Evidence of a Perceptual-Encoding Deficit in Narcolepsy?

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Summary: Body temperature, vigilance, memory, information processing and motor function were examined in 10 unmedicated narcoleptics and 10 matched controls at four different times of day. Time of day and body temperature were not related to performance. Narcoleptics displayed selective cognitive deficits in response latency, word recall, and estimation of frequency. Narcoleptics did not differ from controls in motor speed, vigilance, information processing speed or decision-making accuracy. We propose that a perceptual-encoding deficit may underlie the problems in memory and complex reaction time associated with narcolepsy. Key Words: Narcolepsy—Perceptual encoding.

Neuropsychological assessment of cognitive functioning in narcolepsy has received little attention, while completely ignoring the potential influence of time-of-day effects on both physical and cognitive abilities. The first systematic study of vigilance performance in untreated narcoleptics (1) revealed that narcoleptics performed significantly worse than matched controls on auditory vigilance and serial choice reaction time tasks, but not on tasks assessing rate of information processing and simple attention span. A second study (2) found that narcoleptics displayed lower critical flicker fusion, but normal choice reaction times. A controlled study of narcoleptics on and off medication failed to find any objective evidence for memory disturbance (3). A more recent study (4) reported significant improvements in vigilance, estimation of frequency of occurrence and response latency as measured by the Sternberg short-term memory scanning task for narcoleptics treated with protriptyline compared to an untreated condition.

Diurnal variation or time-of-day effects has been reported for a host of physical and cognitive abilities, including tapping speed (5), elbow flexion strength, eye–hand coordination, simple reaction time, rate of information processing (6), vigilance (7) and memory (8). The relationship between physiological arousal and time-of-day effects on cognitive performance has been difficult to assess secondary to methodological differences between studies. The lack of adequate controls and failure to control for practice and order effects have further confounded the issue.

Narcoleptics have been shown to display deficits in physiological arousal (9–12) as well as body temperature (13). In addition, the well-documented disturbance in sleep and wakefulness has led some to postulate a circadian rhythm disturbance in narcolepsy (14–16).

Therefore, we chose to investigate the relationship between physiological arousal and time-of-day effects on neuropsychological performance in narcolepsy. Oral body temperature readings were chosen to provide an index or measure of physiological arousal.

METHODS

Subjects in our study were referred from various sleep laboratories in the Southern California area. A diagnosis of narcolepsy was confirmed through documentation of sleep-onset rapid eye movement (REM) episodes during polygraphically monitored nocturnal sleep or daytime naps with the multiple sleep latency test (MSLT). For nocturnal sleep, sleep-onset REM was defined as the occurrence of stage REM within 20 minutes of initial sleep onset (first appearance of stage 2). REM sleep occurring within 10 minutes of the first appearance of any stage of sleep on two of five daytime naps qualifies as sleep-onset REM on the MSLT. Ten newly diagnosed and unmedicated narcoleptics (eight

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female and two male) displayed at least two episodes of sleep-onset REM. Narcoleptics ranged in age from 18-50 (mean = 34.2 ± 12.7) with 12-20 years of formal education completed (mean = 14.4 ± 2.2). All narcoleptics presented with excessive daytime sleepiness (EDS) and at least one other feature of the narcoleptic tetrad (i.e. cataplexy, sleep attacks, sleep paralysis and vivid hypnagogic hallucinations). None of the narcoleptics had additional sleep disorders (i.e. apnea, myoclonus), and none suffered from psychiatric disorder, brain injury or medical condition interfering with visuomotor performance. Nonnarcoleptic control subjects were matched for sex (eight female and two male) and ranged in age from 18-50 (mean 34.5 ± 12.0) with 12-22 years of education (mean 15.4 ± 2.3) and were recruited from the student body and professional staff at the UCLA Neuropsychiatric Institute. Clinical interviews were used to select appropriate control subjects with unremarkable medical or psychiatric histories. The two groups did not differ on the matching variables of sex, age and education.

Procedures

All subjects underwent four 60-minute testing sessions scheduled at 8:00 a.m., noon, 4:00 p.m. and 8:00 p.m. to examine the influence of time of day and body temperature on cognitive performance. To control for practice and order effects, all subjects were quasi-randomly assigned to begin their initial testing session at one of the four scheduled times, and all subjects completed the four assessment sessions within a 24-hour period. All subjects reported no change in their normal sleep patterns the night before the testing day. All subjects had conventional sleep schedules. No subject was required to awaken unusually early to attend the 8:00 a.m. session, and the sleep patterns of those who started at a later session were not recorded in the lab on the day of testing.

At the beginning of all testing sessions, each subject's oral body temperature was recorded with a digital thermometer. The order of tests was changed within subjects and between sessions to control for fatigue effects. For example, computerized tasks were alternated with standard memory and pure motor tasks. Alternate and equivalent forms of the memory task were used to control for practice effects. The following measures were used:

- **Memory tests.** Eight 30-item word lists were constructed in a manner similar to that reported by Weingartner et al. (17). Each word on the list occurred either one, two, three or six times and was printed on 3 x 5-inch index cards. Each subject was presented one word per card at the rate of one card every two seconds. Each word was also pronounced aloud by the examiner at the time of presentation. After presentation of the first 30-item word list, subjects were asked to count backward by ones for 30 seconds and then recall as many words from the first list as they could remember. This task served as a measure of effortful or semantic memory. Subjects were then presented with a second 30-item word list in a similar manner, with serial subtraction as a distractor following presentation. Subjects were then shown a list of 16 words, including eight distractor words randomly interspersed among each of the eight target words from the second list of 30 words. Subjects were asked to judge whether each word occurred on the second list, and if so, how often? This task served as a measure of automatic or incidental memory. The absolute difference between actual and reported frequency of occurrence was calculated. These tasks were chosen because they included a high memory load component (free recall of the first 30-item word list) and a low memory load element (estimation of frequency of occurrence). These tasks required four minutes to complete.

- **Continuous Performance Test** (18). Subjects sat in a chair facing a monitor interfaced with a computer. Stimuli consisted of random letters presented at the rate of one letter every 900 milliseconds. Each letter was displayed on the screen for 100 milliseconds, giving a total time of 1,000 milliseconds or 1 second for each trial. Each subject was presented with 1,000 trials. Subjects were required to press a hand-held control button whenever they saw the letter “A” followed by the letter “X”. Errors of omission and commission were recorded as well as simple mean reaction time. This simple signal detection task was selected because it represents a low memory load condition, and provides a measure of vigilance performance which has been shown to be diminished in narcolepsy. Task duration was 16.6 minutes.

- **Finger Oscillation Test** (19). Subjects were given five 10-second trials on the manual finger-tapping apparatus with their dominant hand. A digital counter measured the number of times the index finger traversed a 45-degree arc in 10 seconds. The highest and lowest trials were eliminated and a mean value was calculated for the remaining three trials. This served as a measure of pure motor speed. The finger oscillation test was chosen to provide a direct measure of motor execution independent of higher cognitive processes. This task was completed in about two minutes.

- **Sternberg Memory Scanning Task** (20). In this test (a) subjects were visually presented on the computer screen one, three, or five digits to remember (memory set size); (b) probe digits were presented one at a time on the computer screen following a 1-second visual warning consisting of an asterisk in the middle of the screen; (c) subjects classified each probe digit as belonging or
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FIG. 1. Mean reaction time for narcoleptics (open circles and dotted line) and controls (filled circles and solid line). The equation for each line is $Y = a + bX$, where $b = \text{slope}$ and $a = \text{intercept or point of crossing of the Y axis}$.

not belonging to the set of digits held in memory by pressing one of two hand-held control buttons interfaced with a computer; and (d) the computer recorded reaction time and accuracy. A session consisted of 192 trials broken into 12 blocks of 16 trials. There were four blocks of trials for each memory set size. This task required approximately 15 minutes to complete. A mean reaction time for each memory set size was calculated for the four blocks of 16 trials. Median reaction times were also computed in order to minimize the influence of periodic extreme reaction times. These periodic extreme reaction times were occasionally recorded on individual trials and were identified whenever the time to make a response exceeded 2,000 milliseconds. For a more detailed description of the memory scanning procedure, see Hart et al. (21). The Sternberg is a complex choice reaction time (CRT) task that represents a high memory load condition. This task was selected to provide data on central processing speed, whereas the zero intercept of the reaction time-set size function is taken as a sum required for perceptual-encoding and response-related processes (motor execution).

RESULTS

Simple $t$ tests on the matching variables of age and education revealed no significant group differences. Given the relatively high number of memory and vigilance-related variables, we carried out a multivariate analysis of variance (MANOVA) collapsed across all four testing sessions to control for Type 1 error. Independent MANOVAs were performed for the word lists, continuous performance test (CPT), and Sternberg test. Repeated measures analysis of variance (RMANOVA) was carried out between the two groups across the four testing sessions as well as analysis of covariance (ANCOVA), with temperature as the covariate to better understand significant MANOVAs as well as the effects of temperature, if any, on neuropsychological performance.

MANOVAs revealed no significant main effects for group or time of day and no significant group x time-of-day interaction effects for vigilance as measured via the CPT. Thus, narcoleptics and controls did not differ in vigilance performance, as measured by CPT errors of omission, commission and simple reaction time.

MANOVAs for the Sternberg test indicated a significant main effect for group (p < 0.01), but nonsignificant main effect for time and no significant group x time-of-day interaction effect. Thus, narcoleptics performed significantly worse than controls on rate of information processing across all testing sessions. To better clarify the nature of this deficit, a $2 \times 4$ repeated measure analysis of variance was conducted for Sternberg intercept, slope and errors. RMANOVA revealed a significant main effect for group for memory set sizes of one (p < 0.02), three (p < 0.02) and five digits (p < 0.02), but no main effect for time of day or group x time-of-day interaction. There were no significant differences in the number of errors committed on the Sternberg. Linear trend analysis revealed no main or interaction effects for Sternberg slope values. Thus, narcoleptics displayed a selective deficit in response latency (higher intercepts), but did not differ from controls in slope values or decision-making efficiency (error rate). Statistical analyses employing median reaction times did not differ from analyses using mean values. Thus, for convenience, mean values were reported for the Sternberg. Mean reaction times across all three memory set sizes as well as intercept and slope functions are presented in Fig. 1.

MANOVAs for word list recall and estimation of frequency of occurrence revealed a significant main
effect for group (p < 0.006) but nonsignificant main effects for time and no group × time interaction. RMANOVA revealed a significant main effect for group on the word list recall task (p < 0.006), as narcoleptics recalled significantly fewer total words than controls, but this was not related to time of day. Narcoleptics also displayed a deficit in the ability to estimate frequency of occurrence relative to controls (p < 0.01), as they tended to underestimate the frequency of occurrence of target words previously presented. There were no significant main effects for time or group × time-of-day interaction.

ANCOVA with temperature as the covariate was carried out to investigate what effects, if any, body temperature imposed upon cognitive and physical abilities. The pattern of significant differences between the two groups across all neuropsychological variables remained unchanged. Thus, in our small sample, body temperature was not in any systematic way related to neuropsychological performance in narcoleptics or controls. Narcoleptics and controls did not differ in motor speed, as measured by the finger oscillation test.

Neuropsychological test results are presented in Table 1. Given the absence of significant time or group × time interaction effects across all dependent measures, mean values were calculated by collapsing performance across all four testing sessions.

**DISCUSSION**

Our study provided no evidence for a time-of-day effect on cognitive and motoric abilities in narcoleptics and controls. No direct relationship was demonstrated between physiological arousal, as indexed by body temperature, and neuropsychological performance in either group. The lack of time-of-day effects on neuropsychological performance in both groups may have been related to methodological differences between previous research efforts and our study, which controlled for practice and order effects. It also remains tenable that the dependent measures chosen for our study are not influenced by the time of day, but rather by intrasubject variables, such as motivation and effort.

Narcoleptics did not differ from controls in mean body temperature, motor speed (finger oscillation test), vigilance (CPT) or central processing speed (Stemberg slope values). Narcoleptics did perform significantly worse than matched controls on word recall, incidental memory (estimation of frequency of occurrence) and response latency (Stemberg intercept values).

CRT tasks, like the Sternberg, typically include motor and nonmotor elements. Sternberg (22) identified four stages in memory scanning tasks: (a) stimulus encoding, (b) serial comparison, (c) binary decision and (d) response organization and execution (23). Stimulus encoding, serial comparison and binary decision represent the nonmotor stages of CRT, whereas response organization and execution represent the motor stages. Perceptual-encoding is synonymous to the first stage (i.e. stimulus encoding in Sternberg’s model), whereas central processing relates to stages two and three.

The lack of significant findings for vigilance performance between the two groups is a bit surprising. However, narcoleptics have been shown to detect signals at a normal rate during sustained wakefulness, with poor detection associated during episodes of drowsiness (11). Although EEG-polygraphic monitoring of alertness was not conducted in narcoleptics in our study, there was no evidence of behavioral drowsiness in continuous observation. Thus, physiological arousal appeared to be consistent with a state of sustained full wakefulness.

The relatively poorer performance of narcoleptics on the Sternberg task was consistent with a recent study (8), as narcoleptics displayed significantly higher intercepts than controls across all memory set sizes and all testing sessions. Nonsignificant slope difference between the two groups suggest that both narcoleptics and normal controls search or scan items in memory at the same rate, with no differences in central processing speed. However, the finding of significant differences in intercept values suggests that slowed complex reaction times in narcolepsy must be related to deficits in perceptual encoding, time to execute appropriate motor responses and/or reflect a perceptual-motor integration deficit. We argue that narcoleptics display a deficit in perceptual-encoding and not slowed motor responses to explain the observed difference in Sternberg intercept values, as motor speed (measured by the Finger Oscillation Test) did not differ between the two groups. However, this still does not rule out the possibility of a perceptual-motor integrative deficit.

Recent research investigating the effects of aging on

![Table 1. Mean and standard deviations of test results](https://academic.oup.com/sleep/article-abstract/16/2/123/2749331/1.123746831?download=true)

<table>
<thead>
<tr>
<th>Test</th>
<th>Narcoleptics</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°F)</td>
<td>97.7 ± 1.1</td>
<td>97.8 ± 0.5</td>
</tr>
<tr>
<td>CPT reaction time (milliseconds)</td>
<td>383.3 ± 46.9</td>
<td>362.0 ± 51.6</td>
</tr>
<tr>
<td>CPT omission errors</td>
<td>1.3 ± 1.6</td>
<td>0.9 ± 1.2</td>
</tr>
<tr>
<td>CPT commission errors</td>
<td>0.8 ± 1.0</td>
<td>0.7 ± 1.0</td>
</tr>
<tr>
<td>Sternberg errors</td>
<td>4.4 ± 3.8</td>
<td>2.4 ± 1.8</td>
</tr>
<tr>
<td>Sternberg slope</td>
<td>53.6 ± 32.0</td>
<td>39.8 ± 11.4</td>
</tr>
<tr>
<td>Sternberg Y intercept (milliseconds)</td>
<td>519.1 ± 107.5</td>
<td>446.7 ± 79.5*</td>
</tr>
<tr>
<td>Estimation of frequency</td>
<td>10.8 ± 4.0</td>
<td>8.3 ± 2.5**</td>
</tr>
<tr>
<td>Word list recall</td>
<td>8.9 ± 2.3</td>
<td>11.2 ± 1.7***</td>
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*p < 0.02; **p < 0.01; ***p < 0.006; p values based on MANOVA F tests. Values represent absolute differences, which were calculated by subtracting the reported from the actual differences.
information processing speed in normals using the Sternberg task and event-related brain potentials (24) revealed that younger subjects (ages 20–26) did not differ from older subjects (ages 53–65) on Sternberg slope values, but produced significantly faster complex reaction times (lower intercept values). The authors concluded that memory search rate (slope values) was not slowed with age; rather, the slowing (higher intercept values for the elderly as reflected in longer complex reaction times) lies predominantly in the perceptual-motor systems. Thus, we suggest that the finding of significantly slower reaction times that were displayed in narcoleptics in our study represents dysfunctional preprocessing of relevant stimulus properties, contributing to a perceptual-encoding deficit that is reflected in greater Sternberg intercepts but not slope values.

A deficit in perceptual-encoding might be expected to diminish the efficiency to which target stimuli are attended and processed. Our narcoleptics demonstrated significant memory impairment relative to controls on a separate word list recall task and incidental memory paradigm (estimation of frequency). Our findings are in disagreement with an earlier study depicting normal memory functioning in narcoleptics (7), however the earlier study did not sufficiently control for order and practice effects and relied primarily upon the Wechsler memory scale (WMS). The WMS measures for stories, designs and paired words with cued recall. It is likely that different memory processes are involved in remembering stories (i.e. elaborative rehearsal and chunking), whereas memory for a list of unrelated words may activate rehearsal and mnemonic strategies. Our estimation of frequency task represents an incidental memory paradigm, as subjects are not instructed to remember the frequency of occurrence of specific target words. Thus, deficits in word list recall and incidental memory may represent further manifestations of the perceptual-encoding deficit in narcolepsy.

Although these preliminary results suggest some interesting differences in memory ability between narcoleptics and normals and offer some speculation as to the nature of the cognitive deficits in narcolepsy, future research is needed to replicate our findings.

REFERENCES

1. Valley V, Broughton R. Daytime performance deficits and physiological vigilance in untreated patients with narcolepsy-cata-