Scheduled Naps in the Management of Daytime Sleepiness in Narcolepsy-Cataplexy

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Summary: A repeated testing paradigm was used to assess the efficacy for the management of daytime sleepiness in narcolepsy-cataplexy of single long, multiple short and no-nap sleep/wake schedule conditions, with total sleep per 24 hours held constant. Eight narcoleptic subjects participated and followed each experimental schedule for two consecutive days, the second of which served as a test day during which simultaneous electroencephalogram (EEG) polygraphic recordings were made. Performance tests reported here include a grammatical transformation test and a four-choice reaction time test. A single long nap placed 180° out-of-phase with the nocturnal mid-sleep time improved sustained performance over the no-nap condition. Reaction time performance was significantly improved in the long nap condition over the no-nap condition. Time-of-day analyses found that the greatest improvement was in the afternoon and evening. By contrast, the grammatical transformation test results suffered under the napping compared to no-nap schedules, suggesting that continuity of wakefulness and/or a long nocturnal sleep period may be important for this test. In addition, unscheduled sleep episodes tended to occur earlier in the day than the period of maximum afternoon sleep tendency seen in normal subjects. Two napping strategies are suggested for further study. Key Words: Napping—Sleepiness—Narcolepsy—Performance.

Naps have often been recommended in the management of excessive daytime sleepiness (EDS) associated with narcolepsy-cataplexy (1–4). However, few studies have assessed the effects of naps in narcolepsy on objective measures of sleepiness such as EDS-sensitive performance indices or sleep pressure as measured by the multiple sleep latency test (MSLT) (5) and maintenance of wakefulness test (MWT) (6).

A behavioral management strategy would be useful in the management of EDS in narcolepsy-cataplexy for those patients in whom stimulant medications may be ineffective (7,8). In addition, there are individuals who cannot tolerate these medications due to adverse side effects such as nervousness, decreased appetite, palpitations or tachycardia, or for whom it is contraindicated due to other medical complications such as allergies or cardiac problems (8). Finally, even if the stimulant medication is well tolerated by the patient, drug holidays are sometimes recommended (9,10), and naps might minimize EDS at such times.

Four studies have investigated the alerting effects of naps in narcolepsy and their results have been mixed. Roehrs et al. (11) employed a modified MSLT paradigm and found that, although naps of 15 and 30 minutes significantly reduced sleep latency as measured by a nap test 15 minutes later, a 30-minute nap did not increase sleep latency relative to a 15-minute nap. This finding suggests that napping in narcolepsy does not proffer sustained benefits. However, sleep onset has a strong behavioral (learned and volitional) component, and the MSLT may not be an optimum test for this application because it measures both pressure for sleep and ability to fall asleep (12). A test measuring ability to resist sleep and/or to maintain performance would better address the question of the utility of naps for the management of excessive daytime sleepiness in narcoleptics.

In a more recent study, Rogers and Aldrich (13) assessed the treatment value of regularly scheduled daytime naps in narcoleptic subjects. MWT data were compared before and after subjects attempted to follow a 4-week schedule of three daily naps of 15 minutes each (based on the subjects' own desired times). Sleep latencies were significantly increased at posttreatment assessment, a difference mainly attributable to the second resisting sleep trial (at 1200 hours). However, the number of MWT periods without sleep did not sig-
SCHEDULED NAPS FOR EDS IN NARCOLEPSY

TABLE 1. Subject characteristics for narcolepsy-cataplexy patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>SOL (n)</th>
<th>Apnea index</th>
<th>PMS index (%)</th>
<th>Medication (pre-study)</th>
<th>Further auxiliary symptoms</th>
</tr>
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<tbody>
<tr>
<td>1. SD</td>
<td>F</td>
<td>53</td>
<td>2.3</td>
<td>4</td>
<td>0.0</td>
<td>22.0</td>
<td>Chlomipramine, GH, methylphenidate</td>
</tr>
<tr>
<td>2. CP</td>
<td>M</td>
<td>22</td>
<td>2.6</td>
<td>2</td>
<td>21.5</td>
<td>22.3</td>
<td>Untreated</td>
</tr>
<tr>
<td>3. SG</td>
<td>M</td>
<td>48</td>
<td>4.8</td>
<td>2</td>
<td>1.2</td>
<td>4.6</td>
<td>Carbamazine</td>
</tr>
<tr>
<td>4. SM</td>
<td>F</td>
<td>19</td>
<td>1.0</td>
<td>5</td>
<td>1.6</td>
<td>19.5</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>5. RK</td>
<td>F</td>
<td>54</td>
<td>.8</td>
<td>4</td>
<td>3.5</td>
<td>55.0</td>
<td>Chlomipramine, methylphenidate</td>
</tr>
<tr>
<td>6. PE</td>
<td>M</td>
<td>45</td>
<td>3.0</td>
<td>4</td>
<td>0.2</td>
<td>0.0</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>7. PL</td>
<td>M</td>
<td>46</td>
<td>3.3</td>
<td>3</td>
<td>1.7</td>
<td>19.7</td>
<td>Chlomipramine, GH, methylphenidate</td>
</tr>
<tr>
<td>8. ED</td>
<td>F</td>
<td>55</td>
<td>2.4</td>
<td>3</td>
<td>0.0</td>
<td>4.0</td>
<td>Untreated</td>
</tr>
</tbody>
</table>

Abbreviations: SOL = mean sleep onset latency, SOREMPs = sleep onset REM periods, PMS = periodic movements in sleep (% of night with PMS).

Slightly increase and the number of sleep attacks reported in sleep logs did not change after the 4 weeks of napping treatment.

When properly employed, performance tests may be the most ecologically valid method for assessing the impact of excessive daytime sleepiness upon the ability to maintain vigilance. Using reaction-time performance measures, Billiard (14) and Godbout and Montplaisir (15) found some support for the recuperative effect of naps, particularly nonrapid eye movement (NREM) naps, in narcolepsy-cataplexy. In these studies, however, there were no significant improvements in performance when comparing napping days with non-napping days for the same subjects tested just prior to and immediately following 20-minute naps administered in an MSLT paradigm. However, "sleep inertia", i.e. the decrement seen immediately following sleep (16), may have suppressed the beneficial effects. In addition, because half of the tests on napping days were made immediately upon waking, any improvement in performance may have been masked. Because sleep inertia has not been investigated in narcoleptics, it is not possible to estimate to what degree these results might have been compromised.

Subjects

Eight (four male, four female) narcolepsy-cataplexy patients aged 19–55 participated. Full patient characteristics are detailed in Table 1. All subjects had a history of irresistible sleep attacks, cataplexy and EDS. Subjects had sleep onset latencies <5 minutes and at least two daytime sleep onset rapid eye movement periods (SOREMPs) as determined by MSLT or 24-hour ambulant polysomnographic screening. They were withdrawn from stimulant medications (methylphenidate or pemoline; none had been on amphetamines) for at least 10 days prior to participating in the protocol. Those taking tricyclic REM-suppressant medication for cataplexy, which is known not to affect day-
FIG. 1. Schematic representation of sleep/wake schedules followed by narcoleptic subjects during no-nap, single long nap and multiple short nap conditions. The 24-hour sleep total was held constant with, in the nap conditions, 75% taken in the nocturnal period and 25% in the naps. The midpoint of nocturnal sleep was also constant across conditions and represents 0°. The midpoint of the long nap and the third short nap are 180° out-of-phase, with the other short naps equidistant in degree across the daytime period. The figure represents the schedules in an hypothetical 8-hour sleeper with nocturnal midpoint at 0400 hours.

time sleepiness (25,26), were not required to discontinue that medication. One narcoleptic was taking carbamazepine for suspected coexistent seizures and continued this medication. One subject (PL) on gamma-hydroxybuterate (GHB) for consolidation of night sleep in narcolepsy (27) stopped this medication at the same time as he ceased taking his methylphenidate. However, another subject (SD) was unable to maintain her nocturnal sleep without GHB and so was permitted to keep taking it throughout the study period.

Procedure

In-home baseline

Subjects kept a sleep log for 10 days prior to the performance testing part of the study. The final five days (or 10 days for subjects not previously taking stimulant medications) of the sleep log period were used in the design of the individualized schedules, which will be described below.

Sleep–wake schedule testing

The study involved eight consecutive days and was carried out at a bed-and-breakfast establishment in a quiet rural setting. All subjects spent the first and second days on an ad libitum protocol, sleeping whenever they wished. During these two days, subjects completed a bank of performance tests (detailed below) immediately prior to both nocturnal sleep and daytime nap(s), immediately after waking from each sleep period, and every 30 minutes during wakefulness. These two ad libitum days served to adapt subjects to the procedures employed in the three sleep–wake schedules that followed in counterbalanced order, each maintained for 2 days (an adaptation day and a test day).

Design

Schedule construction

Average total sleep time per 24 hours was calculated for each subject based on stimulant-free sleep log data. The average total sleep time per 24 hours for each subject was carried over into the experimental period to become the total sleep time permitted in each treatment schedule. The average nocturnal midsleep time, as determined by sleep logs, was also held constant in order to minimize any circadian disruption. The resulting conditions (see Fig. 1) were scheduled as described below. Outside of sleep periods and the first two test periods following sleep, subjects were in a group setting at all times and were continuously supervised by experimenters.

No-nap (consolidated) sleep schedule

For the no-nap condition, total scheduled sleep was given in a single nocturnal period, maintaining the
nocturnal midsleep time of the baseline sleep logs. Naps were not permitted.

Long nap schedule

In both nap conditions, 75% of the average total sleep time was scheduled for the major bed period, with 25% for naps. This division was based upon the 76%:24% ratio for nocturnal vs. daytime sleep documented in the real-life home environment ambulatory monitoring study of Broughton et al. (19). For the single long nap schedule, the midnap point was positioned 180° out of phase with the nocturnal midsleep time. This nap placement position was chosen because it has been shown to be the approximate time of greatest likelihood of napping in normal healthy sleepers (28) and also that of greatest sleep propensity in normals (18,29) and in narcoleptic subjects included in the ambulatory home study mentioned above (19).

Multiple short nap schedule

As in the long nap condition, 75% of the 24-hour total sleep time was scheduled as the major bed period. The remaining 25% was distributed in five naps positioned equidistantly throughout the day, with the midnap time of the third nap set at 180° out of phase with the nocturnal midsleep time and the others equidistant between the hours of morning awakening and evening sleep onset.

Sleep and performance test schedules for each subject were controlled and administered by notebook computers (Compaq LTE), which were left running for the duration of the study. These were the most lightweight computers available at the time that contained a necessary math coprocessor. This approach was chosen so that subjects could easily carry the test equipment in a tote bag up- and downstairs from their bedrooms to the testing room. Computers were programmed not only to initiate (by loud signal) and administer all test sessions, but also to sound a similar alarm at wake-up time (measuring approximately 75 dB at the subject’s pillow). An alarm also sounded during a test session whenever the subject did not respond within 30 seconds (excepted during the four-choice reaction time test, which ran its duration uninterrupted).

The entire protocol took approximately 180 hours for each subject to complete, resulting in >1,000 total test sessions and >1,000 hours of physiological recordings. Subjects had private rooms. Meals and snacks were served buffet style to accommodate the staggered scheduled mealtimes. Ambient temperature was maintained between 21–24°C. The study was run during the winter months of February and March.

Physiological recordings

Physiological recordings were made using Oxford 9000 ambulant Medilog units. Electrodes were placed at sites C3-M2, C4-M1, O1-M2, REOG-M1, LEOG-M2 and submental electromyogram (EMG). Electrocardiogram (EKG) and tympanic temperature were also recorded. Electrodes were applied on the first evening at the bed-and-breakfast and left on for 36 hours at a time. For scalp electrodes, a commercial dermatological cream (EC2) was used in conjunction with normal electrolyte jell because this combination had been found to be preferable for long-term physiological recordings in previous laboratory studies. For each of the three counterbalanced 2-day conditions that followed, electrodes were applied between test sessions during the evening of the adaptation day. In this way, polygraphic recordings were made for all nights during the study and for the postadaptation experimental daytime periods.

Recordings were printed out at 20 × real time using the Medilog 9000 playback unit and a Siemens-Elema Mingograf polygraph. Speed of playback was fine tuned with the assistance of a decade box that resulted in a paper speed accuracy for each 24 hours of over 99%. Paper records were scored using 30-second epochs. Nocturnal sleep was scored according to standardized criteria (30). Wakefulness was divided into active and quiet wakefulness according to criteria of Volk et al. (31) with the addition of substage 1A (32) drowsiness consisting of slowing and diffusion of the alpha rhythm, with or without slow eye movements. Substage 1B was scored identical to stage 1 of Rechtschaffen and Kales (30).

Performance testing

Individually scheduled sleep periods and performance test sessions were initiated by computer, the software of which is described in detail elsewhere (33). Each session took approximately 13 minutes to complete and consisted of a fixed sequence of the descending subtraction test (16,34), a grammatical transformation (or logical reasoning) test (35), four-choice reaction time test [computerized after Wilkinson and Houghton (36)], grip strength test (37), a measure of oral temperature, the Stanford sleepiness scale (38) and a number of additional subjective evaluation questions, most of which were based on Thayer’s (39) activation checklist. The tests were administered in fixed sequence to preserve consistency in time from waking. Results from the grip strength, oral temperature measures and subjective estimations of sleepiness will be presented elsewhere.

At the start of test sessions and bed periods, subjects were instructed to press both the event marker on their
Medilog recorder and a designated computer key to synchronize the performance test and EEG/polygraphic recordings. On adaptation days for each condition, tests were performed every hour outside of sleep periods or meal times. On experimental days, performance tests were administered for the no-nap schedule every 30 minutes during the daytime and, on nap days, approximately 15 minutes prior to a nap, immediately upon waking, 20 minutes after waking and every 30 minutes thereafter, with the exception of mealtimes and sleep periods. Given the design of sleep scheduling, the precise number of tests for each subject was variable and depended on the percentage of 24 hours that the subject normally slept. Subjects performed an average of 28.5 test sessions on test days and 20.2 on practice days. There were an average of 28.0 tests (range 25–31) on no-nap, 28.0 (range 26–30) on the long nap and 29.4 (range 27–32) on the multiple short nap condition test days.

*Descending subtraction test*

The descending subtraction test (DST) was primarily included in the battery for its sensitivity to sleep inertia (16) and therefore was the first performance test in each session. In this 2-minute test, subjects were presented with a randomly generated three-digit number between 500–999, were instructed to begin subtracting backwards starting with 9, enter the subtrahend into the computer (using a numeric keypad), then subtract 8, then 7 and so on down to 2. The cycle of subtraction was continued for the duration of the test, when the computer automatically ended the session, tallied and stored the number completed, number of correct responses, number of errors and percent correct.

*Baddeley’s grammatical transformation test*

Next was the grammatical transformation test, a logical reasoning task that also ran for 2 minutes. In this test, a logical statement is presented that refers to a pair of letters and the subject is required to make a true or false choice. For example:

B is not followed by A — BA

True False

Subjects selected a key on the computer to highlight their choice response. The number of items completed, number correct, number of errors and percent correct were retained by the computer.

*Four-choice reaction time test*

The four-choice reaction-time test followed and lasted 5 minutes. External hardware was designed and attached to the printer port of the computer with four keys corresponding to four red diodes that lit up in random sequence, essentially identical to the original design (36). The dependent measures saved included: mean reaction time of correct response without gaps (i.e. responses > 1 second), of wrong responses without gaps and of gap responses, as well as the number completed and number of correct responses made in each 5-minute session.

**RESULTS**

A priori hypotheses were tested using Student’s paired two-tailed t tests with alpha set to the 0.05 level of rejection. The reduction of the nocturnal bed period plus the redistribution of 25% of total sleep time in the normal waking hours in the napping conditions was expected to facilitate consolidation of sleep and wakefulness, based on the view of narcolepsy-catalepsy as a disorder of state-boundary control (40). It was hypothesized that the ability to maintain state would be facilitated by the redistribution of sleep periods, which would result in an overall greater recuperation, manifested in higher sleep efficiency and REM efficiency, fewer unscheduled sleep episodes and higher performance levels. In addition, we wanted to test the possibility that one of the napping strategies would produce better results than the other. For these a priori hypotheses Student’s two-tailed paired t tests were made. Further post-hoc explorations of the data were made using Student’s paired t tests with Bonferroni adjustments for multiple comparisons (41).

**Sleep recordings**

*Total scheduled and unscheduled sleep*

Despite the different schedule manipulations, stage totals for scheduled sleep per 24 hours did not differ significantly across conditions, although there was a trend toward greater amounts of REM sleep in the multiple short nap condition (see Table 2). The number of unscheduled sleep episodes did not differ significantly across conditions, although there were notably fewer in the long nap condition relative to the no-nap condition, and this approached significance (p = 0.08). The mean number of unscheduled sleep episodes (lasting >3 minutes) and the associated standard deviations were as follows: for the no-nap condition, 7.1 (SD = 4.0); for the long nap condition, 4.3 (SD = 2.6) and for the multiple short nap condition, 6.5 (SD = 6.0). Consistent with this trend, the number of unscheduled minutes of sleep obtained in the long nap condition was lower than in the other conditions, and it approached significance when compared with the no-nap condition (p = 0.07).
Scheduled Naps for EDS in Narcolepsy

TABLE 2. Twenty-four-hour totals of scheduled and unscheduled sleep*

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long nap</th>
<th>Short naps</th>
<th>N vs. L</th>
<th>N vs. S</th>
<th>L vs. S</th>
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</thead>
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<tr>
<td>SCHEDULED NAPS FOR EDS IN NARCOLEPSY</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Scheduled</td>
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<td></td>
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</tr>
<tr>
<td>QWS</td>
<td>6.5 (11.6)</td>
<td>1.5 (2.6)</td>
<td>1.4 (2.6)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Stage 1A</td>
<td>27.8 (23.1)</td>
<td>25.6 (21.2)</td>
<td>20.2 (19.5)</td>
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<td>ns</td>
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<tr>
<td>Stage 1B</td>
<td>50.9 (25.8)</td>
<td>51.1 (32.6)</td>
<td>59.2 (34.1)</td>
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<td>ns</td>
<td>ns</td>
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<tr>
<td>Stage 2</td>
<td>132.3 (52.0)</td>
<td>133.1 (43.0)</td>
<td>111.3 (42.2)</td>
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<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Stage 3</td>
<td>49.8 (11.7)</td>
<td>41.2 (10.3)</td>
<td>45.4 (21.4)</td>
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<td>ns</td>
<td>ns</td>
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<tr>
<td>Stage 4</td>
<td>88.3 (41.1)</td>
<td>103.1 (34.1)</td>
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<td>SWS</td>
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<td>144.3 (38.9)</td>
<td>137.2 (56.0)</td>
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<tr>
<td>REM</td>
<td>133.3 (31.4)</td>
<td>139.5 (35.6)</td>
<td>165.2 (28.5)</td>
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<td>ns</td>
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<td>MT</td>
<td>11.8 (9.3)</td>
<td>10.4 (7.2)</td>
<td>10.5 (4.7)</td>
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<tr>
<td>TST</td>
<td>454.6 (61.0)</td>
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<td>ns</td>
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<td>Unscheduled</td>
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<td></td>
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<td>Stage 1B</td>
<td>28.7 (15.8)</td>
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<td>26.6 (30.4)</td>
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<td>ns</td>
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<td>Stage 2</td>
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<td>0.4 (1.1)</td>
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<tr>
<td>REM</td>
<td>1.8 (2.3)</td>
<td>1.2 (3.4)</td>
<td>5.1 (7.9)</td>
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</tr>
<tr>
<td>TST</td>
<td>31.3 (17.5)</td>
<td>17.4 (11.5)</td>
<td>33.0 (30.7)</td>
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</tbody>
</table>

Abbreviations: QW = quiet wakefulness, AW = active wakefulness, SWS = stages 3 plus 4, MT = movement time, N = no-nap condition, L = long nap condition, S = multiple short naps condition.

* Sleep episodes >3 minutes.

Most of the sleep episodes outside of the scheduled sleep periods were brief and consisted of stage 1B. Subjects slept for an average of <5 minutes at a time in all conditions (average duration of sleep episodes per subject across all conditions ranged between 3 minutes and 4 minutes 51 seconds). Unscheduled sleep periods >5 minutes in duration were infrequent (only 31 out of 142 in the study), but were variable in frequency per subject and ranged from 0-18 events per test day. There were only eight unscheduled sleep episodes of >7 minutes duration.

The timing of unscheduled sleep episodes is of particular interest in the no-nap condition because subjects were not permitted to nap at all, but nocturnal sleep was not reduced. The timing of these sleep episodes is illustrated in Fig. 2 as a frequency histogram. The phase time of greatest likelihood of unscheduled sleep occurred between 150-170° out of phase with the nocturnal midsleep time, with a secondary peak between 250-270°. With respect to group average clock times, the first peak corresponds to a range of approximately 1340-1500 hours and the second to 2020-2140 hours.

Structure of long vs. multiple short nap sleep

On average, scheduled long naps were 129 minutes and short naps were 26 minutes in duration. Post-hoc analyses (Table 3) found that long nap sleep periods had a tendency for less percent stage 1A (p < 0.10) and more stage 4 and slow wave sleep (SWS; stages 3 plus 4) (p < 0.10) than the short naps. Concerning time of the short naps compared with the long nap condition. In addition, percent of the scheduled bed period spent in active wakefulness was higher in the long nap compared to the multiple short nap condition.

Nocturnal sleep

It was hypothesized that nocturnal REM efficiency would be higher in the napping conditions compared to the no-nap sleep condition, but a difference was found only between the no-nap and long nap conditions and the direction was opposite to that expected.

Nocturnal and daytime sleep data are presented in Table 3 for the no-nap, single long nap and five short naps schedules. Post-hoc exploratory analyses found that sleep efficiency was higher for the nocturnal period...
(minutes) in stage, there were no significant differences, but there was a tendency for substage 1A (drowsiness) to be lower in the long nap condition (p < 0.10).

Performance testing

Tests performed immediately after awakening were excluded to avoid possible confounding sleep inertia effects. No differences were found in direct comparison between long and multiple short nap conditions for any of the performance measures. Hypothesis testing found significant differences between the long and no-nap conditions for the grammatical reasoning and the four-choice reaction time tests, which are detailed below. The descending subtraction test, included in the battery mainly for its sensitivity to sleep inertia, did not yield any significant test day differences and therefore will not be considered further in this paper.

Grammatical transformation test

Grammatical transformation test results (number correct) were significantly higher in the no-nap condition when compared to the long and also the short nap conditions. Means and standard deviations are presented in Table 4. When test sessions immediately upon waking plus those 20 minutes after waking were excluded from analyses, the grammatical transformation test results (number correct) remained significantly higher during the no-nap condition than the long nap condition. The difference between the multiple short and no-nap conditions was not significant. Thus, this reasoning task showed better performance in the no-nap condition. In terms of percent change, there was an average decrement in performance of 16.2% for subjects performing the grammatical reasoning test in the long nap condition compared with the no-nap condition, whereas the average relative decrement was only 4.5% for the multiple short nap condition.

Four-choice reaction time test

Reaction time data are summarized in Table 5. Data excluding immediate post-wake sessions were analyzed and are provided to show number completed and number correct. In addition, the number of correct reaction time responses made without gaps, the average reaction time and the standard deviations of reaction time responses made without gaps, the

### TABLE 3. Scheduled sleep characteristics

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long</th>
<th>Short</th>
<th>p-value*</th>
<th>Long</th>
<th>Short</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE</td>
<td>89.8 (7.1)</td>
<td>91.8 (3.6)</td>
<td>93.8 (4.4)</td>
<td>p &lt; 0.05</td>
<td>92.6 (6.9)</td>
<td>90.1 (5.3)</td>
<td>ns</td>
</tr>
<tr>
<td>REMeff</td>
<td>76.0 (6.6)</td>
<td>68.6 (10.3)</td>
<td>73.4 (16.7)</td>
<td>p &lt; 0.05</td>
<td>80.0 (20.2)</td>
<td>95.2 (4.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Percent of bed period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>2.4 (1.9)</td>
<td>2.3 (1.8)</td>
<td>2.5 (1.2)</td>
<td>ns</td>
<td>1.2 (1.4)</td>
<td>0.7 (0.9)</td>
<td>ns</td>
</tr>
<tr>
<td>OW</td>
<td>1.2 (2.0)</td>
<td>0.3 (0.6)</td>
<td>0.2 (0.5)</td>
<td>ns</td>
<td>0.2 (0.4)</td>
<td>0.3 (0.5)</td>
<td>ns</td>
</tr>
<tr>
<td>AW</td>
<td>5.5 (4.7)</td>
<td>4.8 (3.1)</td>
<td>2.9 (3.4)</td>
<td>p &lt; 0.05</td>
<td>5.1 (6.1)</td>
<td>6.1 (4.0)</td>
<td>ns</td>
</tr>
<tr>
<td>1A</td>
<td>1.3 (2.0)</td>
<td>1.1 (1.3)</td>
<td>0.7 (0.9)</td>
<td>ns</td>
<td>0.8 (1.0)</td>
<td>2.3 (1.7)</td>
<td>p &lt; 0.10</td>
</tr>
<tr>
<td>Percent of sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>11.3 (6.0)</td>
<td>11.3 (7.9)</td>
<td>12.1 (8.1)</td>
<td>ns</td>
<td>9.4 (6.5)</td>
<td>13.5 (8.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Stage 2</td>
<td>29.1 (10.3)</td>
<td>31.3 (10.4)</td>
<td>26.1 (9.8)</td>
<td>ns</td>
<td>19.6 (6.2)</td>
<td>17.1 (13.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Stage 3</td>
<td>10.6 (1.7)</td>
<td>10.0 (3.6)</td>
<td>11.3 (5.7)</td>
<td>ns</td>
<td>5.5 (5.0)</td>
<td>5.5 (6.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Stage 4</td>
<td>19.5 (7.9)</td>
<td>17.6 (8.2)</td>
<td>20.0 (7.9)</td>
<td>ns</td>
<td>34.8 (9.6)</td>
<td>14.4 (16.4)</td>
<td>p &lt; 0.10</td>
</tr>
<tr>
<td>SWS</td>
<td>30.1 (8.7)</td>
<td>27.6 (10.0)</td>
<td>31.3 (11.6)</td>
<td>ns</td>
<td>40.3 (10.0)</td>
<td>19.9 (21.5)</td>
<td>p &lt; 0.10</td>
</tr>
<tr>
<td>REM</td>
<td>29.3 (4.9)</td>
<td>29.5 (9.1)</td>
<td>30.5 (7.8)</td>
<td>ns</td>
<td>30.4 (6.1)</td>
<td>49.6 (27.1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: REMeff = REM period efficiency, QW = quiet wakefulness, AW = active wakefulness, SWS = stages 3 plus 4, MT = movement time, N = no-nap condition, L = long nap condition, S = multiple short naps condition.

* Values are presented as mean percent data (SD).
* Bonferroni alpha adjustments applied.
SCHEDULED NAPS FOR EDS IN NARCOLEPSY

TABLE 4. Grammatical transformation test

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long nap</th>
<th>Short naps</th>
<th>N vs. L</th>
<th>N vs. S</th>
<th>L vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-wake data</td>
<td>18.1 (8.1)</td>
<td>16.2 (8.9)</td>
<td>16.8 (7.7)</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td>Excluding immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and + 20-minute data</td>
<td>17.9 (7.9)</td>
<td>16.0 (8.7)</td>
<td>16.7 (7.4)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: N = no-nap condition, L = long nap condition, S = multiple short naps condition.

* Values are for test day, means (SD), p-values presented are for two-tailed paired t tests, 7 df.

significant differences between the no-nap and multiple short nap conditions.

The only significant difference between the multiple short nap and no-nap conditions was found in the mean standard duration of wrong responses, which was lower for short naps. There was no significant improvement in performance seen for the multiple short nap compared to the no-nap condition, despite the fact that six of the eight subjects had higher mean scores with multiple short naps. The standard deviation of the mean difference was too great to achieve statistical significance.

Time-of-day effects

Test sessions were matched across conditions so that the period associated with the 180° phase category, which involved sleep in both nap schedules, was excluded from time-of-day comparisons between conditions. Phase-angle time bins were divided into six categories around the deleted one at 180°, with three “early” and three “late”. The medians, in degrees (°) of each of the six category boundaries were: 72.5, 107.5, 142.5, 217.5, 252.5 and 287.5 (rounded up for further discussion). These corresponded to group average clock times of 0800, 1020, 1240, 1740, 2000 and 2220 hours. Test results from the two performance test sessions that spanned each median split were averaged together for that time category.

Post-hoc tests for time of day differences on grammatical reasoning found significant condition effects for number completed at the 143° category. Performance was slightly better in the no-nap and in the multiple short nap conditions compared to the long nap condition.

There were significantly fewer grammatical transformation items performed correctly at the 143° category in the multiple short nap vs. the long nap condition and also for the no-nap over the long nap condition. No significant differences were found at any other time of day for this performance test. Number correct data from the grammatical reasoning test for time-of-day category bins are illustrated in Fig. 3; data for both number completed and number correct are provided in Table 6.

Reaction time, number completed and number correct were used in time-of-day analyses because they had been most sensitive in test day analyses. These

TABLE 5. Four-choice reaction time test

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long nap</th>
<th>Short naps</th>
<th>N vs. L</th>
<th>N vs. S</th>
<th>L vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-wake data</td>
<td>413.5 (61.0)</td>
<td>443.3 (40.7)</td>
<td>442.6 (38.8)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No. completed</td>
<td>413.5 (61.0)</td>
<td>443.3 (40.7)</td>
<td>442.6 (38.8)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Correct responses</td>
<td>387.7 (72.8)</td>
<td>420.8 (49.0)</td>
<td>419.0 (43.5)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Correct responses (w</td>
<td>373.3 (81.3)</td>
<td>409.0 (55.5)</td>
<td>404.9 (47.2)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No. correct</td>
<td>373.3 (81.3)</td>
<td>409.0 (55.5)</td>
<td>404.9 (47.2)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>RT (msec)</td>
<td>437.3 (57.3)</td>
<td>422.6 (47.5)</td>
<td>418.8 (51.6)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean SD</td>
<td>115.3 (33.4)</td>
<td>110.3 (30.3)</td>
<td>111.5 (31.9)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Wrong responses (w</td>
<td>23.2 (17.9)</td>
<td>20.5 (11.9)</td>
<td>21.9 (12.2)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No. incorrect</td>
<td>23.2 (17.9)</td>
<td>20.5 (11.9)</td>
<td>21.9 (12.2)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>RT (msec)</td>
<td>398.4 (69.9)</td>
<td>388.1 (63.3)</td>
<td>382.1 (62.9)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean SD</td>
<td>135.2 (37.3)</td>
<td>121.7 (34.4)</td>
<td>119.9 (42.8)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Gaps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>17.0 (13.4)</td>
<td>13.8 (9.7)</td>
<td>13.8 (9.4)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Duration (msec)</td>
<td>2,222.5 (923.4)</td>
<td>2,061.5 (457.0)</td>
<td>2,058.9 (529.9)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Excluding immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and + 20-minute data</td>
<td>411.5 (62.1)</td>
<td>441.7 (42.3)</td>
<td>446.6 (42.9)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No. completed</td>
<td>411.5 (62.1)</td>
<td>441.7 (42.3)</td>
<td>446.6 (42.9)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>No. correct</td>
<td>385.3 (74.6)</td>
<td>418.9 (51.5)</td>
<td>422.0 (48.2)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: N = no-nap condition, L = long nap condition, S = multiple short naps condition.

* Values are for test day, means (SD), p-values presented are for two-tailed paired t tests, 7 df.
variables demonstrated time-of-day effects for the 143°, 218° and 253° test categories involving both number completed and number correct. Number completed and number correct time-of-day category data are provided in Table 7; Fig. 4 illustrates time-of-day effects for number correct.

Comparisons between the multiple short and long nap conditions for reaction time number completed and number correct at the 143° category were significant at the 0.05 alpha rejection level prior to Bonferroni correction. After correction, they were no longer significant. However, there remained a trend for number completed to be greater in the multiple short nap compared to the long nap condition.

Prior to Bonferroni adjustments, comparisons between the long nap and no-nap conditions for the 218° test category were significant at the 0.02 alpha level of rejection. Following adjustments, the differences approached significance for the long nap vs. no-nap conditions for number completed and remained significant for number correct.

Significant effects were found at the 253° category for both four-choice reaction time number completed and number correct. Reaction time number completed and number correct were greater in each of the long and multiple short napping conditions compared with the no-nap condition.

**DISCUSSION**

This study confirms the utility of napping in improving daytime functioning in narcolepsy-cataplexy, at least with respect to the four-choice reaction time test. Previous within-subjects studies (11,14,15) were unsuccessful in demonstrating a sustained recuperative value of naps on any measures, but these studies did...
not employ high-frequency testing protocols. This is the first study to do so, although this result was limited to the four-choice reaction time (RT). When four-choice RT tests immediately following sleep periods were excluded from analyses, a single long nap placed 180° out of phase with the nocturnal midsleep time significantly improved performance over a no-nap condition, despite the fact that sleep per 24 hours was held constant. Although the performance advantage of the long nap over no-nap condition was small for correct mean reaction time without gaps, number of wrong responses and number and duration of gaps, these small differences cumulated to result in an appreciable difference in mean number of correct responses made in the 5-minute test. This improvement was substantial in magnitude, an average of 11% for individual subjects.

Reaction time performance in the afternoon and evening hours was improved by the napping strategies, again especially by the single long nap. However, prior to the long nap there was a steady decline in performance from time of awakening, which, as would be expected, was similar to the pattern seen in the no-nap condition. Such morning impairment might be curtailed by the addition of a single short nap, perhaps even 15 minutes of sleep, at the time of the second short nap in this study, followed later by the long midday nap.

Performance on the other tasks, however, was not improved by naps. The grammatical transformation data appear to contradict the results of the four-choice reaction time test, as it showed on average a 16% decrement relative to the no-nap condition. Although there was a trend toward an increase in performance following the long nap, these results are difficult to resolve. The grammatical transformation test has demonstrated sensitivity in sustained operations studies with normal subjects involving sleep deprivation (42,43), but

### TABLE 6. Grammatical transformation summary data for six time categories

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long nap</th>
<th>Short naps</th>
<th>N vs. L</th>
<th>N vs. S</th>
<th>L vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number completed</td>
<td>73°</td>
<td>121.8 (9.0)</td>
<td>20.3 (9.8)</td>
<td>21.8 (6.9)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>108°</td>
<td>22.1 (8.1)</td>
<td>19.6 (6.8)</td>
<td>21.3 (9.3)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>143°</td>
<td>21.3 (6.7)</td>
<td>17.5 (6.6)</td>
<td>21.6 (7.6)</td>
<td>p &lt; 0.05</td>
<td>ns</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>218°</td>
<td>19.1 (6.4)</td>
<td>18.2 (7.7)</td>
<td>19.8 (6.2)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>253°</td>
<td>19.3 (3.9)</td>
<td>18.7 (7.6)</td>
<td>19.8 (5.8)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>288°</td>
<td>19.2 (6.4)</td>
<td>17.1 (5.0)</td>
<td>18.8 (5.9)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Number correct

|                  | 73°    | 19.7 (11.4) | 17.6 (11.9) | 18.9 (9.3) | ns      | ns      | ns      |
| 108°             | 19.8 (10.3) | 16.7 (8.7) | 18.1 (11.5) | ns      | ns      | ns      |
| 143°             | 18.9 (9.1) | 14.9 (8.8) | 18.7 (9.9) | p < 0.02| ns      | p < 0.02|
| 218°             | 17.2 (8.1) | 16.2 (9.4) | 17.4 (8.4) | ns      | ns      | ns      |
| 253°             | 17.3 (6.7) | 15.8 (9.6) | 17.3 (7.4) | ns      | ns      | ns      |
| 288°             | 17.4 (7.5) | 14.8 (7.6) | 16.1 (7.1) | ns      | ns      | ns      |

Abbreviations: N = no-nap condition, L = long nap condition, S = multiple short naps condition.

a Values are for means (SDs) of the time-of-day phase degree categories; Bonferroni adjusted p-values are presented for two-tailed paired t tests, 7 df.

### TABLE 7. Four-choice reaction time summary data for six time categories

<table>
<thead>
<tr>
<th></th>
<th>No-nap</th>
<th>Long nap</th>
<th>Short naps</th>
<th>N vs. L</th>
<th>N vs. S</th>
<th>L vs. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number completed</td>
<td>73°</td>
<td>462.9 (65.3)</td>
<td>459.6 (52.8)</td>
<td>428.9 (76.2)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>108°</td>
<td>434.2 (57.8)</td>
<td>434.2 (64.2)</td>
<td>433.7 (89.2)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>143°</td>
<td>412.7 (57.5)</td>
<td>413.8 (59.2)</td>
<td>450.6 (25.9)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.10</td>
</tr>
<tr>
<td>218°</td>
<td>392.3 (107.4)</td>
<td>486.3 (55.5)</td>
<td>447.8 (50.5)</td>
<td>p &lt; 0.10</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>253°</td>
<td>399.8 (56.5)</td>
<td>473.2 (73.6)</td>
<td>475.2 (29.0)</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.02</td>
<td>ns</td>
</tr>
<tr>
<td>288°</td>
<td>406.8 (113.4)</td>
<td>436.6 (75.5)</td>
<td>449.5 (61.5)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Number correct

|                  | 73°    | 442.7 (67.4) | 444.8 (53.6) | 405.4 (92.2) | ns      | ns      | ns      |
| 108°             | 414.6 (59.2) | 410.9 (71.8) | 412.4 (100.5) | ns      | ns      | ns      |
| 143°             | 385.3 (70.2) | 394.0 (71.3) | 431.2 (37.0) | ns      | ns      | ns      |
| 218°             | 363.9 (112.6) | 469.9 (60.3) | 426.4 (46.4) | p < 0.05| ns      | ns      |
| 253°             | 366.3 (69.8) | 446.3 (88.3) | 456.7 (34.1) | p < 0.05| p < 0.01| ns      |
| 288°             | 390.1 (113.1) | 411.5 (96.8) | 429.8 (61.9) | ns      | ns      | ns      |

Abbreviations: N = no-nap condition, L = long nap condition S = multiple short naps condition.

a Values are for means (SDs) of the time-of-day phase degree categories; Bonferroni adjusted p-values are presented for two-tailed paired t tests, 7 df.
although this test has undergone assessment (44), results of its use with narcoleptic or other clinically sleepy subjects have not been published in the entrained condition. However, there is some suggestion that logical reasoning can be maintained with very little sleep. For instance, Webb (45) found only a 3% decrement in performance on this test in subjects permitted to sleep for only 4 hours within a period of 60 hours of sleep deprivation. In addition, it has recently been shown in sustained operations studies that multiple napping strategies may actually have a detrimental effect on this kind of cognitive performance test (46).

The grammatical transformation test assesses logical reasoning performance, i.e. is a test requiring cognitive manipulations. The performance levels for narcoleptic subjects in this study were low and not substantially different from those seen in normals after a day of sleep deprivation (42,43). Although in this within-subjects protocol there were no normal controls, it may be that the chronic sleepiness in narcolepsy is sufficient to depress performance on this type of cognitive task and that naps only serve to further reduce performance by introducing a break in cognitive continuity, which may be useful for logical reasoning. However, this interpretation does not fit the data satisfactorily, because performance was actually somewhat better in the multiple short nap than in the long nap condition. Certainly the test results were different from those reported for memory tasks in untreated and treated narcoleptics which, due to apparent motivation effects, are not different from results for normals (47). The large between-subjects variability certainly reflects the fact that these subjects represented a diverse group with respect to their aptitudes on this test, a factor that may have contributed to the results. Another explanation might be that the longer nocturnal sleep period in the no-nap condition was responsible for the better performance on logical reasoning.

The importance of the sleep/wake schedule manipulations for the performance benefits seen under the

**FIG. 4.** Performance on serial four-choice reaction time for all three sleep/wake schedules. Number correct (mean, SE) are plotted as a function of sleep/wake schedule and time-of-day as in Fig. 3.
long nap condition is underscored by the finding that
the sleep characteristics themselves did not change sig-
nificantly. Sleep structure remained essentially con-
stant despite the different circadian manipulations made
in the three schedules. It is not surprising that REM
was somewhat increased in the short nap condition,
owing to the number of sleep onset REM periods, but
this increase was not significant. Although the amount
of SWS was not significantly different across condi-
tions, there was a rather high amount seen overall.
However, two of the subjects were quite young (19 and
22 years old) and a third subject was taking GHB, a
drug known to increase slow wave activity (22). The
amount of slow wave sleep was relatively higher in the
long nap condition, which is consistent with earlier
support for the recuperative value of NREM naps
(14,15).

The descending subtraction test did not show any
differences between the no-nap, single long nap and
multiple short nap conditions. However, this test is
known to be mainly sensitive to sleep inertia effects
and these are currently being analyzed.

Subjects had some degree of unscheduled sleep dur-
ding the day, particularly in the no-nap and short nap
conditions. Subjects were being continually tested and
supervised, so such sleep episodes were never long in
duration and consisted predominantly of stage 1B
drowsiness. The timing of such sleep in the no-nap
condition is of particular interest, as it is earlier (at
160°) than that (180°) of greatest likelihood of napping
in normal subjects (28). This is consistent with our
findings elsewhere in 24-hour ambulant home record-
ings (48) of a phase advance in the timing of day sleep
relative to that of nocturnal sleep in narcolepsy. Sim-
ilarly, Lavie (49) recently reported a phase advance in
the midafternoon peak of sleep facility in narcoleptic
subjects following an ultrashort sleep–wake paradigm.
In those studies and the present one, the afternoon nap
zone of narcoleptics is situated at least an hour before
that of normal subjects and may indicate an abnor-
mality of 2-day (circasemidian) sleep/wake regulation
in this disorder. These results also suggest that the
placement of a single long nap might yield even better
results were it scheduled somewhat earlier in the day.

Reaction time data have been shown to be sensitive
to sleep deprivation in normal subjects and have also
demonstrated significant improvement following naps
under a variety of experimental conditions. Although
the grammatical transformation and descending sub-
traction tests did not show improvement under either
of the napping conditions, this does not minimize the
results of the four-choice reaction time test but rather
emphasizes the multidimensional aspects of sleepiness
and its influence on performance. Along with this per-
formance data, we have collected subjective estimates
for a number of adjectives designed to tap into cog-
nitive vs. physiological sleepiness. These data will be
reported elsewhere.

In summary, the results of this study support the
potential utility of napping strategies for the manage-
ment of EDS in narcolepsy. The protocols tested were
not intended as actual treatment schedules but rather
as a means of assessing the utility of such pursuits and
to begin to investigate issues of nap frequency and
duration. These data suggest that sleep can be profit-
ably redistributed such that nocturnal sleep is reduced
and supplemented by scheduled diurnal sleep. The data
support previous reports that daytime sleep in patients
with narcolepsy-cataplexy is phase advanced relative
to that of normals and they indicate that even better
optimization of performance might be attained by the
addition of a morning short nap or a phase advance
of the single long nap.

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