10.08 ± 2.77	6.0–15.0	20	0.48
Pursuit rotor learning (change in percentage time)[c]	7.00 ± 11.05	−14.70–26.39	30	8.43 ± 11.34	−13.83–35.19	15	0.35
Information processing efficiency							
Gilmore-Royer symbol digit	67.07 ± 12.36	44.03 ± 103.07	32	69.48 ± 12.63	44.97–92.97	20	0.26
Executive functioning							
Digits backward: WAIS-R	6.12 ± 2.20	2.0–12.0	31	7.55 ± 2.22	3.0–14.0	19	0.02
WCST: perseverative errors[b]	20.16 ± 10.75	8.0–72.0	32	16.39 ± 10.90	9.0–32.0	20	0.095
Trails A time (seconds)	35.23 ± 9.78	21.0–59.0	32	37.37 ± 9.91	21.0–72.0	20	0.23
Trails B time (seconds)[b]	80.79 ± 25.92	41.0–154.0	32	79.29 ± 26.29	37.0–190.0	20	0.35
Digit subtraction: percent correct	64.00 ± 18.89	11.1–96.0	30	66.12 ± 19.17	15.4–91.2	19	0.36

SDB, sleep-disordered breathing; WAIS-R, Wechsler adult intelligence scale–revised; CPT, continuous performance test; CVLT, California verbal learning test; WCST, Wisconsin card sorting test.
[a] Means were adjusted for age, race, and estimated IQ.
[b] Values of p based on transformed values (see Methods).
[c] Adjusted for age, race, estimated IQ, and sex.

IQ, and race adjusted analyses performed for the entire sample. Specifically, in European Americans, the CPT d′ was 3.0 ± 0.25 in controls and 2.5 ± 0.15 in cases ($p = 0.03$), and the digits backwards score was 7.9 ± 0.83 in controls and 6.8 ± 0.46 in cases ($p = 0.10$). In a group of predominantly African Americans, the CPT d′ was 2.2 ± 0.17 in controls and 1.7 ± 0.16 in cases ($p = 0.04$), and the digits backwards score was 6.9 ± 0.62 in controls and 4.8 ± 0.76 ($p = 0.03$).

Several exploratory analyses were conducted to evaluate potential contributors to the group differences observed. As would be expected, because MSLT and ESS measures did not differ between the two groups, inclusion of these variables in ANCOVA did not alter group differences. The relationship between level of sleepiness and each of the neuropsychological measures also was explored with simple regression analyses performed on the entire sample. Level of objective sleepiness (as measured by the MSLT) was significantly correlated with the number of perseverative errors made on the Wisconsin card sort test ($r = -0.37$, $p = 0.02$) and with the number of words learned over five trials of the CVLT ($r = 0.34$, $p = 0.02$). ESS scores were not correlated with these or other measures of neuropsychological function. The relationship between sleep fragmentation and hypoxemia was evaluated in the group with SDB (in-laboratory polysomnography was unavailable for the controls) by correlating these measures with neuropsychological test scores on which the groups differed. There was a significant relationship between the number of upward sleep shifts and the number of perseverative errors on the WCST ($r = 0.4$, $p < 0.05$). No other correlations performed within the SDB group approached significance.

DISCUSSION

A broad range of neuropsychological deficits has been previously described in patients with severe sleep apnea in comparison with normal volunteers (4,5) and with sleepy, nonapneic controls (5). In these severely affected individuals, deficits have been attributed to hypoxemia (5,24) and to the effects of sleepiness and impaired vigilance (4). A larger proportion of the population has lower levels of SDB (1) than the severe levels reported from clinical settings, and many such subjects are not markedly hypoxemic or pathologically sleepy. Impairment in these subjects with relatively low RDIs has been suggested to occur as a result of snoring, recurrent respiratory disturbances, or arousals (25). However, there are few data that address whether this potentially large segment of the population (with an RDI in the range of 5–30) suffers cognitive and performance deficits in comparison with subjects without SDB.

This study addresses the question of whether subjects with mild SDB, as defined by RDIs in the range of 10–30, perform worse in various tests of neuropsychological function than similar subjects without SDB. Subjects were enrolled solely on the basis of their RDI and were carefully screened to exclude serious medical, social, or neurological problems that could independently influence neuropsychological test performance. Furthermore, in this initial report from a larger ongoing study of functional status and neuropsychological performance in subjects with mild SDB, analyses were limited to subjects within a restricted age range (40–65 years) and who differed clearly on level of apnea (<5 vs. 10–30). To further minimize misclassification, the results of two sleep studies were used, when available, to classify apnea status. Thus, by design, we minimized the effects of age and misclassification by apnea status. The groups thus assembled were well matched on IQ, education, and age.

Cases and controls did differ in their distribution of "traits" associated with SDB: frequency of snoring and observed apneas and level of obesity. Thus, use of the RDI data to define "controls" and "cases" (<5 and 10–30) from predominantly nonclinical recruitment sources successfully distinguished groups with clinically distinct features. Subjects with and without mild SDB did not differ according to levels of objective or subjective sleepiness. Thus, these results should only be generalized cautiously to clinical samples where referral patterns may identify more susceptible individuals with SDB who may have greater functional impairment, who are sleepier, or who, because of greater comorbidities, may be more susceptible to any neuropsychological impairment associated with SDB. The use of volunteers raises the potential for a selection bias (e.g. participation by those with SDB could be influenced by their underlying concerns about their neuropsychological functioning). The nonrandom sampling and the extensive medical and neurological screening procedures necessary to achieve a nonclinical sample with clear differences in the distribution of apneic activity did not allow us the opportunity to collect sufficient data on nonparticipants to exclude this possibility. However, during recruitment, the goals of the study were not specifically discussed, minimizing the likelihood that more impaired apneics would selectively participate (and thus bias the result away from the null). The likelihood that subjects without SDB (controls) would selectively participate only if more impaired (biasing toward the null) was minimized by rigorously excluding subjects with any sleep complaints unrelated to snoring and apnea.

Group differences were demonstrated for only se-

lected neuropsychological tests that required sustained attention and monitoring of sequences of information. On the CPT, subjects must detect successively identical stimuli over a 10 minute testing period. SDB subjects show a decline in this ability over a relatively short time; controls do not show this decline. The differences in this study in visual vigilance were observed only after a period of performance, not at the beginning of the test. This vigilance decrement is consistent with the conclusion of Dinges and Kribbs that sleepiness affects the ability of individuals to sustain attention to tasks over time (18). Additionally, subjects with SDB did worse on the digits backwards test, which also makes attentional demands by requiring the use of earlier information (the previous digit) to guide one's next response. The WCST perseverative error score tended be greater in those with SDB. This error score, which is the most sensitive indicator of deficit on this test (17), reflects a failure to modify a response on the basis of information about one's immediately preceding response. All these tasks involve working memory and other neuropsychological processes.

Other than vigilance (measured by the CPT) and working memory (measured by the digits backwards test), which had effect sizes (d) of 0.87 and 0.65 SDs, respectively, group differences are relatively small. The effect sizes for other neuropsychological measures in this study (mean d = 0.14, range 0–0.36) are also quite small in comparison with previous reports of patients with severe SDB, which range from d = 0.6–1.5 (4,5,24). The sample size in the present study was sufficient to detect moderate effect sizes (0.5 SD) with a power of 0.8. Accordingly, sample size is unlikely to account for the lack of significant effects on other neuropsychological measures or to account for differences between the findings of this study and those of previous studies. Rather, the present results suggest that a broad range of neuropsychological deficits of substantial effect sizes are not likely to be seen in mild sleep apnea, as defined strictly by the RDI. Instead, mild and subtle deficits in working memory components of attention may be the principal cognitive concomitant of mild sleep apnea. The preserved ability of subjects with SDB to perform tasks involving learning, information processing, and several executive functions was not due to a "ceiling" effect; i.e. a broad range of performance was demonstrated in both cases and controls. The findings appear to be more consistent with the notion that, despite a mild vigilance impairment, subjects with mild SDB are able to compensate sufficiently to perform stimulating tasks that do not heavily tax working memory.

Exploratory analyses did not reveal consistent relationships between measures of sleepiness or sleep fragmentation with neuropsychological test performance. Thus, the mediators of vigilance and working memory deficits in subjects with mild SDB who do not suffer from marked hypoxemia or pathological sleepiness are not clear. It is possible that vigilance tests are more sensitive to mild sleepiness than are more traditional sleepiness measures (the MSLT and ESS). Individual differences in susceptibility to sleep fragmentation (or differences in individual compensatory abilities) also may attenuate any "dose-response" relationship between sleep fragmentation/sleepiness and performance.

Analyses in this study employed multiple comparisons, increasing the likelihood of detecting a relationship by chance alone. However, we think it is unlikely that significance levels achieved for the CPT and digits backwards test were spurious. Our a priori hypothesis was, in fact, that vigilance is disproportionately affected in SDB. The consistency of the findings from three distinct tests—the CPT, digits backwards, and Wisconsin card sort tests—further supports the validity of the observations. However, it should be noted that one test that has been previously validated as a sensitive measure of the effects of sleep deprivation, the digit subtraction test (18), did not differentiate cases and controls. There are at least three reasons for the task's failure to discriminate as expected. In pilot testing, our subjects [who are less educated than the college students studied by Dinges and Kribbs (18)], balked at the task, finding it too difficult, so we simplified it. The sensitivity of a neuropsychological test to group differences is partially a function of test difficulty in unimpaired subjects (26), and our modification to increase the acceptability of this task may have made it too easy to be adequately discriminating between groups. Second, performance on this task was highly correlated with mathematical ability (as assessed by the arithmetic subset of the WAIS-R, r = 0.56). Thus, differences in mathematical abilities may have obscured effects associated with vigilance. Third, the continuous subtraction test is highly associated with induced sleepiness. The cases in this sample were not abnormally sleepy or sleepier than the controls.

In summary, the demonstration of vigilance and working memory deficits in mildly affected individuals (defined by an RDI in the range 10–30) further extends the work of Bedard et al. (4), who reported large deficits in severely affected individuals and smaller deficits in subjects with moderate sleep apnea. The absence of large deficits in executive functions and short and long-term memory in this study suggests that the previously reported deficits observed in severe sleep apnea may have been secondary to severe hypoxemia, sleepiness, or both. Alternatively, in comparison with subjects with more severe SDB, subjects with mild SDB may have a greater capacity to com-

pensate for mild attentional deficits during tasks of executive functioning, memory, and learning, despite some vigilance impairment. The extent to which the vigilance and working memory deficits observed may cause impaired performance in tasks of daily living, including an increased vulnerability to accidents during driving, or to mistakes during daily or occupational tasks, is still unknown.

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