Sleepiness and Daytime Sleep in Narcolepsy-Cataplexy:

Chronobiological, Napping and Performance Aspects

Janet Mullington

A thesis submitted to the School of Graduate Studies of the University of Ottawa
as partial fulfilment of the requirements for the degree of
Doctor of Philosophy.
December 10, 1993.

ISBN 0-315-95941-X

Canada

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

Acknowledgements

Firstly, I would like to thank my mother and stepfather, father and stepmother, and all my siblings and their families, for their undaunting support. They have regularly had to do without my social input, and they have always been patient and understanding. I would especially like to acknowledge my father for his belief in the value of higher education and for the financial contributions he has made so that I could attain this. I would also like to thank my partner, Hans Meier-Ewert, for the joy and strength he has prompted and for his patience and support through three years of my PhD while I was in Ottawa, and he in Munich.

The studies presented in Chapters 4 and 5 required extensive computer programming, patient supervision, data downloading and processing; there are many people who have contributed to the work contained herein. I would like to thank them all for helping to make it happen. It was a very labour intensive study and I am grateful and respectful for all they did and for the way they gave of their time and good will.

Martin Rivers did a brilliant job of programming the sleep-wake schedule and performance testing software which kept everything on schedule during the experimental period. Without this automated software it would not have been possible to run four subjects in parallel, and in fact, would have been exceedingly difficult to carry out such a protocol on a single subject. Dick Mowrey and Martin Rivers programmed the sleep architecture report program used. Adrian Kellett helped to re-design the 24h clock used in the sleep logs. Martin Rivers helped to print out, and Wayne Dunham to score the EEG; and both helped to keep subjects awake throughout the protocol, as well as lending technical support. There were others who also volunteered to help keep subjects awake during the protocol, applying electrodes and generally helping to keep things

running at the Packenham Bed and Breakfast. I would like to mention in particular: Janice Newman, Andrew Bissisar, Yone Simidzu, Otavio Gomez Lins, Sonia Nevsimalova, Jose de Campos, Thora Pugh, Wendy Buchanan and my supervisor, Roger Broughton. I would also like to thank Barbara Reynolds, Kathy Lutley and Michele Castonguay for helping with the recruitment and subject screening. Special thanks to Krys Pritchard, Sonia Vanek and my father and stepmother, Hugh and Gayle Mullington, for helping to type references, merge and assemble the thesis for submission. It was an enormous job done under impossible time constraints, but it happened, by virtue of their help. I thank those narcoleptic subjects who participated in the study, who donated so much effort and time for something that they hoped would find a way to combat the excessive daytime sleepiness they know too well, for their own benefit and for the benefit of others.

I have had the pleasure and privilege of being a regular member of the "Ottawa Sleep Club", a lively and informal group which meets monthly to discuss important matters pertaining to sleep research past, present and future. I would like to congratulate those who have carried the tradition through the years: Roger Broughton, Keith Busby, Ken Campbell, Joseph DeKoninck and Terry Pivic, as well as the many students, post-docs and visitors who have contributed to the vitality of the group. I have learned much from you all, and you have made Ottawa a great place to study sleep.

I would like to thank Dr. David Dinges, whose research I have respected for a long time and has actually been inspirational, for agreeing to be the external examiner on my thesis committee, and for doing such a wonderful job of it. I thank my internal examining committee: Doctors Terry Pivik, Terry Picton and Ken Campbell. They had a

complex and large thesis to review and critiqued it well. I thank them all for their enthusiasm and the interest they shared at the thesis defence.

Finally, I would like to thank Roger Broughton for being the best supervisor I could have found; his enthusiasm is infectious, his dedication, stamina and intellect, inspiring. He has taught me much about sleep research, but also about daring to think and express. I thank he and his wife, Wendy Buchanan, for their confidence and encouragement, for their time, and for their friendship.

Abstract

This dissertation deals with the chronobiology of sleep and sleepiness in narcolepsy-cataplexy. The text consists of a series of papers: three research papers, and a theoretical paper, with a technical paper appended. The first research paper presents an ambulatory EEG study in which subjects were free to go about their routine home activities, wearing the portable recorder for 24 hours. The timing and duration of sleep episodes were calculated relative to nocturnal midsleep time. Results demonstrated that the most frequent timing of naps was about 1-1.5 h in advance of that found for normal healthy subjects who show greatest sleep propensity 180 degrees out of phase with nocturnal midsleep time. The second paper is a theoretical review of circasemidean sleep-wake propensity and proposes a new modelling approach. The third and fourth papers represent companion papers from a 3-condition within-subjects experiment on the effects of scheduled naps on performance. Sleep schedules were based on habitual total sleep time amounts and experimental sleep schedules devised for each subject. A no-nap condition scheduled 100% of total sleep time at night, and nap conditions scheduled 25% of total sleep time in either a single long nap or 5 equidistantly spaced short naps. The first of these papers measures the efficacy of naps in terms of their effects on performance over the whole day and by time-of-day category divisions. Results indicated that for reaction time, performance in the single long nap condition was significantly improved over a no-nap control condition, attributable to post-nap improvements in performance. However, logical reasoning test results were actually better in the no-nap condition, but this may indicate that a longer nocturnal sleep period may be necessary

for optimal performance on this task. The timing of unscheduled sleep episodes was again seen to be in advance of the most frequent nap time for normal subjects. The second of these papers examines the related sleep inertia effects. Sleep inertia was found after the short naps as measured by the descending subtraction task, is evident following all but the first and is most prolonged following the third, short nap. Sleep inertia was also found for reaction time variables following short, but was absent following the long nap. Sleep inertia effects on reaction time were significantly greater on SWS arousals. A paper on the technical details of the sleep-wake scheduling and performance testing software is appended.

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CHAPTER 1

Introduction

Narcolepsy-cataplexy (hereafter referred to as narcolepsy) is a neurological, primarily genetically transmitted, disorder of unknown etiology closely associated with the HLA-DR2 haplotype (Honda, Juji, Matsuki et al., 1986). It affects between 0.03 and 0.16 percent of the population (ASDA, 1990), and is about as common as multiple sclerosis (Mitler, Nelson and Hajdukovic, 1987). Yoss and Daly (1957) introduced the term "tetrad" to designate the four cardinal symptoms characterizing narcolepsy-cataplexy: excessive daytime sleepiness (EDS), cataplexy, sleep paralysis and vivid hypnagogic hallucinations.

Excessive daytime sleepiness (EDS) refers to the overwhelming sleepiness that is the hallmark of the disorder, so irresistible that it usually culminates in "sleep attacks", usually 5-11 min in duration, often occurring after a failure to fight off overwhelming sleep pressure. Cataplexy is a sudden loss of muscle tone during wakefulness which occurs in response to emotional stimuli. Cataplectic attacks generally last for less than one minute (Guilleminault, 1976). The individual may lose full muscle control and drop suddenly to the ground, or alternatively, the loss of muscle tone may be partial and

involve only the head or legs. There is no accompanying loss of consciousness in these attacks, and extraocular muscles are not involved (Guilleminault, 1989).

Sleep paralysis refers to an inability to move which generally occurs when awakening from sleep (hypnopompically), but can also occur hypnagogically when entering sleep, and reflects a dissociation of the mechanisms which keep REM sleep and wakefulness distinct and separate states (Broughton, 1990). The fourth symptom in the tetrad is that of vivid hypnagogic hallucinations, that is intense hallucinatory experience upon falling asleep. These hallucinations may consist of as little as a simple display of colours, sometimes accompanied by sound, to full-blown dreamlike imagery. The symptoms of sleep paralysis and hypnagogic hallucinations can occur in the normal population. Cataplexy is the ciosest to a pathognomonic symptom, although there are reports of isolated cataplexy (Hartse, Zorick, Sickelsteel and Roth, 1988) in the literature.

Narcolepsy usually begins in adolescence or early adulthood, with sleep attacks being the most common first symptom to appear (Billiard, 1985). However, it has also been described in paediatric populations (Roth, 1980; Young, Zorik, Wittig, Roehrs, and Roth, 1988). The onset of narcolepsy is frequently preceded by an abrupt change in the sleep-wake cycle or by psychological stress (Broughton, Ghanem, Kishikawa, Sugita, Nevismalova, and Roth, 1981; Billiard, 1985).

In addition to the tetrad of symptoms, narcoleptics frequently suffer from vivid nightmares as well as heightened nocturnal body motility (Rechtschaffen, Wolpert, Dement, Mitchell, and Fisher, 1963) and the inability to consolidate and maintain nocturnal sleep (Rechtschaffen, Wolpert, Dement, Mitchell, and Fischer, 1963; Montplaisir, Billiard, Takahashi, Bell, Guilleminault, and Dement, 1978; Broughton and Mamelak, 1980). Other features related to vigilance problems are very brief 'lapses' (Granado, 1958) or microsleeps (Guilleminault and Dement, 1977) and amnestic automatisms (Granado, 1958; Guilleminault, Billiard, Montplaisir and Dement, 1975).

Psychological and social problems very often arise from the debilitating symptoms of narcolepsy, particularly the excessive and overwhelming sleepiness which interferes with the personal, occupational and recreational life of the individual at many levels. These include job security, interpersonal difficulties and family stress. In a study of the impact of the symptoms of narcolepsy on narcoleptics, over 75% reported being occupationally handicapped in terms of performance, promotion and earning capacity as well as job security. In addition, about half of narcoleptics complained of memory problems, mainly for recent events. The disabilities reported were most strongly attributed to the most difficult narcoleptic symptom to treat, that of the excessive and overwhelming daytime sleepiness (Broughton et al, 1981; 1983).

Diagnosis of narcolepsy-cataplexy

According to the International Classification of Sleep Disorders (ASDA, 1990), narcolepsy-cataplexy is diagnosed by a clinical history or polygraphically demonstrated excessive sleepiness (mean sleep latency of less than 5 min with 2 or more of 4 or 5 naps containing REM sleep with a latency less than 10 min, i.e., with a sleep onset REM period (SOREMP), plus a history of cataplexy. Associated features of sleep paralysis, hypnagogic hallucinations, and automatic behavior may also be present.

Nocturnal polysomnograms are often also performed to document the characteristic (but not always present) low sleep efficiency, fragmented nocturnal sleep, more even distribution of SWS across the night and REM sleep onset period. It is particularly useful to have a nocturnal polysomnogram performed to determine if there are co-existent sleep disorders. Approximately 20-25% of narcoleptics also have either periodic movements in sleep, or sleep apnea requiring separate treatment (Baker, Guilleminault, Nino-Murcia and Dement, 1986).

By way of introduction it should be noted that a number of comprehensive reviews of the topic of daytime sleepiness exist (e.g., Dement and Carskadon, 1982; Broughton, Valley, Aguirre, Roberts, Suwalski, and Dunham, 1986; Broughton, 1992; Pivik, 1991). The phenomenon of sleepiness/alertness is a rather elusive one, ranging across subjective, physiological, performance and other dimensions. Our knowledge is

heavily dependent upon available methodologies. The different research techniques used to study sleepiness will be noted including self-assessments, physiological measures, and performance. Experimental design approaches which provide theoretical underpinnings and methodological background for the doctoral project will be discussed including napping, sleep deprivation, time isolation and constant routine techniques. Sleepiness in narcolepsy will then be reviewed with respect to these same perspectives. Theoretical considerations related to research on sleep and sleepiness more broadly will then be reviewed as they pertain to modelling sleep-wake (sleepiness-alertness) regulation.

Techniques

1. Self-assessment

a. Sleep logs

Sleep logs are extremely simple and effective for use in longitudinal studies of normal routine sleep-wake behavior, when properly designed and when regular contact is maintained with subjects throughout the record keeping period. As few as 5 days of data can reliably predict the average total sleep time over a 42 day sleep log collection period (Mullington, Speilman, Wells, and Hoffmann, 1988). Based on a 35-day sleep log study, Dinges (1989) has reported that the period of highest napping frequency (based on midnap times) is 180 degrees out of phase with the nocturnal midsleep time. Of

additional theoretical importance was the finding that this phase relationship persisted even on the weekends despite the fact that the nocturnal midsleep time was delayed by an average of 47 min, and duration of nocturnal sleep was 44 min longer.

b. Subjective sleepiness: SSS; VAS

Self-assessment techniques have been developed and used extensively to document subjective changes in vigilance. The most widely used measure is the Stanford Sleepiness Scale (SSS; Hoddes, Zarcone, Smythe, Phillips and Dement, 1973) appreciated for its sensitivity as well as ease of administration, particularly under multiple testing protocols. While Hoddes et al. (1973) found the test of limited reliability in predicting performance following a night without sleep, in a more controlled study, Glenville, Broughton, Wing and Wilkinson (1978) found that SSS ratings were significantly correlated with performance deficits after one night of sleep deprivation.

The visual analog scale of sleepiness (VAS; Folstein and Luria, 1973) is another readily available tool for measuring subjective fluctuations in vigilance and/or mood variables. The VAS consists of a single line along which a subject is asked to assess his/her current subjective state with the polar ends of the continuum representing opposite extremes defined relative to the subject's own range of experience. This method is useful in repeated testing protocols because it is easily administered and demonstrates circadian fluctuations in subjective level of alertness (Monk, Leng,

Folkard, and Weitzman 1983) and shift work (Folkard, Monk, Krauth and Rutenfranz, 1978).

c. Behavioral self-rating - Epworth

Johns (1991) has introduced a self-applied behavioral assessment scale, with which subjects rate their likelihood of falling asleep under various conditions, such as watching TV, sitting and reading, or while having a conversation. In this scale there are 8 such scenarios with the likelihood of each assessed on a 4 point scale. This new tool successfully differentiated narcoleptics from matched controls and proved reliable for the detection of excessive somnolence (Johns 1992), as defined by the multiple sleep latency test to be described below.

2. Physiological

a. Sleep latency: MSLT, MWT, ultrashort schedules

The multiple sleep latency test (MSLT) was devised by Carskadon and Dement, (1977), further developed by Richardson et al., (1978) and had guidelines for its use later published in Sleep (Carskadon and Dement, 1982; Carskadon, Dement, Mitler, Roth, Westbrook and Keenan, 1986). In this test subjects are instructed to fall asleep as quickly as possible in each of 5 daytime naps. Sleep onset is defined as 3 or more

consecutive epochs of stage 1 or a deeper sleep stage. In an altered version of the test, the maintenance of wakefulness test (MWT), subjects are recorded in a dark room and asked to lie down and try to resist sleep (Mitler, Gujavarty and Browman, 1982). Both of these tests have been used in repeated testing protocols throughout the day to assess sleepiness. The MSLT tests "sleep ability" whereas the MWT tests "ability to resist sleep". Normal subjects have been studied for daytime fluctuations in alertness using these protocols, and daily peaks in sleepiness have been observed for both younger and older adults in the mid-afternoon period between about 1500 and 1600h (Richardson et al., 1978; 1982).

In addition to these protocols, other approaches involving fragmenting the normal circadian sleep/wake pattern have been used to investigate the temporal fluctuations of sleep propensity. Carskadon and Dement (1975) initially developed an ultrashort paradigm which was used to investigate the circadian placement of sleep stages under entrained conditions. Using a 90 min "day" protocol (60 min wakefulness and 30 min sleep), these researchers found SOREMPs in 70% of scheduled sleep periods, occurring primarily between 0730 and 1400h, while SWS (slow-wave sleep) was found to be more evenly distributed around the 24h day.

Lavie and colleagues (Lavie and Scherson, 1981, Lavie and Zomer, 1984; Lavie, 1986; 1987) have further developed this polyphasic ultrashort sleep scheduling paradigm to investigate the circadian distribution of sleep propensity as defined by sleep onset, and

also to investigate in more detail, the pressure for specific sleep stages. The "7-13 protocol" developed by this group requires subjects to attempt to sleep for 7 and remain awake for 13 min. In another version of the protocol, subjects attempt to resist sleep for 7 min while in bed with the lights out. Using these techniques, they have found that there is an afternoon facilitated entry point into sleep at 1500-1700h in addition to the major nocturnal sleep initiating period (at about 23-2400h). In addition, there is a period where sleep tendency is markedly reduced (1900-2100h). There are large individual differences with respect to these tendencies but the pattern within subjects is remarkably regular. There appears to be a "fingerprint" of sleep tendency (Lavie, 1991), which remains consistent whether subjects are attempting or resisting sleep.

b. Prolonged recordings

Long-duration in-lab recordings a well as 24 hour ambulant recording techniques have been essential tools in the study of sleep and sleepiness ultradian and circadian patterns. Long-duration recordings employing traditional polysomnography have been used by a number of laboratories. Of particular importance for the issue of sleepiness and sleep/wake regulation is the appearance in extended sleep of a midafternoon pulse of SWS (Gagnon and DeKoninck, 1984). This second SWS pulse can be shifted by phase delaying the nocturnal sleep period (Gagnon, DeKoninck and Broughton, 1985) and appears to be related to an increase in core body temperature (DeKoninck, Christ, Carrier, Herbert and Fortier, 1990).

Ambulatory monitoring has proven useful for home recording and field studies. One of the problems facing researchers is the environmental constraints of the sleep laboratory. The ambulant recording device enables EEG research to be conducted outside of the laboratory in both normal and clinical populations (Healey, Maru and Broughton, 1975). It has been shown repeatedly that sleep parameters so recorded are reliable and not different from recordings made after adaptation in the laboratory (Sewitch and Kupfer, 1985a,1985b; Broughton, 1989a). Ambulant EEG recording devices have also been used in a field study of scheduled polyphasic sleep and performance, allowing the assessment of performance in relation to timing and duration of naps (Stampi, Broughton, Mullington, Rivers and Campos, 1990b). Ambulant EEG recorders are the recording technique of choice for fully ambulant field studies of polypahsic sleep-wake patterns. The relative immobility imposed upon subjects in non-ambulatory techniques has a profound effect on increasing sleepiness. It is important to avoid this confound, particularly when sleep propensity is a central component of the investigation.

c. Evoked response potentials

Evoked potentials (EPs) have been useful in the investigation of sleep onset mechanisms. Fruhstorfer and Bergstrom (1969) found that N1 and P2 were attenuated (to approximately 50%) when vigilance decreased as evidenced by increased alpha, and

noted that in actual sleep, N1(a and b) were at their smallest levels and P2 was absent. In a study which examined reaction time in conjunction with sleep onset and EPs, Noldy, McGarry and Campbell (1988) found reaction time and corresponding slow auditory evoked potential changes. They found, as Fruhstorfer and Bergstrom did, that N1 decreased, but in addition that N2 increased; P2, rather than decreasing, increased for some subjects with longer reaction times as polygraphically defined sleep became prevalent. Ogilvie and colleagues (Ogilvie et al., 1991; Segalowitz et al., 1990) have also found that, as reaction time increases, N1 amplitude decreased and N2 and P2 increased. Campbell, Charbonneau and Beaudoin (1989) have shown, using the P300 cognitive event related paradigm, that sleep deprivation is associated with a reduction of component P300 amplitude with no change in latency.

d. Quantified EEG

Electroencephalographic signs of drowsiness have been well known and described for many years (Loomis, Harvey and Hobart, 1938; Oswald, 1962; Gastaut and Broughton, 1965), and recent technological advances have made it feasible to record simultaneously from many scalp locations, digitize, quantify and map the EEG output. Quantified EEG measures have been shown to reflect decreased levels of vigilance. Techniques which employ spectral analysis (Matovsek and Petersen, 1983; Ogilvie, Simons, Koderian, MacDonald, Rustenberg, 1991) and period analysis (O'Hanlon and Beatty, 1977) have been of particular interest, and a recent "adaptive segmentation"

technique developed by Creutzfeldt, Bodenstein, and Barlow (1985) has shown utility in detecting points of change in alertness levels (Varri, Hirvonen, Hasan, Loula, and Häkkinen; in press).

e. Pupillometric assessment

A large and stable pupil diameter has been associated with alertness, and increasing pupillary constriction or a constricted and unstable pupil occurs with sleepiness (Lowenstein and Lowenfeld 1958). These observations have received support from researchers who found that sleep deprivation increases pupillary variability (Hertz, Spielman Hackerem, and Pressman, 1988). In a protocol which induces sleepiness through use of the ultrashort paradigm described earlier, Lavie (1979) found increased pupillary variability associated with sleepiness in normal subjects.

3. Performance

a. Auditory vigilance

Wilkinson's auditory vigilance task (1970) involves efforts to detect, over a one hour period, 40 slightly shorter signal tones randomly occurring in a series of tones which are presented every 2 sec. All stimuli are presented with a significant background noise

level. It is a long and boring task, very sensitive to sleepiness, and constitutes the "gold standard" against which other measures of behavioral sleepiness are often compared (Broughton, in press). The pioneering work of Wilkinson and colleagues has shown it to be sensitive in normals to total sleep deprivation (Wilkinson, 1970; Glenville et al, 1978), partial sleep deprivation (Hamilton, Wilkinson and Edwards, 1972) and a number of further sleep-wake manipulations including sleepiness.

b. Reaction time

There are two types of serial reaction time tests which are particularly well-suited for research in the field and which have been used extensively to investigate sleepiness in conjunction with many different types of protocols. These are Wilkinson's serial reaction time (Glenville, et al., 1978) and 4-choice reaction time (Wilkinson and Houghton, 1975) tests. These tests have been shown to be sensitive to performance decrements due to sleep loss and workload during sustained operations protocols (Englund et al., 1985); following a night of total sleep deprivation (Glenville et al., 1978), and during partial sleep deprivation (Herscovitch and Broughton, 1981a) and have also been shown to be sensitive to performance improvement following recovery sleep of restricted durations (Rosa et al., 1983). Performance measures, especially those most sensitive to fluctuations in alertness and sleepiness have been found to show decrements in the midafternoon, "post-lunch-dip" period, but this decrement is not directly attributable to meals, as shown by Blake, (1967).

When performance variability increases in magnitude, as occurs under conditions of sleep deprivation (reviewed in Dinges and Kribbs, 1991), it is due in large part to increased lapsing or periods of failure to respond. These lapses have been operationalized as "gaps" defined as reaction times over 1000 msec. Data from Williams et al., (1962) were in support of the lapse hypothesis. These authors found further, that EEG changes preceded lapses by 2-3 seconds.

As Dinges and Kribbs (1991) point out, lapsing is due to the inability to sustain attention under conditions of sleep deprivation, and may also involve microsleeps, i.e., brief transitions into electrophysiologically defined sleep. In addition to lapsing, Dinges and colleagues have investigated slowing in the optimal performance ranges, i.e., the fastest 10% of responses (Dinges et al., 1987; Dinges and Powell, 1989). Their results have emphasized that the impairment seen in normal sleep deprived subjects is not simply due to lapsing but also consists of cognitive slowing of best responses, as initially noted by Oswald (1962), Morrell (1966) and others.

c. Other measures of sleepiness

While reaction time tests measure sensory-motor output and in general have shown a relationship parallel to circadian body temperature (Kleitman, 1963), other measures have been used to investigate more complex cognitive processing. These include Baddeley's (1968) logical reasoning test, the memory and search test (Folkard,

Monk, Knauth, and Rutenfranz, 1976) and the Wisconsin card sort test (Milner, 1963). In general, while performance on memory load tasks is better in the morning (Folkard et al., 1976), reaction time and other speed-based testing (i.e., visual search) tend to increase throughout the day in parallel with body temperature (Blake 1971). Studies using repeated testing paradigms consistently demonstrate that the nature of the cognitive demands inherent in the test will influence the time of day pattern seen in the results.

Experimental Approaches

1. Nap schedules

Research has demonstrated the efficacy of napping in alleviating the excessive sleepiness and resulting performance decrements which follow extended work hours due to emergency operations, endurance competitions, jet lag and shift work (reviewed in Dinges and Broughton, 1989). The best circadian time for a nap appears to be the afternoon or evening, rather than the morning (Naitoh, 1981; Gilberg, 1984). Naitoh found that a 2h nap following 45h of wakefulness, taken near the lowest circadian point of body temperature, was less restorative with respect to cognitive functioning than a 2h nap taken in the afternoon (1200-1400h) somewhat in advance of the circadian peak in core body temperature. In another sleep deprivation protocol, Dinges (1985) did not replicate this time of day difference, but did find that a 2 h nap in the afternoon trough

produced greater sleep inertia (performance decrement upon waking), particularly after more than 36h of continuous wakefulness had preceded the nap. In addition, this sleep inertia was significantly correlated with SWS arousals.

Minors and Waterhouse (1980) have shown that 4 hours of "anchor" or shortened nocturnal sleep, can maintain levels of performance for a single day. Studies from our laboratories (Stampi, Broughton, Mullington and Campos, 1990a 1990b) demonstrated the utility after 4 hours of nocturnal anchor sleep, of replacement naps of 20, 50 and 80 min and found that 20 and 80 min naps improved performance with little associated sleep inertia, and were seldom associated with SWS awakenings, whereas 50 min naps frequently led to sleep inertia and arousals were often from SWS.

Sleep inertia is clearly more profound following arousals from SWS as compared with REM or stage 2 arousals. Efforts to investigate the preferential benefits of one stage of sleep over another are, however, very difficult due to circadian influences on sleep and the difficulties associated with depriving a particular stage of sleep. Johnson, Naitoh, Moses and Lubin, 1974, and Lubin, Moses, Johnson and Naitoh (1974) found that selective deprivation or recovery sleep consisting of either REM or stage 4 sleep, did not lead to differential effects in terms of performance.

2. Unmasking: temporal isolation and constant routine

Individuals have been studied under isolated conditions, free of time cues or "Zeitgebers" (as they have been termed after the German word meaning "time giver"), for extended periods of time in order to uncover what were thought to be endogenous rhythms of activity, rest and core body temperature (Wever, 1979). When individuals remain in an environment free of time cues for extended periods of time, the sleep-wake rhythm was found to separate from the rhythm of core body temperature and to cycle at a longer periodicity and longer subjective day. This phenomena was termed "internal desynchronization". Desynchronization also provided the opportunity to investigate other biological rhythms to see whether they either followed the sleep-wake or the temperature rhythm. Virtually all other circadian rhythms, including cortisol (Weitzman, Nogeire, Perlow, Fukushima, Sassin, McGreggor, Gallagher, Hellman, 1974), melatonin (Nakagawa, Sack and Lewey, 1992), and urinary catacholamines (Mills and Stanbury, 1954) follow quite closely the rhythm of core body temperature. Interestingly, only the behavioral variables of self-selected eating (Pollak and Green, 1990) and sleeping times appear to be exceptions to this pattern.

Temporal isolation studies also demonstrated a regular relationship between the onset of sleep and its duration. When subjects are instructed to initiate nocturnal sleep periods whenever they wish but to avoid napping, self selected sleep onset time demonstrates a consistent phase relationship with core body temperature. When

temperature is high and falling, long sleeps ensue; when temperature is low and rising, relatively shorter sleeps result (Czeisler et al., 1980). If napping is permitted, sleep remains in synchrony with core body temperature with naps occurring in advance of, but near the peak of, body temperature and with the long sleeps occurring on the descending phase near the temperature nadir (Zulley and Campbell, 1985).

More recently, constant routine techniques have been widely used as they provide more pragmatic methods for uncovering the endogenous circadian rhythms. In these protocols, subjects are generally in bedrested conditions, receiving equal aliquots of calorie-balanced nutritional intake, usually on an hourly basis (Mills, Minors and Waterhouse 1978).

3. Sleep deprivation

Sleep deprivation techniques have been employed for a number of reasons. One is in order to assess sleepiness with respect to the quality of recovery sleep. Quantitative EEG studies have demonstrated that slow wave activity increases in response to sleep deprivation (Moses et. al. 1975; Webb and Agnew 1971; Williams et al., 1964). Borbely et al., (1981) examined the effects of approximately 40h of sleep deprivation on quantified EEG of recovery sleep and found that the baseline progressive decline in power density across the night for all frequency ranges was increased relative to baseline nocturnal sleep.

In addition to electrophysiological findings, sleep deprivation has been used as a method for examining circadian variations in performance as they interact with duration of prior wakefulness. Froberg (1977) described the circadian time course of alertness and performance across 72 h of continuous wakefulness and found a tight coupling with core body temperature. There was a progressive decline in performance across the sleep deprivation period, but in addition there was renewed alertness and performance during the "day".

Work load, in addition to length of prior sleep deprivation, must be considered when assessing the effects of sleep loss (Babkoff, Thorne, Sing Genser, Taube and Hegge, 1985). The latter authors found that the time spent to complete a task increased in parallel with duration of prior wakefulness. In addition, the data of these authors, when plotted by hours and days into the experiment, demonstrate a clear circadian modulation in addition to a sleep deprivation effect. This linear decline in performance was in agreement with the pattern seen in the Froberg (1977) data and is also seen in the continuous wakefulness (60h) data of Horne, Anderson, and Wilkinson (1983). The results of the latter study again show a continuous linear decline in performance, modulated by a circadian component.

In addition to sleep deprivation and partial sleep deprivation, the fragmentation of sleep is a critical factor affecting the maintenance of performance. Bonnet (1986) found that performance after a night of sleep disruption after 1 min (of stage 2 or

greater stage) resulted in performance levels as low as after a full night of sleep deprivation.

Sleepiness in Narcolepsy

The experimental doctoral research involves studies in narcoleptics of aspects of the chronobiology of sleep and sleepiness, the performance levels of patients with the condition and the positive and negative effects of napping on these levels. Our current knowledge of sleepiness in this population will now be reviewed.

1. Self-assessment

Daytime sleepiness in narcolepsy has been investigated using subjective self-assessment tools such as the Stanford Sleepiness Scale, the visual analog scale and the Epworth Sleepiness Scale, which were discussed previously with respect to their use with normal populations. The Stanford Sleepiness Scale has not reliably demonstrated its usefulness as a predictive tool of performance decrement in narcoleptic subjects (Valley and Broughton, 1981) or induced in other patients with EDS. This may be due to the chronicity of sleepiness experienced in this condition, as the ability of the SSS to predict impaired performance decreases among normal control subjects after a few nights of partial sleep deprivation (Friedmann et al., 1977; Herscovitch and Broughton, 1981a; 1981b). The visual analog scale has also demonstrated limited use in

pathologically sleepy subjects (Broughton, in press). Epworth's Sleepiness Scale has been successful in differentiating between patients with EDS and normal controls (Johns 1992), demonstrating its promise as a diagnostic tool. However, the potential utility of this scale as a predictive measure of performance remains to be explored.

2. Physiological

a. Sleep latency: MSLT; MWT; and ultrashort schedules

The MSLT has been incorporated into several experimental designs for investigating narcolepsy. The first was by Richardson, Carskadon, Flagg, Van Den Hoed, Dement and Mitler (1978). This study documented overall short sleep latencies plus a further shortened latency in narcoleptic subjects and controls in the midafternoon, between 1330 and 1400h. The MSLT test was also used in a test of the differences between naps of 15 and 30 min duration in affecting sleep latency of a subsequent nap (Roehrs et al., 1986). Although there was an increase in sleep onset latency on the 5th (15 min maximum duration) nap of the day relative to naps 1-4, there were no within-subject benefits associated with a 30 relative to a 15 min nap. However, there are problems associated with using the MSLT approach with narcoleptic subjects if the intent of the research is to assess the severity of sleepiness. In a study such as that of Roehrs et al., the results might have been different if the MWT had been used to assess the ability to resist sleep instead.

In a recent study employing the MWT, Rogers and Aldrich (in press) found that the ability to resist sleep was improved following a one month nap therapy program. Lavie (1991) used the ultrashort resisting sleep paradigm and found that narcoleptics had a peak of sleepiness between 1300-1500h and a period of relatively reduced sleepiness at 1800h.

b. Continuous recording

Continuous recording was used as early as 1968 (Passouant et al., 1969) to investigate 24h patterns of sleep and wakefulness in narcoleptic patients. Problems arise from such bed-rest recordings in narcoleptics, however, due to the augmentation of sleepiness and sleep (Volk et al., 1990). The availability of ambulant EEG recorders has made it possible to monitor narcoleptics in their home environment, and this has led to the confirmation that narcoleptics do not sleep for periods significantly longer than matched controls with respect to 24h totals (Broughton et al., 1988). Continuous recordings in temporal isolation studies have also demonstrated that narcoleptics do not sleep more per 24h than do normals, and that these patients appear to have normal circadian temperature rhythms (Schulz et al., 1983; Kamei, 1978).

c. Evoked response potentials

An evoked potential approach to the study of excessive daytime sleepiness was described by Broughton (1982). Simple auditory evoked potential paradigms used have included responses of narcoleptics to click stimuli (Pressman, Spielman, Pollack and Weitzman, 1982) and tone stimuli (Broughton, Low, Valley, daCosta and Liddiard, 1982). Broughton et al. (1982) found that N0 was delayed, and N1, P2 and N2 were reduced in amplitude. The responses had been selected from periods during sustained wakefulness on the Wilkinson auditory vigilance task when narcoleptics performed as well as normals, indicating the sensitivity of the EP approach.

Complex ("cognitive") evoked potentials including the P300 "odd-ball" (Picton et al., 1978) and CNV paradigms (Walter et al., 1964) have been used in a series of studies by Broughton and colleagues (Aguirre and Broughton, 1984; 1987; Broughton and Aguirre, 1985; 1987). Using the P300 paradigm, narcoleptics demonstrated lower P3 and higher P1 amplitudes, and time of day differences were found using the CNV paradigm. In later analyses, P300 amplitude was found to be almost as sensitive as MSLT in diagnosing sleepiness levels in narcoleptics versus controls (Broughton et al., 1988). Moreover, the approach along with MSLT and Stanford Sleepiness Scales gave evidence for greater sleepiness and qualitative differences between so-called "REM sleepiness" (wakefulness prior to REM-containing MSLT naps) and "NREM sleepiness" (prior to NREM-only naps) (Broughton and Aguirre, 1987).

d. Quantified EEG

Based in part on their findings on the time course of the decline in SWS across the night following sleep deprivation using standard stage scoring techniques, Tafti, Villemin, Carlander, Besset and Billiard, (1992) hypothesized that there might be an altered homeostatic process in narcolepsy. They subsequently analyzed their electrophysiological data from sleep deprived narcoleptics using spectral analysis and claimed that non-REM sleep homeostasis was essentially normal (Tafti, Rondouin, Besset and Billiard, 1992). However, these authors also found that, relative to contols, power density in the delta and sigma frequencies was enhanced in the narcoleptic subjects in both baseline and sleep deprived conditions. The effects of sleep deprivation were, however, more pronounced than in normals; and the narcoleptics demonstrated a more even distribution of SWS across the night as initially described by Broughton and Mamelak (1980). Given their findings, one could alternatively argue that the processes involved in the restitutive function of sleep, (i.e., the homeostatic process) are in fact impaired, as evidenced by the fact that delta power did not get as low by the end of the night as it did for the control subjects, even when pressured by sleep deprivation.

e. Pupillometric assessment

Pupillometry has long been thought to be a technique providing a sensitive measure of sleepiness, and has been used as a diagnostic tool in some clinical sleep

disorders centres, particularly in the United States. While Pressman, Spielman, Korczyn, Rubenstein, Weitzman and Pollak (1984) found it to be a sensitive measure, few controlled studies have been carried out to test its efficacy as a diagnostic tool for use in discriminating sleepy patients from control subjects. In a recent study by Newman and Broughton, (1991) this test failed to discriminate between untreated narcoleptic and normal subjects on virtually all dependent measures, the only exception being for spontaneous oscillations during dark adaptation which were more frequent in narcoleptics.

3. Performance

a. Auditory vigilance

Valley and Broughton (1983) found that subjects were unable to maintain continuous EEG patterns of wakefulness throughout the Wilkinson auditory vigilance task. These subjects spent considerable time in stages of drowsiness and light sleep, and were in fact only fully awake for less than half the time. In addition, narcoleptics performed worse on this test when compared with normals and their performance deteriorated rapidly when the shorter "signal" stimuli (slightly shorter tones) occurred in sustained wakefulness (>10 sec), fragmented wakefulness, stage 1A and stage 1B. No detections occurred in stage 2 (Valley and Broughton, 1981; 1983).

b. Reaction time

Valley and Broughton (1981) applied the Wilkinson and Houghton (1975) 4-choice reaction time and found that untreated narcoleptics showed longer RTs, had more "gaps" and had greater RT variability than normals. Billiard (1976) and Godbout and Montplaisir (1986) investigated the recuperative effects of naps in terms of performance indices. Billiard examined the performance of non-medicated narcoleptics on a protocol of one adaptation night and two consecutive experimental days. In one of two experimental groups of narcoleptics, subjects were allowed to sleep whenever they chose to on both experimental days, but on the first were awakened after 1 min, and on the second were awakened after 10 min. The second group of narcoleptic subjects were not allowed to sleep on the first day, but on the second day were allowed 15 min naps at 0900, 1145, 1615, and 1830h. On a serial alternating task, performance was improved following REM and combined REM and NREM naps relative to pre-nap levels. However, because tests were performed immediately upon waking, the benefits of naps may have been limited by confounding sleep inertia effects. When comparing days with 15 min naps and days without sleep, paired t-tests were not significant, although there was a tendency for better performance when subjects slept between tests. In terms of their subjective value, longer naps (average 67 min) were found to be more satisfying.

Godbout and Montlaisir (1986) compared the performance on the four-choice reaction time test in 10 non-medicated narcoleptics and controls on days with naps

compared to days without naps. Ten min of reaction time performance testing administered immediately before and after sleep periods was compared to performance at the same times on the day without naps. These researchers found that on days without naps, narcoleptics were significantly impaired compared to control subjects without naps, but when performance on days with and without naps was compared within subjects for the narcoleptics, differences were not significant. However, once again, sleep inertia effects constitute a possible confound, and time of day effects were not assessed.

4. Other Measures

The paced auditory serial addition task (PASAT) and the digit span did not find narcoleptics to be significantly impaired compared to controls (Valley and Broughton, 1981) apparently because of the challenging nature of these short tasks during which both populations showed no drowsiness. In a temporal isolation study comparing logical reasoning (Baddeley, 1968) performance of narcoleptics in relation to that of controls, Pollak, Wagner, Moline, and Monk, (1992) found that, while means were lower for narcoleptic subjects, the differences were not significant.

5. Treatment of narcolepsy

Treatment of the auxiliary REM sleep based features of narcolepsy (the cataplexy, sleep paralysis and nightmares) is well accomplished through use of tricyclic medications such as imipramine in very small doses (200mg per day or less) taken before bed (Guilleminault, 1989). The control of excessive daytime sleepiness is more difficult and is attempted through use of stimulant medications such as methylphenidate, pemoline or amphetamines. Methylphenidate is a short acting stimulant taken between 2-3 times per day in doses of 10-20mg and pemoline is a longer acting stimulant requiring a single daily administration of 37.5 or 75.0mg. Stimulant medications are not always well tolerated and may have unpleasant side effects such as palpitations and heightened anxiety. In addition, they do not always adequately control the sleepiness, tolerance may develop and sleep attacks may persist despite their use (Parkes and Fenton, 1973; Soldatos et al., 1983; Scharf et al., 1988).

Gammahydroxybuterate (GHB) was originally used with the goal of consolidating nocturnal sleep in the hope that this would have a beneficial effect on daytime functioning (Broughton and Mamelak, 1980). While it was found to reduce cataplexy and sleep paralysis, GHB has had limited success in alleviating daytime sleepiness in experimental trials but it was associated with an increase in periodic leg movements during sleep (Bedard, Montplaisir, Godbout and Lapierre, 1989). Other more experimental drug approaches include the use of L-Dopa (Boivin, Montplaisir and

Poirier, 1989; Boivin and Montplaisir, 1991), L-tyrosine (Mouret, Lemoine, Sanchez, Robelin, Taillard and Canini, 1988), and codeine (Fry, Pressman, DePhillipo and Forst-Paulus, 1986).

There is a need for non-drug treatments for those patients who find that their sleepiness is inefficiently controlled by stimulant medications and also because they are desirable for use during drug holidays. Hajek, Meier-Ewert, Wirz-Justice, Tobler, Arendt, Dick and Fink (1989) attempted a bright light treatment to inhibit melatonin production during the day, since melatonin induces sleepiness in normal subjects. However, this approach was unsuccessful.

Another approach to the management of EDS is the judicious use of naps. While they are often recommended, there are few studies assessing their efficacy. In 1989, a letter commenting on the paucity of research on napping in the management of daytime sleepiness of narcolepsy appeared in Sleep:

> "...the potential benefits of adjunctive behavioral interventions have not received adequate attention. For example, anecdotal reports suggest that daytime naps may be helpful in treating EDS; yet, programmatic controlled studies on the effectiveness of naps do not exist." (Burton, 1989).

Theoretical Considerations

1. Circadian Models

a. The two-process model.

The studies demonstrating that power density increases with duration of prior wakefulness were important in prompting Borbely (1982) to elaborate an homeostatic model of sleep propensity in which sleepiness is a function of prior wakefulness. This was a single oscillator, two-process model. Process "S" represented the homeostatic factor, or the buildup of sleepiness through hours of wakefulness, and "C" the second process, represented the circadian base upon which the homeostatic process fluctuated. The model was elaborated with more emphasis on circadian factors by Daan et al., (1984), who incorporated lower and upper setpoint thresholds within which sleep propensity could fluctuate. The primary impetus for this later expansion came from isolation studies which demonstrated that sleep episodes initiated when temperature is high and falling are of longer duration than those initiated when temperature is low and rising (Zulley, 1979; Czeisler, 1980). Under these conditions the setpoint was assumed to be raised through volitional powers. Once sleep was initiated, it would continue until the sleepiness indicated by process S intersected with circadian offset thresholds. The changes to the model could also account for the increased sleep time seen when subjects

were studied under bedrest conditions. The lowering of an upper threshold would induce sleep at an earlier time.

b. The dual-oscillator model.

The uniquely human phenomenon of internal desynchronization led Wever (1975) to propose the existence of two circadian oscillators. Following along these lines, Kronauer, Czeisler, Pilato, Moore-Ede and Weitzman, (1982) developed a 2 oscillator van der Pol model of sleep-wake regulation in which the "deep" oscillator, the strongest oscillator which they referred to as "X", governed core body temperature, whereas sleep was governed by a second labile oscillator, "Y".

2. Circasemidian Models

a. Harmonics, integer ratios.

Broughton, (1975) first proposed the existence of a circa-12 hr endogenous rhythm in sleep/wake regulation and postulated that it might be either a harmonic of a fundamental 24 hr circadian rhythm or perhaps due to a 12 hr SWS rhythm. The concept of evolutionary selection of multiple oscillators showing a fixed integer ratio (24, 12, 6, 4, 3, 1.5) was later developed (Broughton, 1985b), and the possibility that the

circa-12 hr rhythm of sleep propensity is a passive phenomena interdigitated between a more fundamental 2/day rhythm in intensity of arousal was subsequently introduced (Broughton et al., 1990).

b. Modified two-process model.

In 1989, Borbely and colleagues (Borbely, Achermann, Trachsel and Tobler, 1989) modified their 2-process model further to attempt to include the afternoon sleep propensity and sleep inertia. Based on empirical sleep onset latency data they constructed a "propensity of sleep initiation" curve, and added a sleepiness function at the beginning of the day to represent morning sleep inertia. While these attempts acknowledge that the model does not adequately account for the existing data on sleep inertia and sleep propensity, it loses some of its original elegance by the addition of features which do not follow from a theoretically coherent base.

c. Modified dual-oscillator model.

The original 2-oscillator model was modified by Kronauer (1987) in an effort to account for the afternoon nap facilitation period. The labile "Y" oscillator controlling sleep was split into 2 sub-components "Y1" and "Y2". This model was then able to account for napping but wasn't able to demonstrate the skipping of naps. In addition,

the mathematical simulations which resulted from this model were too regular to be accurate representations of naps.

d. The three-process model.

Folkard and Akerstedt (1992) modeled sleep and alertness in a format similar to the Daan et al., (1984) two-process model, but they added a third component which represents the process of awakening. This "process W" is a short-lived deviation from process S, measured upon waking from sleep at different times, which reflects the rising alertness levels and was modeled after empirical data. The model accounts well for morning sleep inertia but does not account for the midday period of heightened sleep propensity.

3. Ultradian

a. BRAC

Kleitman (1963) first proposed that there was a fundamental physiological periodicity of brain activation which continued throughout wakefulness and into sleep to manifest as REM sleep in a more primitive form. In support of this notion were a

number of findings which demonstrated 90 min periodicities, from EEG to vigilance measures (comprehensively reviewed in Schulz and Lavie, 1985).

b. Gates

Lavie and his colleagues have used ultrashort sleep-wake scheduling techniques described earlier to further investigate ultradian rhythmicities in sleep propensity. Lavie (1985) described the ultradian rhythms in ability to initiate sleep as "gates" of sleep-ability. In addition to these 1.5 h rhythms, Lavie has described punctate gates for sleep initiation and maintenance of wakefulness (reviewed in Lavie 1989; 1991b).

Doctoral Research

In summary, sleepiness in both normals and narcoleptics is a significant and complex problem. Quantitatively speaking, sleepiness is seen to vary with amount and quality of prior sleep, amount of prior wakefulness, time-of-day (circadian, circasemidian, ultradian) effects, and a host of other factors. All of the measurement techniques (subjective, physiological, performance) appear to get at only a part of the phenomena. The issues are further compounded by the possibility of qualitative differences as well: awaking from or pressure for REM sleep versus SWS may be as different as the fundamental states themselves (Broughton 1992). Much remains to be done on this topic.

The present doctoral research focuses on three major issues: narcolepsy; chronobiology; and performance. The involvement of REM and NREM sleep mechanisms make narcolepsy-cataplexy a particularly interesting disorder from the perspective of sleep/wake regulation.

The first section (Chapters 2 and 3) emphasizes chronobiology. Chapter 2 looks in a closer manner than done heretofore at the temporal placement of daytime relative to night sleep in narcoleptics and finds evidence for a difference in circasemidian sleep-wake regulation. The authors of this paper were, in order: J. Mullington, J. Newman, W. Dunham, and R. Broughton. The phase advance of napping in narcolepsy-cataplexy was an original finding subsequently confirmed by two other groups (Pollak et al., 1992; Lavie 1991a). Chapter 3 develops the circasemidian theme more completely in a theoretical paper. This paper by R. Broughton and J. Mullington represents an invited (to R.B.) presentation at an international workshop in Zurich on sleep-wake modelling. The second half of the paper, involving a neural network approach, is entirely the contribution of the second author.

Chapters 4 and 5 represent the comparison papers by J. Mullington and R. Broughton on the efficacy of scheduled naps of varying durations and circadian placements for alleviating excessive daytime sleepiness in narcoleptics. The first emphasizes effects on baseline performance levels and time-of-day effects. The second looks at the transitory negative sleep inertia effects. Studies were designed by the co-

authors and executed by the first author with support from the supervisor's laboratory, including help from research assistants M. Rivers and W. Dunham.

In analyzing the data presented in chapter 4, the first tested hypothesis was that there would be a difference between no-nap, single long and multiple short nap conditions. Therefore, analysis of variance across all 3 conditions, was performed for the central variables: reaction time, grammatical transformation, and descending subtraction. Further statistical testing was performed with paired t-tests, for the a-priori hypotheses that either of the napping conditions would proffer improved performance over the no-napping condition. Time of day analyses were performed, also using paired t-tests, for the a-priori hypotheses that there would be greater sleepiness in the afternoon. A liberal statistical approach was taken in analyzing the data because statistical analyses were driven by a-priori hypotheses. While the use of liberal statistics and multiple testing may lead to type 1 errors, we have attempted to reduce this risk by using Bonferroni corrected alpha levels of rejection. Narcolepsy-cataplexy is a rare neurological disorder and stringent screening procedures reduce the available population for recruitment even further. Of 11 narcoleptics in the Ottawa area who met our criteria and could possibly participate, 8 took time off work or studies to do so. While a larger number of subjects would have been desirable and even advisable from a statistical perspective, the rarity of the disorder made this unfeasible. Using a more stringent statistical approach to the data analysis would have unacceptably elevated the possibility of making type 2 errors. In research of this kind, it is the author's opinion that replication studies become of particularly high importance.

Chapter 6 provides general conclusions with a brief interpretive discussion of the results of the 4 papers. A fifth paper by M. Rivers, J. Mullington, and R. Broughton is presented as an Addendum and describes the software used in Chapters 4 and 5. It was developed by the first author under guidance by the other authors, and tested in the field by its second author.

CHAPTER 2

Phase Timing and Duration of Naps in Narcolepsy - Cataplexy: Preliminary Findings

Midnap time of narcoleptic subjects was found to occur with highest frequency between 150-170 degrees out of phase from nocturnal midsleep time. The longest naps were found at earlier phase angles, between 120 and 140 degrees.

Numerous research paradigms using normal subjects have demonstrated the recuperative effects of napping. While there have been a few studies aimed at assessing the recuperative effects of naps in narcolepsy-cataplexy, there have been no controlled studies designed to evaluate the circadian timing and duration of naps and their effects on performance. Preliminary to this question is the examination of circadian timing and duration of naps taken by narcoleptics in their natural surroundings. In a 24-hour home ambulatory monitoring study of the sleep-awake behaviour of narcoleptics, Broughton et. al. (1988) reported high variability in nocturnal sleep and daytime nap durations, with total sleep time of naps peaking in the afternoon. A napping treatment narcolepsy-cataplexy would therefore need to be sensitive to the timing and duration of sleep episodes relative to the circadian rhythms of the individual. The purpose of the present

study is to examine the circadian phase placement and duration of naps taken by narcoleptics in natural settings, with the aim of devising a napping treatment schedule.

Methods

Twenty-four hour ambulatory EEG recordings from 10 narcolepsy-cataplexy patients were used in this study. Seven subjects were participating in a laboratory research project, and the other three were recorded as part of routine testing for narcolepsy-cataplexy. The seven subjects came to the laboratory for hook-up early in the morning (approximately 0800 hours). Recordings for the remaining three subjects began at 1210, 1700 and 1730 hours. Subjects got up within one hour of their self-reported normal rising time on the day that recording began. Diagnoses were made in the Ottawa General Hospital Sleep Clinic, using criteria that included manifested sleep onset REM periods, excessive daytime sleepiness, and positive history of cataplexy. Exclusion criteria consisted of a sleep apnea index of greater than 5 per hour, or a PMS index of greater than 20%. Subjects were withdrawn from tricyclics for three weeks, and from stimulant medications for one week prior to participation in the study. Four-channel Oxford Medilog recorders were used, with electrodes at C4A1, right EOGM1, left EOGM2, and EMG. Subjects were instructed to go home and follow normal activities for the day.

In order to analyze the timing and placement of naps in relation to the circadian sleep-wake rhythm, the midsleep point of nocturnal sleep was designated as the zero phase. Phase angles move forward through the day after this point.

Results

Naps under 5 minutes were excluded from analysis. Sixty percent of nocturnal sleep periods began with REM, and 53% of daytime naps had sleep onset REM periods. The average nocturnal sleep period was 484 min (96.7 SD). The average nap length was 46.1 min (33.7 SD), and the number of naps per subject was 3 (1.2SD). Subjects spent an

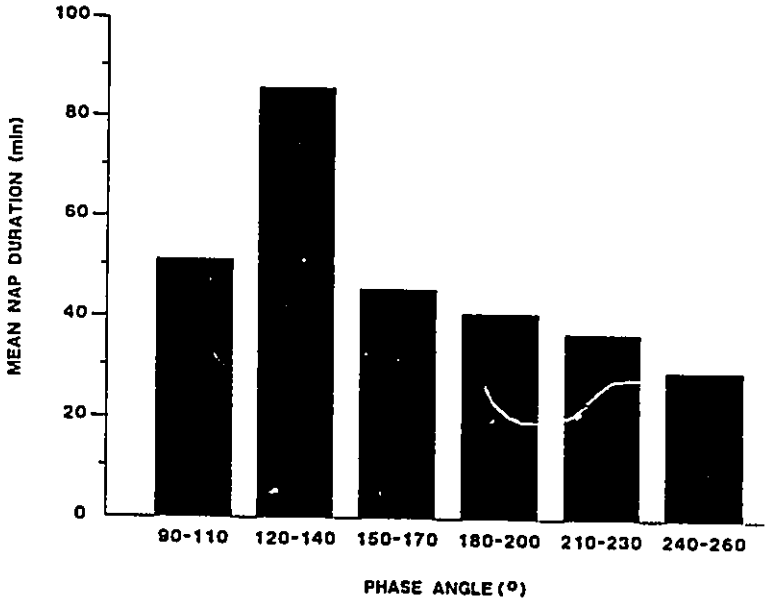

FIGURE 2.1: Nap duration by phase angle

average of 138.2 min (64.1SD) napping per 24 hours. As can be seen in Figure 2.1, the midnap times of the longest naps occurred 120-140 degrees out of phase with nocturnal midsleep time (-x= 121.9 degrees, SD = 3.1). The greatest number of naps (midnap times) are found in the 150-170 degree phase categories (see Figure 2.2). The average phase angle of naps falling within this range was 160.0 (5.5 SD).

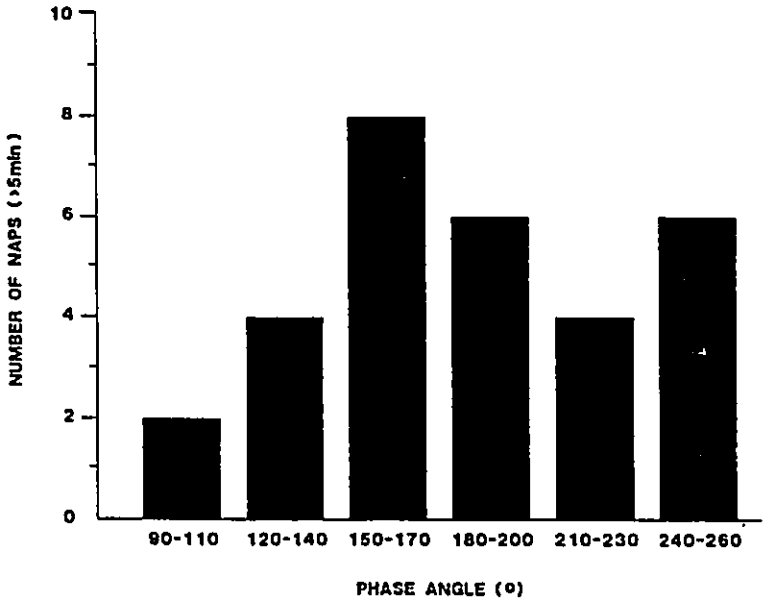

FIGURE 2.2: Frequency of naps by phase angles

Discussion

Studies investigating the circadian timing of naps in normal subjects in natural settings have found the period of greatest likelihood of sleep to occur approximately 180 degrees out of phase with the midsleep time (Dinges 1989). These "human nadirs", 180 degrees out of phase, have also been observed in studies of performance rhythms (Broughton 1975). The present study has found the phase range of greatest likelihood of napping in narcoleptics to be between 150-170 degrees out of phase with nocturnal midsleep time. In clock terms, a normal subject who has a major bed period between 2300 and 0600 hours and a midsleep time of 0230 would be most likely to nap with a midnap time at 1430. However, our findings indicate that a narcoleptic subject with the same nocturnal midsleep time would have the greatest likelihood of having a midnap time between 1230 and 1350 hours. The longest naps would be likely to occur even earlier. Given this example, 120-140 degrees would correspond to a clocktime range of 1030-1150 hours.

The circadian interpretation of this finding would be that naps in narcoleptics are phase advanced relative to normal subjects. This is consistent with Mosko et al., (1983), who found that the temperature nadir in narcoleptic subjects occurs about 1 hour after sleep onset, as opposed to 4-5 hours after sleep onset for normal subjects. We are currently collecting longitudinal sleep log data, and additional 24-hour ambulatory recordings in order to further these preliminary investigations.

CHAPTER 3

Circasemidian Sleep Propensity and the Phase-Amplitude Maintenance Approach to the Modelling of Human Sleep-wake Regulation

Summary

Evidence for circasemidian sleep/awake regulation is reviewed with repect to protocols used to quantify sleep propensity. Existing models of sleep/awake regulation are examined in view of their ability to accommodate data which demonstrate an afternoon sleep period. Finally, a modelling approach is briefly outlined which emphasizes the maintenance of the phase and amplitude characteristics of the circadian rhythm of body (and brain) temperature and predicts the circasemidian phenomena.

This paper derives from a request by the organizers for the senior author to review at the workshop the current evidence for a 2 per day (circasemidian, hemidian) regulation of sleep propensity and the extent to which existing models accommodate evidence for polyphasic sleep. Models of sleep regulation have primarily addressed monophasic sleep placement in circadian time and the within sleep ultradian NREM/REM alternation. In general they have de-emphasized, or totally ignored,

evidence for the inherently polyphasic nature of human sleep. The present paper briefly reviews evidence for a 2 per day regulation of sleep and the status of this process in current models. It closes with an outline of a relevant new modelling approach we have been developing.

Evidence for Circasemidian Sleep-wake Regulation

The experimental evidence supporting an endogenous 2 per day biorhythmic modulation of sleep is compelling (reviewed in Broughton, 1989b). The first proposal of such a control mechanism (Broughton, 1975) postulated that it represented a harmonic of the fundamental circadian sleep distribution and might reflect a quasi-12h rhythm of SWS.

The ubiquity of napping, which spans cultural and age groups, supports sleep's temporal complexity. During early childhood there is an evolution from a polyphasic pattern to a nocturnal sleep period with several naps and then a single daytime nap taken in the afternoon. Students, who have flexible hours, are frequently afternoon nappers. After retirement, when social restrictions are lifted, napping is common. Naps are again regularly selected in the mid-afternoon period rather than randomly as a non-rhythmic, exclusively recuperative, homeostatic mechanism would predict.

Performance studies since the initial report of Blake (1967), have repeatedly shown a 'post-lunch' dip in task variables sensitive to lowered vigilance (sleepiness)which is, moreover, not explicable by food intake.

Sleep latency as a measure of ability to get to sleep is a particularly important measure: in order for the (undoubtedly multiple) functions of sleep to occur, the individual must be able to fall asleep. Sleep latency measures by MSLT have typically shown a mid-afternoon decrease indicative of greater ease of wake/sleep transitions at that time but with considerable variability and timing in various reports. The latter may be related to several factors: differences involving control, if any, in the temporal placement and duration of both the previously entrained and immediately prior nocturnal sleep; differences in nap variables such as duration of sleep permitted; and differences in groups studied such as age range and, for patient data, medical diagnosis.

Dijk et al., (1987) have shown the mid-afternoon decrease in sleep latency in volunteers to be stable and independent of the homeostatic function of recuperative naps (as measured by EEG power density) to varying amounts of prior sleep deprivation. Carskadon (1991) recently used the constant routine paradigm in combination with continuous monitoring with repeated MSLT measures. She reported both that unintended sleep episodes showed a peak and that sleep latency showed a transient decrease at the time of the afternoon 'nap zone' (as well as at night) in each of the 3 age groups studied: children, adolescents and the elderly.

Ultrashort sleep paradigms with sleep fragmented into attempts to repeatedly nap around the 24 h, such as in Lavie's 7-13 min sleep/wake schedule, again show this powerful 2 per day rhythm in sleep propensity with a major nocturnal period and much smaller but distinct midafternoon nap period interdigitated with periods of relative inability to sleep (the 'forbidden zones' of Lavie 1986).

Time isolation studies are useful to unmask the endogenous nature of the 2/day rhythm of sleep propensity. The major sleep period occurs around the circadian temperature minimum and the minor sleep period (equivalent to the daytime nap zone) around temperature maximum. Strogatz (1986) termed the intercalated periods of low sleep probability, 'wake maintenance zones'. Time-free studies also show a secondary 'day' peak of SWS about 12 h after SWS onset in the major sleep period (Campbell and Zulley 1989). The extended sleep protocol, has similarly shown a delayed (about 13hr) return of SWS (Gagnon et al., 1985). The latter correlates negatively with prior within-sleep wakefulness (Broughton et al., 1990).

The remarkable temporal consistency of this 2 per day phenomenon can be appreciated by superimposing data from quite varied paradigms. Fig. 3.1 compares in young normal adults the 24 h distribution of: sleep latency of Richardson et al. (1982b); sleep latency during the constant routine by Caskadon et al., (pers. comm.); sleep amount in the 20 min ultrashort day of Lavie (1986) using his data from non-sleep deprived subjects requested to sleep; and sleep probability in the disentrained studies of

Zulley and Campbell (1985). The 24 h MSLT and ultrashort data are essentially superimposable, as are the results of all four protocols after 24.00 hours. Earlier, the constant routine sleep latency data suggest rather less sleepiness in the early morning. Also, the disentrained data show greater sleep in the morning reflecting the strong tendency under these conditions for subjects to extend the nocturnal sleep period. All four paradigms show a robust midafternoon increase in sleep propensity followed by a deep decrease reflecting the evening wake maitenance zone.

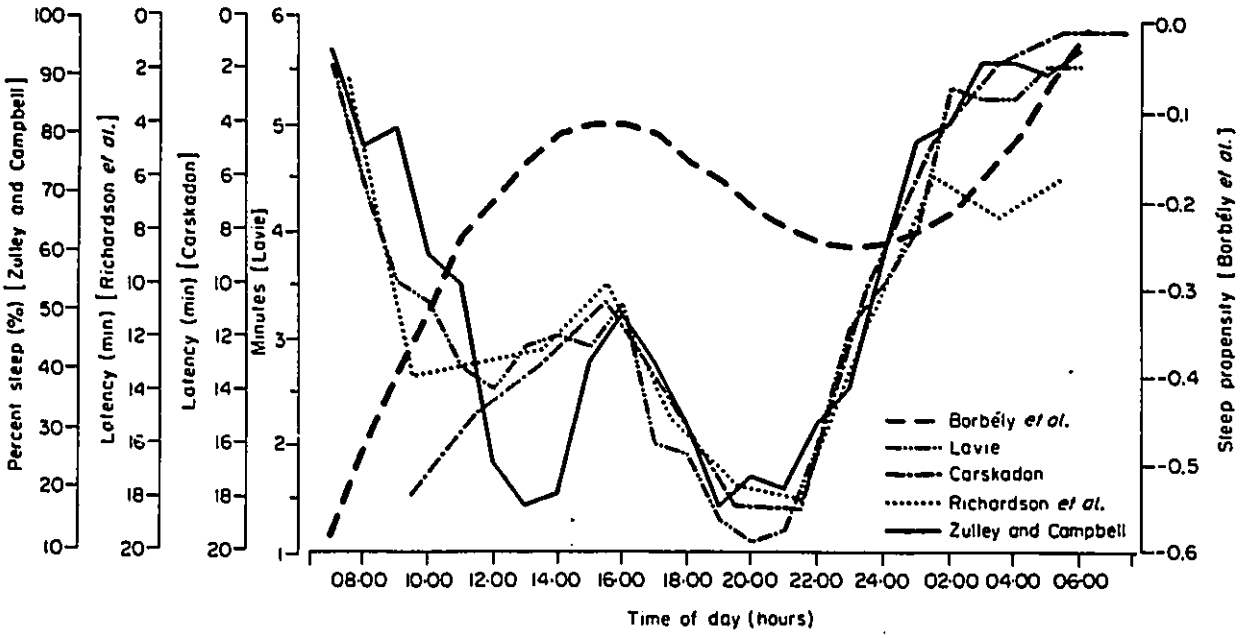

FIGURE: 3.1: Evidence for an endogenous 2/day sleep propensity rhythm. Data are aligned from: temporal isolation studies of Zulley and Campbell (1985) with percent of subjects asleep (100% at top); MSLT studies of Richardson *et al.* (1982) with short sleep onset latencies (min) at the top; constant routine studies of Carskadon (pers. comm.) similarly plotted; and ultrashort sleep studies of Lavie (1986) with amount of sleep (min in each 7 min scheduled nap, longest duration at top). All four approaches show a circasemidian distribution with an afternoon peak between 15.00 hours and 16.00 hours followed by a strong evening wake-maintenance zone.

Circasemidian Sleep Propensity and Current Models

The proposal of a circadian harmonic rhythm at about 12 h (Broughton, 1975) was followed by the Pittendrigh and Daan (1976) model for "activity splitting" in lower animals. They proposed a 2-oscillator model each generating an activity peak. Kronauer (1987) split his y oscillator into two reciprocally inhibitory y1 and y2 oscillators and applied the resultant altered equations both to split activity patterns in lower animals and to the circasemidian data in human time free studies reanalyzed by Strogatz (1986). This approach helped explain the data but did not allow for the homeostatic properties of sleep, nor account for the fact that naps are often skipped.

The two-process model has been further modified to account for the circasemidian pattern. Borbely et al., (1989) replaced the previously skewed sinusoidal shape of the sleep onset threshold (level H) by a sinusoidal one. Sleep latency was estimated as level of process S minus level H. This change gave rise to a transient midafternoon period of increased sleep propensity. However, when one plots their predicted results against actual laboratory data (Fig. 3.1), the fit is far from perfect. First, there is a marked dissociation up to about 11.00 hours with inverse tendency of the model to the data which cannot be explained by sleep inertia effects which are mainly over within 30 min of awakening. Secondly, the model predicts an already high and increasing sleep tendency by 0800-1000hrs, whereas laboratory data show a morning

wake-maintenance zone of low sleep probability. Thirdly, the extreme reduction of sleep propensity from about 1900-2100h (the evening wake-maintenance zone) is not predicted by the model. The model does predict the hour of peak of daytime sleepiness; however, the predicted peak's shape is too broad to fit the real data.

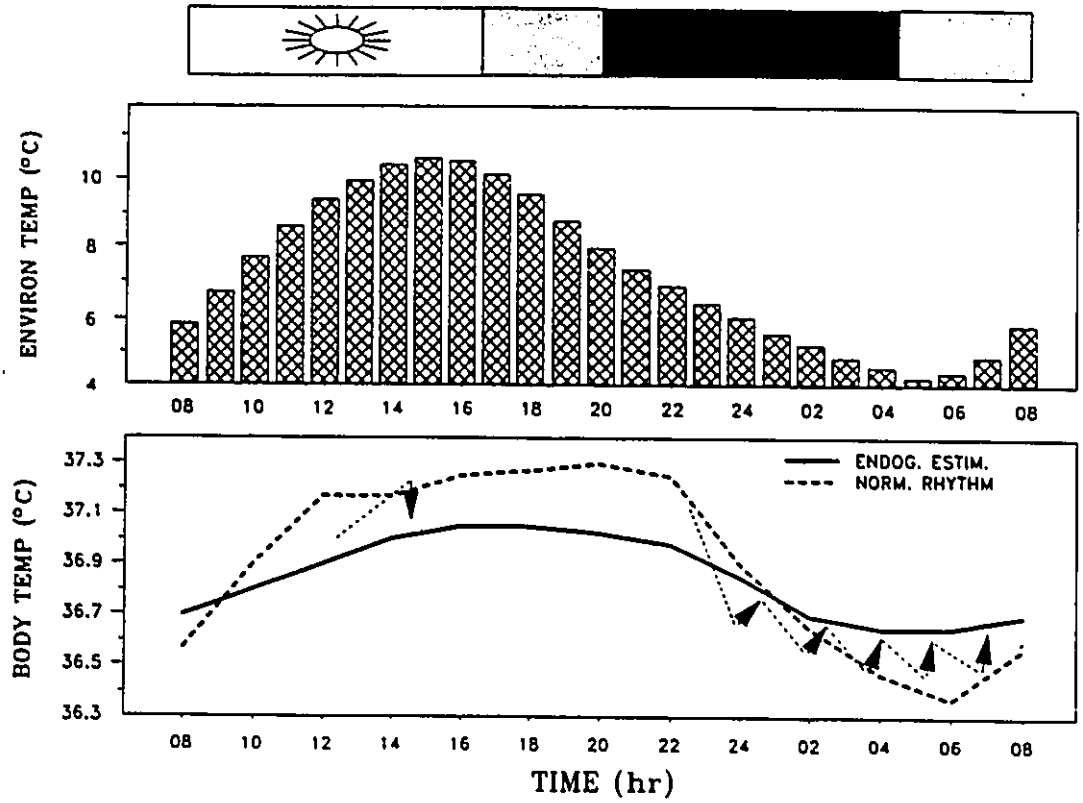

FIGURE 3.2: Schematic representation of aspects of the phase-amplitude maintenance model. Above, the times of earliest and latest normal sunrise and sunset are depicted in the bar. The grey zones correspond to times of seasonally varying sunrise and sunset, marking longest and shortest monthly day length averages (04.15-19.52/07.35-16.19 hours). Below, annual average hourly high (15.00 hours) and low (05.00 hours) temperatures are illustrated. The bottom graph illustrates some of the model's maintenance properties. The major sleep period occurs at night when environmental temperatures are dropping, with SWS facilitating the descent of body and brain temperature. During sleep, REM periods (black arrows) may limit the descent of the rhythm and facilitate its upward climb after the nadir of the rhythm is reached. When temperature is rising too quickly, it may exceed its circadian time appropriate level. Therefore, a nap may represent an evoked response (open arrow) of the sleep/wake regulating system to reduce actual temperature within its time-appropriate range.

We are unfortunately handicapped in our attempts to model the 2 per day rhythm by an incomplete understanding of its fundamental properties. It remains uncertain whether the daytime "nap zone" is an integral feature harmonic of the circadian rhythm or whether, as proposed later (Broughton, 1985b), it is an independent rhythm with a fixed integer ratio (2:1) which shows a typical phase relationship to the circadian one. Proof of ability to independently phase shift the two phenomena would support the latter hypothesis. It also remains unknown whether the 2 per day rhythm is fundamentally one of ability to go to sleep (i.e., sleep onset mechanisms), of pressure for a particular type of sleep state (e.g., SWS), or one of arousal with consequent intercalated periods of easier sleep onset (Broughton, 1989b). In fact, it might relate to none of these but be secondary to another process, such as temperature regulation. We have been exploring a model of maintenance of phase and amplitude of circadian temperature in relationship to sleep regulation, to be presented in detail elsewhere (Mullington and Broughton, in prep).

The Phase-amplitude Maintenance Approach

The phase-amplitude maintenance model employs an adaptive network approach which involves modification ('learning' in information theory terms) through repeated association and feedback. Network modelling allows for the construction of features through repetition and probability of association (McClelland and Rumelhart, 1986) applied here to the maintenance of phase and amplitude of core body (and brain)

temperature. This approach can be used in the construction of a model which can incorporate a number of important factors for the regulation of human sleep and wakefulness. The model gets its name from the notion that manipulation of either phase or amplitude will require reinterpretation and reorganization within a multifactorial system in order to maintain the integrity of the characteristics of the rhythm itself.

The phase-amplitude maintenance model posits that there is a genetic component of the temperature rhythm, which parallels the environmental circadian temperature pattern. There is economy in a system which maintains the circadian rhythm of body temperature. It is energy efficient, in biological terms, to sleep when the environment is at its coolest, thereby reducing the amount of energy required to bridge the temperature differential, and to be mobile and perform food gathering and other activities during daylight hours. In hot climates, an afternoon sleep may also serve to counter the body warming effect of heat. Living in climate controlled environments, these factors may seldom have a direct impact, but may have influenced the evolutionary development of human circadian and circasemidian sleep/wake patterns.

While the fundamental endogenous component of the temperature rhythm is genetic, it is additionally transformed and shaped through the lifespan. During ontogeny, there is a progressive increase in the amplitude of the circadian rhythm of body temperature from infancy through the first 5 years of life, by which time the rhythm has become similar to that of adults (Mills, 1974). These developments co-occur with the

consolidation of nocturnal sleep through infancy and early childhood. The behavioral pattern thus develops in concert with the underlying temperature rhythm. Elderly subjects show a decreased amplitude in the core body temperature rhythm, under both entrained and free run conditions (Weitzman et al., 1982); and an increased frequency of napping during these years is also described (reviewed in Webb 1989).

Within the lifespan, entraining behavioral, metabolic and environmental 'input' factors (including activity levels, food intake, sleep hygiene, sleep/wake and light/dark patterns, and ambient temperature cycles), through repeated association, build upon the genetically given rhythm to shape its manifest amplitude and phase characteristics. This manifest rhythm is what the phase-amplitude maintenance model purports to maintain. Using a network approach, input factors contribute to the shaping of the endogenous rhythm; but once it has been established it demonstrates a measurable degree of resilience in the absence of those inputs. The resulting 'shaped' endogenous rhythm is revealed through unmasking protocols such as temporal isolation and constant routines.

The main features of the phase-amplitude maintenance model may be usefully considered when temporally aligned (Fig. 3.2). The solar day is schematized above with its cycle of bright daylight, dusk "grey zone", night, and dawn "grey zone". Next is plotted the average annual temperature by clock time (Environment Canada; Ottawa, 45°Lat) illustrating the average daily pattern of temperature fluctuation. Below are shown both

the unmasked endogenous core body temperature and the typical masked body temperature (both derived from data of Aschoff and Wever in Folkard 1989).

The periodicity of the system is considered by the model to be modulated by changing light/dark patterns. These involve changes of intensity, duration and phase of ambient light over prolonged periods of time including fluctuations deriving from alterations in latitude and seasons. Such changes in light exposure alter circadian patterns of melatonin secretion which feed back onto the SAN where the postulated neural modification ('learning') of phase information occurs. The model maintains that phase-altering stimuli must be interpreted in order to have an effect on the phase of the rhythm. This may be achieved through a light/dark 'comparator' (Herbert 1989).

In the network approach we are proposing that the degree of effect of a light or melatonin pulse will depend upon its position within an interpretable range; when it passes this range, the phase altering effects cease. Bright light applied during the period of constant light will not produce a phase delay. As the light is moved into the afternoon "grey zone" its phase delaying effect will gradually increase until it falls off precipitously, when the system no longer has an interpretive set for light at this phase position. A pulse applied 180° out-of-phase with its endogenous maximum or minimum should eventually produce an 180° flip in the temperature rhythm as the system attempts to interpret the new information set.

The phase-amplitude maintenance model concurs with thermoregulatory upper and lower brain temperature setpoints modelled by McGinty and colleagues (McGinty and Szymusiak, 1990; Nakao et al., 1991). According to the phase-amplitude maintenance model, it is the circadian rhythm itself that brain temperature setpoints serve to maintain. Brain temperature upper and lower setpoints vary on a circadian basis; and sleep is considered, in part, to be a thermoregulatory response to the appropriate circadian brain temperature setpoint range being exceeded.

The actual setpoints are not illustrated in Fig. 3.2, as they remain to be precisely determined. The temperatures at which the setpoints are exceeded are schematized in Fig. 3.2 using dotted lines attached to arrows. The open arrow indicates the onset of a nap, and the darkened arrows indicate transitions from SWS to REM sleep.

A homeostatic requirement for a certain amount of sleep (especially SWS) per 24 h, as well as an important two-way interaction between core body and brain temperature and sleep/wake patterns are accepted. Metabolic load accumulated during wakefulness is dissipated during SWS, thereby decreasing brain and body temperature. This metabolic load is assumed to be at its highest point at the end of a normal non-napping day, just prior to nocturnal sleep, at a time when environmental temperature is decreasing faster than body temperature. Nocturnal SWS reduces brain and body temperature decreasing the internal-external temperature difference. The descent of brain temperature is limited

during REM sleep, and increases in cool ambient temperatures (Palca et al., 1986; Parmeggiani 1980).

The model incorporates detection of both absolute temperature levels and the important (Broughton, 1989b) parameter of rate of change. We hypothesize that a mid-afternoon peak in sleep is predicted in the case where high rate of change of brain and/or body temperature exceeds what is anticipated by the system at that time. This is illustrated in Figure 3.2 by the downward pointing open arrow around 15.00 hours. The mid-afternoon sleep facilitation is considered to be a response to curtail the rate at which temperature rises and prevent temperature from exceeding its circadian appropriate setpoint level. Therefore, assuming no sleep debt, if the setpoint levels are not exceeded there will be little pressure to nap, even though a facilitative effect will be present due to the evolutionary circasemidian factor previously mentioned. Of course, if there is pressure to nap but no opportunity, sleep may be voluntarily resisted.

The marked suppression of sleep onsets in the early evening is explained by the model as reflecting the time of day when core body temperature is predictably most stable (lowest rate of change) and well within the circadian setpoints, thereby minimizing any sleep facilitating effects.

When subjects attempt to extend sleep well beyond usual durations (Gagnon et al., 1985), this behaviour conflicts with the normal entrained circadian core body

temperature rhythm which is rising during the intended period of extension. SWS is predicted by the model in order to help down-regulate temperature, thereby minimizing the physiological-behavioral conflict and being more sleep permissive. The interpretation that SWS may be a response to the discordance between maintenance of sleep and rising body temperature has been offered by Berger et al., (1988). Preliminary data (DeKoninck et al., 1990) indicate that the return to SWS may be associated with a relatively high amplitude temperature rhythm. In 3 of 4 subjects who were able to maintain consolidated sleep beyond 1300 h in a recent study by Dijk et al., (1991), the relationship between the return of SWS and amplitude of the temperature rhythm is apparent through visual inspection.

Webb (1988) emphasized that it is essential to consider the combined effects of restorative, biorhythmic and behavioral factors in the modelling of sleep/wake regulation, its temporal and architectural pattern. The phase-amplitude maintenance model outlined here begins this task using a network approach, which has as its strength the potential of taking a multivariate approach and integrating data at multiple levels of analysis.

Scholars who study modelling (as opposed to creating models) have recurrently emphasized the limit of models and advised us that the same data set may be modelled satisfactorily in more than one manner (cf. Denning, 1990). As Karl Dallenbach, discussing theories (models are but a form of theory) wrote, "Love a few, wed none

...(and) carry theory lightly that you may follow where facts may lead" (Dallenbach, 1953, p. 36). We consider the phase-amplitude approach as simply one of many valid approaches, each with apparent strengths and limitations. As for all models, its viability will depend on whether it will have useful and reliable descriptive and predictive properties.

CHAPTER 4

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

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 test 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 midsleep 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.

Naps have often been recommended in the management of excessive daytime sleepiness (EDS) associated with narcolepsy-cataplexy (Zarcone 1973; Regestein et al. 1983; Soldatos et al. 1983; Mitler et al. 1987). 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) (Carskadon et al. 1986) and maintenance of wakefulness test (MWT) (Mitler et al. 1982).

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 (Parkes and Fenton 1973; Yoss and Daly 1959). 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 (Yost and Daly 1959). Finally, even if the stimulant medication is well tolerated by the patient, drug holidays

are sometimes recommended (Guilleminault et al. 1976; Hauri and Orr 1982), 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. (1986) employed a modified MSLT paradigm and found that, while 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 (Broughton, 1989c). 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 (in press) 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 3 daily naps of 15 minutes each (based on the subject's own desired times). Sleep latencies were significantly increased at post-treatment assessment, a difference mainly attributable to the second resisting sleep trial (at 1200 hours). However, the number of MWT

periods without sleep did not significantly 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 (1976) and Godbout and Montplaisir (1986) 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 (Dinges et al. 1985), 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. Since sleep inertia has not been investigated in narcoleptics, it is not possible to estimate to what degree these results might have been compromised.

To date, therefore, there is not strong support for the efficacy of naps in the management of EDS in narcolepsy. However, studies may have been inconclusive due to the frequent absence of performance testing; lack of sufficiently sensitive, prolonged or frequent performance testing across the day or the choice, for this application, of the

MSLT to measure sleep propensity. Within subjects improvements have been limited to NREM naps, but these studies have not considered the possible confounding influence of sleep inertia. In addition, no studies have addressed the issue of whether a single long or multiple short nap schedules would be more efficacious.

Current knowledge indicates that time-of-day may also be important. Like normal subjects, narcoleptics show a strong trend for a transient increase in sleep propensity in the midafternoon (Richardson et al., 1982a; 1982b; and Broughton et al. 1988). Moreover, narcoleptics have difficulties in consolidating nocturnal sleep (Rechtschaffen et al. 1963; Montplaisir et al. 1978; Broughton and Mamelak 1980; Montplaisir and Godbout 1986). Finally, there is evidence for a particularly strong ultradian component of daytime sleep-wake regulation (DeKoninck et al. 1986). Based upon these findings, it is uncertain whether optimum alertness might best be maintained by consolidating total 24-hour sleep into a single nocturnal block, restricting sleep into the two main periods of sleep propensity (i.e. the nocturnal sleep period and midafternoon "nap zone"), or by permitting multiple short daytime naps.

To test between these possibilities, three protocols were designed, each with the same amount of sleep in a single 24-hour period. One condition scheduled all sleep into a single consolidated nocturnal period, while the other two conditions involved schedules of shortened nocturnal sleep supplemented by daytime sleep consisting of

either one or 5 naps spaced equidistantly throughout the remaining waking portion of the day.

Methods

Subjects

Eight (four male, four female) narcolepsy-cataplexy patients aged 19-55 participated. Full patient characteristics are detailed in Table 4.1. 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 daytime sleepiness (Akimoto et al. 1960; Hishikawa et al. 1966), were not required to discontinue that medication. One narcoleptic was taking carbamazepine for suspected co-existent seizures and continued this medication. One subject (PL) on gamma-hydroxybuterate (GHB) for consolidation of night sleep in narcolepsy (Broughton and Mamelak 1979) stopped this medication at the same time as he ceased taking his

Table 4.1. Subject characteristics for narcolepsy-cataplexy patients [a]

Subject	Gender	Age	SOL	SOREMPs (no.)	Apnea Index	PMS Index (%)	Medication (pre-study)	Further Auxillary Symptoms
1. SD	F	53	2.3	4	0.0	22.0	chlomipramine, GHB, methylphenidate	sleep paralysis, hypnagogic hallucinations
2. CP	M	22	2.6	2	21.5	22.3	untreated	none
3. SG	M	48	4.8	2	.2	4.6	carbamazine	hypnagogic hallucinations
4. SM	F	19	1.0	5	1.6	19.6	methylphenidate	nightmares, hypnagogic hallucinations
5. RK	F	54	.8	4	3.5	55.0	chlomipramine, methylphenidate	nightmares, hypnogogic hallucinations
6. PE	M	45	3.0	5	.2	0.0	methylphenidate	sleep paralysis
7. PL	M	46	3.3	3	1.7	19.7	chlomipramine, GHB, methylphenidate	nightmares, sleep paralysis
8. ED	F	55	2.4	3	0.0	4.0	untreated	nightmares

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

methlyphenidate. 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 5 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 mid-sleep time, as determined by sleep logs, was also held constant in order to minimize any circadian disruption. The resulting conditions (see Fig. 4.1) 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. (1988). 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 (Dinges 1989) and also that of greatest sleep propensity in normals (Richardson et al., 1982b; Lavie and Zomer, 1984) and in narcoleptic subjects including in the ambulatory home study mentioned above (Broughton et al., 1988).

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 5 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 which contained a necessary math co-processor. This approach was chosen so that subjects could easily carry the test equipment in a tote-bag up and down stairs 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 sec (excepted during the four-choice reaction time test, which ran its duration uninterrupted).

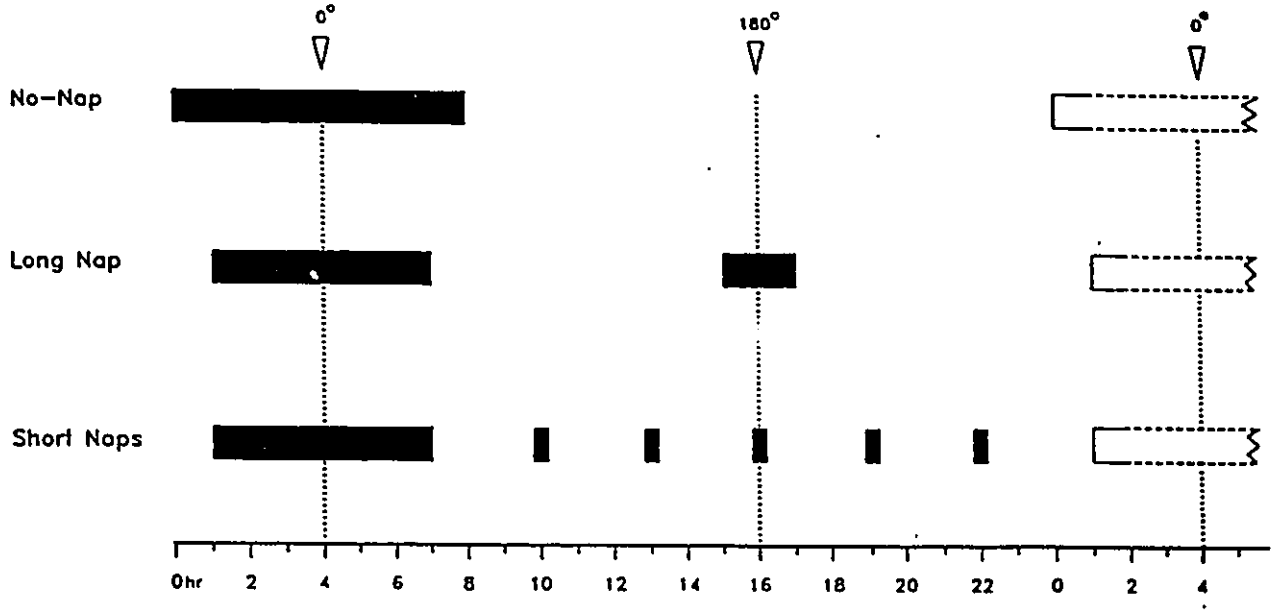

FIGURE 4.1: Schematic representation of sleep/wake schedules followed by narcoleptic subjects during no-nap, single long nap and multiple short nap conditions. The 24-hour sleep total was held constant with, in the nap conditions, 75% taken in the nocturnal period and 25% in the naps. The midpoint of 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.

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 EMG; EKG, and tympanic temperature were also recorded. Electrodes were applied on the first evening at the bed-and-breakfast, and left on for 36h 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 3 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 post-adaptation experimental daytime periods.

Recordings were printed out at 20 times 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 sec epochs. Nocturnal sleep was scored according to standardized criteria (Rechtschaffen and Kales 1968). Wakefulness was divided into active and quiet wakefulness according to criteria of Volk et al. (1984) with the addition of substage 1A (Valley and Broughton 1981) 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- Kales (1968).

Performance Testing

Individually scheduled sleep periods and performance test sessions were initiated by computer, the softwar : of which is described in detail elsewhere (Rivers et al. in press). Each session took approximately 13 min to complete and consisted of a fixed sequence of the descending subtraction test (Dinges et al. 1985; and Evans and Orne 1975), a grammatical transformation (or logical reasoning) test (Baddeley 1968), four-choice reaction time test [computerized after Wilkinson and Houghton, (1975)], grip strength test (Aschoff et al. 1972), a measure of oral temperature, the Stanford Sleepiness Scale (Hoddes et al. 1973) and a number of additional subjective evaluation questions, most of which were based on Thayer's (1978) activation check list. 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 min during the daytime and, on nap days, approximately 15 min prior to a nap, immediately upon waking, 20 min after waking, and every 30 min thereafter with the exception of meal times 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 (Dinges et al. 1985) and therefore was the first performance test in each session. In this 2 min test, subjects were presented with a randomly

generated 3-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, which also ran for 2 min. In this test a logical statement is presented which 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 min. External hardware was designed and attached to the printer port of the computer with 4 keys corresponding to 4 red diodes that lit up in random sequence, essentially identical to the original design (Wilkinson and Houghton 1975). The dependent measures saved included: mean reaction time of correct response without gaps (i.e., responses > 1 sec), of wrong responses without gaps and of gap responses, as well as the number completed and number of correct responses made in each 5 min session.

Results

A priori hypotheses were tested using Student's paired two tailed t-tests with alpha set to the .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-cataplexy as a disorder of state-boundary control (Broughton et al. 1986). 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 (Myers 1979).

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 towards greater amounts of REM sleep in the multiple short nap condition (see Table 4.2).

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 over 3 min) and the associated standard deviations were as follows: for the no-nap condition, 7.1(4.^); for the long nap condition, 4.3(2.6); and for the multiple short nap condition, 6.5(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 ($p=0.07$).

Most of the sleep episodes outside of the scheduled sleep periods were brief and consisted of stage 1B. Subjects slept for an average of less than 5 min at a time in all conditions (average duration of sleep episodes per subject across all conditions ranged between 3 min and 4 min 51 sec). Unscheduled sleep periods over 5 min 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 8 unscheduled sleep episodes of greater than 7 min duration.

The timing of unscheduled sleep episodes is of particular interest in the no-nap condition since subjects were not permitted to nap at all, but nocturnal sleep was not reduced. The timing of these sleep episodes is illustrated in Fig. 4.2 as a frequency histogram. The phase time of greatest likelihood of unscheduled sleep occurred between 150-170 degrees out of phase with the nocturnal midsleep time, with a secondary peak between 250-270 degrees. With respect to group average clock times, the first peak corresponds to a range of approximately 1340-1500h, and the second to 2020-2140h.

Table 4.2. Twenty-four hour totals of scheduled and unscheduled sleep [a]

	No-nap	Long Nap	Short Naps	N *vs* L	N *vs* S	N *vs* S
Scheduled						
QW	6.5 (11.6)	1.5 (2.6)	1.4 (2.6)	ns	ns	ns
AW	27.8 (23.1)	25.6 (21.2)	20.2 (19.5)	ns	ns	ns
Stg 1A	6.0 (8.7)	4.9 (5.3)	5.6 (3.8)	ns	ns	ns
Stg 1B	50.9 (25.8)	51.1 (32.6)	59.2 (34.1)	ns	ns	ns
Stg 2	132.3 (52.0)	133.1 (43.0)	111.3 (42.2)	ns	ns	ns
Stg 3	49.8 (11.7)	41.2 (10.3)	45.4 (21.4)	ns	ns	ns
Stg 4	88.3 (41.1)	103.1 (34.1)	91.8 (42.2)	ns	ns	ns
SWS	138.1 (48.5)	144.3 (38.9)	137.2 (56.0)	ns	ns	ns
REM	133.3 (31.4)	139.5 (35.6)	165.2 (28.5)	ns	ns	ns
MT	11.8 (9.3)	10.4 (7.2)	10.5 (4.7)	ns	ns	ns
TST	454.6 (61.0)	468.3 (41.9)	473.4 (33.1)	ns	ns	ns
Unscheduled [b]						
Stg 1B	28.7 (15.8)	15.8 (11.2)	26.6 (30.4)	ns	ns	ns
Stg 2	.8 (1.9)	.4 (1.1)	.9 (2.7)	ns	ns	ns
REM	1.8 (2.3)	1.2 (3.4)	5.1 (7.9)	ns	ns	ns
TST	31.3 (17.5)	17.4 (11.5)	33.0 (30.7)	ns	ns	ns

[a] Values are presented in mean no. of minutes (SD); QW= quiet wakefulness, AW=active wakefullness, SWS=stages 3 plus 4, MT=movement time, N=no-nap condition, L=long nap condition, S=multiple short nap condition. [b] Sleep episodes > 3 min.

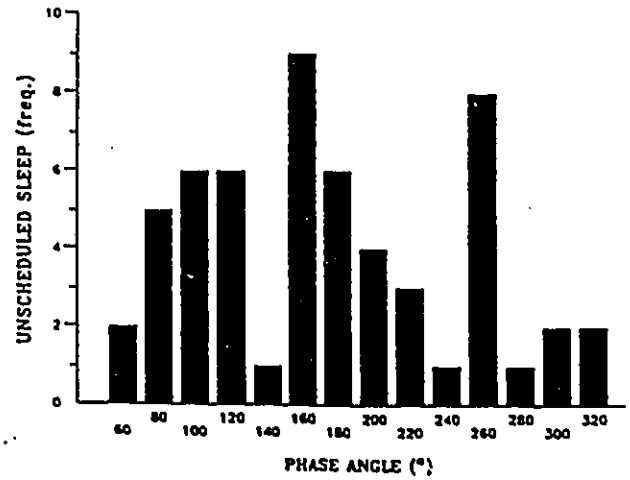

FIGURE 4.2: Frequency of unintended sleep episodes in the no-nap condition as a function of phase angle. The histogram plots 20 degree bins (midphase indicated) relative to the midpoint of nocturnal sleep (phase 0°). Unscheduled sleep showed two main peaks: at 160° (largest) and 260° bins, with deepest minima at 140°, 240° and 280°.

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 4.3 for the no-nap, single long nap and 5 short naps schedules. Post-hoc exploratory analyses found that sleep efficiency was higher for the nocturnal period 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.

Structure of long vs. multiple short nap sleep.

On average, scheduled long naps were 129 min and short naps were 26 min in duration. Post-hoc analyses (Table 4.3) found that long nap sleep periods had a tendency for less percent stage 1A ($p < 0.10$) and more stage 4 and SWS (stages 3 plus 4) ($p < 0.10$) than the short naps. Concerning time (min) in stage, there were no significant differences, but there was a tendency for substage 1A (drowsiness) to be lower in the long nap condition ($p < 0.10$).

Table 4.3. Scheduled sleep characteristics [a]

	Nocturnal Sleep				Nap Sleep		
	No-nap	Long	Short	P-value [b]	Long	Short	P-value [b]
SE	89.8 (7.1)	91.8 (3.6)	93.8 (4.4)	p.<0.05 [c]	92.6 (6.9)	90.1 (5.3)	ns
REMeff	76.0 (6.6)	68.6 (10.3)	73.4 (16.7)	p.<0.05	80.0 (20.2)	95.2 (4.2)	ns
Percent of bedperiod							
MT	2.4 (1.9)	2.3 (1.8)	2.5 (1.2)	ns	1.2 (1.4)	0.7 (0.9)	ns
QW	1.2 (2.0)	0.3 (0.6)	0.2 (0.5)	ns	0.2 (0.4)	0.3 (0.5)	ns
AW	5.5 (4.7)	4.8 (3.1)	2.9 (3.4)	p.<0.05 [c]	5.1 (6.1)	6.1 (4.0)	ns
1A	1.3 (2.0)	1.1 (1.3)	0.7 (0.9)	ns	.8 (1.0)	2.3 (1.7)	p.<0.10 [c]
Percent of sleep							
1B	11.3 (6.0)	11.3 (7.9)	12.1 (8.1)	ns	9.4 (6.5)	13.5 (8.9)	ns
Stg.2	29.1 (10.3)	31.3 (10.4)	26.1 (9.8)	ns	19.6 (6.2)	17.1 (13.4)	ns
Stg.3	10.6 (1.7)	10.0 (3.6)	11.3 (5.7)	ns	5.5 (5.0)	5.5 (6.0)	ns
Stg.4	19.5 (7.9)	17.6 (8.2)	20.0 (7.9)	ns	34.8 (9.6)	14.4 (16.4)	p.<0.10 [c]
SWS	30.1 (8.7)	27.6 (10.0)	31.3 (11.6)	ns	40.3 (10.0)	19.9 (21.5)	p.<0.10 [c]
REM	29.3 (4.9)	29.5 (9.1)	30.5 (7.8)	ns	30.4 (6.1)	49.6 (27.1)	ns

[a] Values are presented as mean percent data (SD); REMeff= REM period efficiency, QW= quiet wakefulness, AW=active wakefullness, SWS=stages 3 plus 4, MT=movement time, N=no-nap condition, L=long nap condition, S=multiple short naps condition. [b] tested using two-tailed paired *t*- tests. [c] Bonferroni alpha adjustments applied.

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 naps conditions. Means and standard deviations are presented in Table 4.4. When test sessions immediately upon waking plus those 20 min after waking were together 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

Table 4.4. Grammatical transformation test [a]

	No-nap	Long Nap	Short Naps	N *vs* L	N *vs* S	L *vs* S
Excluding immediate post-wake data	18.1 (8.1)	16.2 (8.9)	16.8 (7.7)	p.<0.05	p.<0.05	ns
Excluding immediate and +20min data	17.9 (7.9)	16.0 (8.7)	16.7 (7.4)	p.<0.05	ns	ns

[a] Values are for test day, means (SD), P-values presented are for two-tailed paired *t* - tests, 7df; N=no-nap condition, L=long nap condition, S=multiple short naps condition.

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 4.5. Data excluding immediate post-wake sessions were analyzed and are provided for 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 correct responses are listed along with the same variables for wrong responses. Below this, the number of gaps and the average duration in milliseconds are listed by condition. Performance was poorest in the no-nap condition for all measures, although significance levels were only reached for comparisons between the no-nap and long nap conditions. The long nap condition demonstrated significant improvements for number completed, number correct and for number of correct responses without gaps.

The small cumulative benefits evident in dependent reaction time measures for the long nap condition are reflected in the finding that the number of responses and the number of correct responses were significantly higher than in the no-nap condition. When the tests administered immediately upon and 20 min after waking were together excluded from the analyses, performance in the long nap condition was still higher than in the no-nap condition for both number correct and number completed. However, there were no significant differences between the no-nap and multiple short nap conditions.

Table 4.5. Four-choice reaction time test [a]

		No-nap	Long Nap	Short Naps	N *vs* L	N *vs* S	L *vs* S
Excluding immediate post-wake data							
	No. completed	413.5 (61.0)	443.3 (40.7)	442.6 (38.8)	p.<0.05	ns	ns
	No. correct	387.7 (72.8)	420.8 (49.0)	419.0 (43.5)	p.<0.05	ns	ns
Correct responses (Without Gaps)							
	No. correct	373.3 (81.3)	409.0 (55.5)	404.9 (47.2)	p<0.05	ns	ns
	RT (msec)	437.3 (57.3)	422.6 (47.5)	418.8 (51.6)	ns	ns	ns
	Mean SD	115.3 (33.4)	110.3 (30.3)	111.5 (31.9)	ns	ns	ns
Wrong responses (Without Gaps)							
	No. incorrect	23.2 (17.9)	20.5 (11.9)	21.9 (12 2)	ns	ns	ns
	RT (msec)	398.4 (69.9)	388.1 (63.3)	382.1 (62.9)	ns	ns	ns
	Mean SD	135.2 (37.3)	121.7 (34.4)	119.9 (42.8)	ns	p<0.05	ns
Gaps							
	Number	17.0 (13.4)	13.8 (9.7)	13.8 (9.4)	ns	ns	ns
	Duration (msec)	2222.5(923.4)	2061.5(457.0)	2058.9(529.9)	ns	ns	ns
Excluding immediate and +20min data							
	No. completed	411.5 (62.1)	441.7 (42.3)	446.6 (42.9)	p.<0.05	ns	ns
	No. correct	385.3 (74.6)	418.9 (51.5)	422.0 (48.2)	p.<0.05	ns	ns

[a] Values are for test day, means (SD), P-values presented are for two-tailed paired *t* - tests, 7df; N=no-nap condition, L=long nap condition, S=multiple short naps condition.

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 6 of the 8 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 degree 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 6 categories around the deleted one at 180 degrees, with 3 "early" and 3 "late". The medians, in degrees (°) of each of the 6 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 2220h. Test results from the two performance test sessions which 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 versus 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. 4.3; and data for both number completed and number correct are provided in Table 4.6.

Reaction time, number completed and number correct were used in time-of-day analyses since they had been most sensitive in test day analyses. These 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 4.7; Fig. 4.4 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 naps compared to the long nap condition.

Table 4.6. Grammatical transformation summary data for 6 time categories [a]

	No-nap	Long nap	Short naps	N *vs* L	N *vs* S	L *vs* S
Number Completed						
73°	21.8 (9.0)	20.3 (9.8)	21.8 (6.9)	ns	ns	ns
108	22.1 (8.1)	19.6 (6.8)	21.3 (9.5)	ns	ns	ns
143	21.3 (6.7)	17.5 (6.6)	21.6 (7.6)	p.<0.05	ns	p.<0.05
218	19.1 (6.4)	18.2 (7.7)	19.8 (6.2)	ns	ns	ns
253	19.3 (3.9)	18.7 (7.6)	19.8 (5.8)	ns	ns	ns
288	19.2 (6.4)	17.1 (5.0)	18.8 (5.9)	ns	ns	ns
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

[a] Values are for time-of-day phase degree categories means (SD); Bonferroni adjusted P-values presented for two-tailed paired t-tests, 7df; N=no-nap condition, L=long nap condition, S=multiple short naps 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 versus no-nap conditions for number completed and remained significant for number correct.

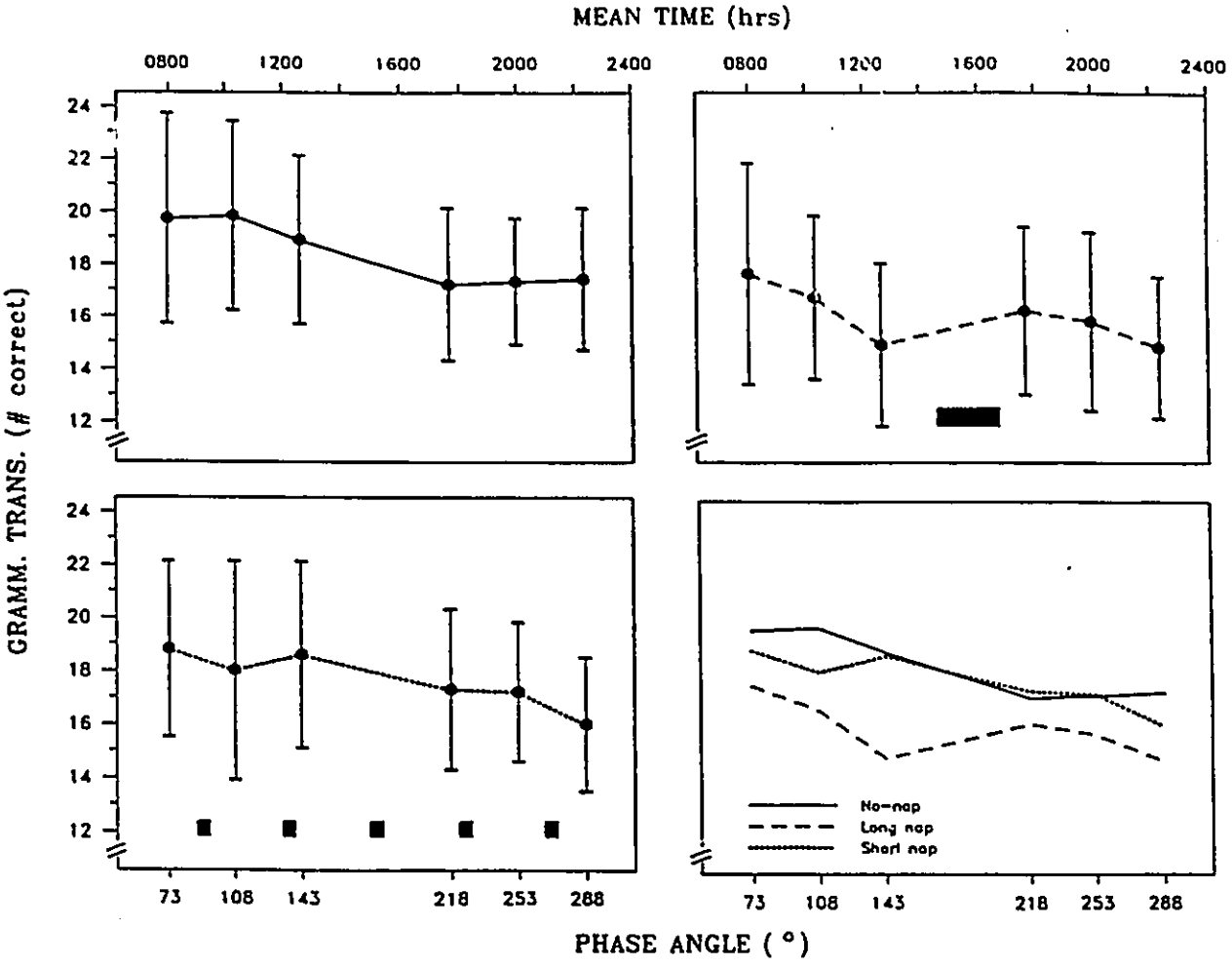

FIGURE 4.3: Performance on the Baddeley grammatical transformation (logical reasoning) task in the three sleep/wake schedules. Number correct (mean, SE) is plotted for each schedule for time-of-day effects as a function of phase angle (with corresponding time of day above) for the no-nap (upper-left), long nap (upper right) and multiple short nap (lower left) conditions with superimposed results in lower right. Placement of naps designated by dark bars.

Table 4.7. Four-choice reaction time summary data for 6 time categories[a]

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

[a] Values are for time od day phase degree categories means (SD); Bonferroni adjusted P-values presented for two-tailed paired *t* - tests, 7df; N=no-nap condition, L=long nap condition, S=multiple short naps condition.

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.

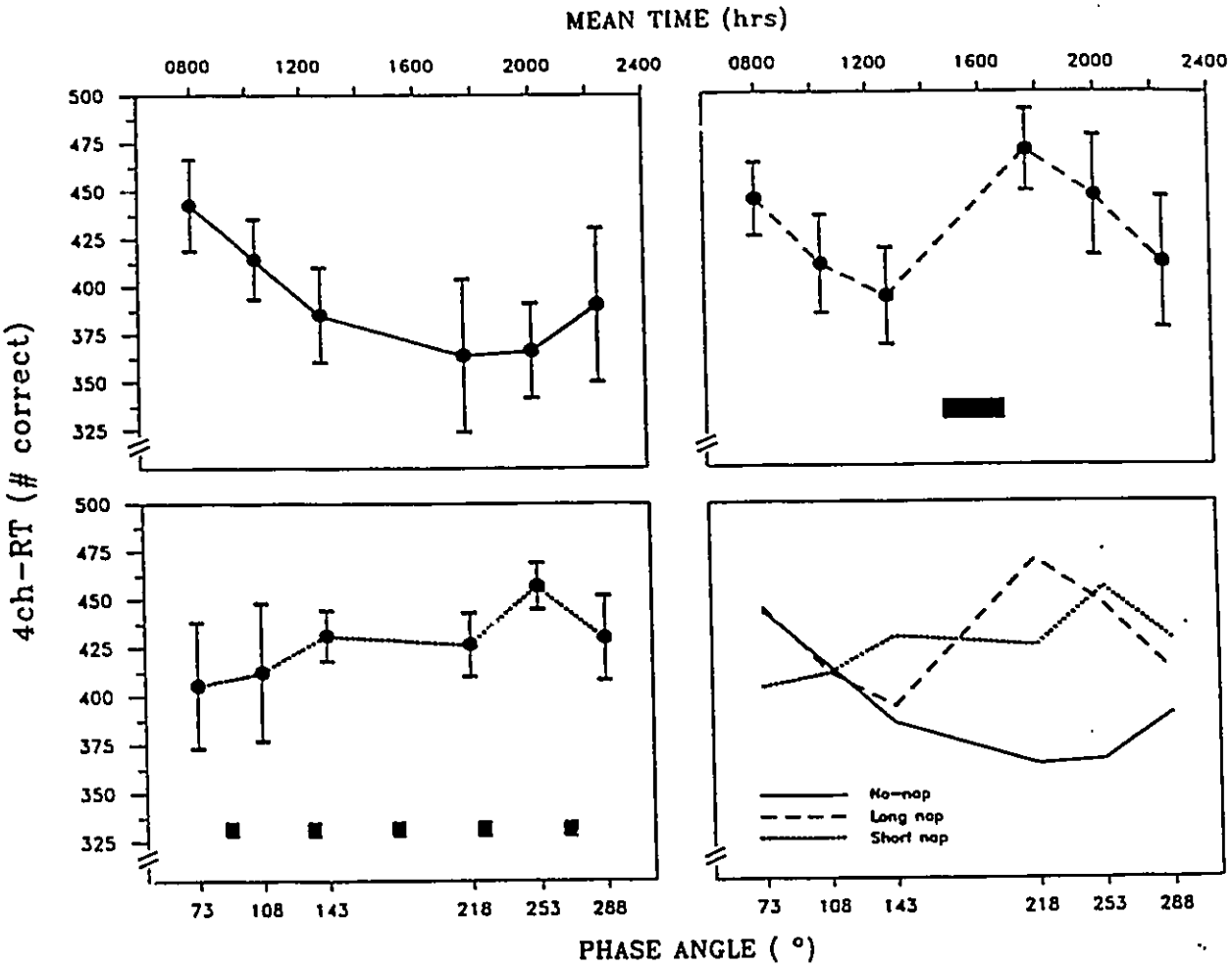

FIGURE 4.4: Performance on serial four-choice reaction time for all three sleep/wake schedules. Number correct (mean 1,SE) are plotted as a function of sleep/wake schedule and time-of-day as in Fig. 4.3.

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 (Roehrs et al. 1986; Billiard 1976; and Godbout and Montplaisir 1986) 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 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 24h was held constant. While 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 min 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 min 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. While there was a trend towards 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 (Angus and Heselgrave, 1985; Heselgrave and Angus, 1985), but while this test has undergone assessment (Carter et al. 1981), results of its use with narcoleptic or other clinically sleepy subjects have not been published. However, there is some suggestion that logical reasoning can be maintained with very little sleep. For instance, Webb (1985) found only a 3% decrement in performance on this test in subjects permitted to sleep for only 4h within a period of 60h 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 (Naitoh et al., in press).

The grammatical transformation test assesses logical reasoning performance, i.e., it 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 (Angus and Heselgrave 1985; Heselgrave and Angus, 1985). While 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 conditions. Certainly the test results were different than those reported for memory tasks in untreated and treated narcoleptics which, due to apparent motivation effects, are not different from normals (Aguirre et al. 1975). 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 which 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 long nap condition is underscored by the finding that the sleep characteristics themselves did not change significantly. Sleep structure remained essentially constant despite the different circadian manipulations made in the three schedules. It is not surprising that REM was somewhat increased in the short naps condition, owing to the number of sleep onset REM periods, but this increase was not significant. While the amount of SWS was not significantly different across conditions,

there was a rather high amount seen overall. However, two of the subjects were quite young (19 and 22), and a third subject was taking GHB, a drug known to increase slow wave activity (Broughton and Mamelak, 1980). 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 (Billiard, 1976; Godbout and Montplaisir, 1986).

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 during 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 (Dinges, 1989). This is consistent with our findings elsewhere in 24h ambulant home recordings (Mullington et al., 1990) of a phase advance in the timing of day sleep relative to that of nocturnal sleep in narcolepsy. Similarly, a Lavie (1991a) 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 abnormality 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 has been shown to be sensitive to sleep deprivation in normal subjects and has also demonstrated significant improvement following naps under a variety of experimental conditions. While the grammatical transformation and descending subtraction 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 performance data, we have collected subjective estimates for a number of adjectives designed to tap into cognitive versus physiological sleepiness. These data will be reported elsewhere.

In summary, the results of this study are supportive of the potential utility of napping strategies for the management 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 profitably 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.

CHAPTER 5

Daytime sleep inertia in narcolepsy-cataplexy

Summary

Eight volunteers with narcolepsy-cataplexy participated in a study of scheduled naps and performance. Sleep inertia was examined following five "short" naps of 5% and a single "long" nap of 25% of total 24-hour sleep time as determined by prior sleep log data. Contrary to some subjective reports, short naps (mean duration of just under 30 min) were accompanied by sleep inertia in narcoleptics. As measured by the descending subtraction task, this sleep inertia can be quite prolonged, and lasted 20 minutes after waking from mid-day short naps which ended on average at 1555h. In addition, sleep inertia as measured by both the descending subtraction task and the four-choice reaction time test was evident throughout both afternoon and evening short naps; however, it was completely absent from reaction time test results immediately following the single long nap (which ended on average at 1640h). Sleep inertia was maximum after SWS arousals and was absent following the first short nap, which also contained the highest amount of REM sleep of all naps.

Napping strategies have been shown to be useful under conditions of sustained operations in which sleep is either markedly reduced or divided into multiple sleep episodes, thereby depriving subjects of a single consolidated nocturnal sleep period (for reviews see Dinges, 1989; Naitoh and Angus, 1989; Stampi, 1989; Dinges and Kribbs, 1991). The benefits obtained from napping strategies depend on at least four factors: amount of prior wakefulness, circadian nap placement, physiological nature and nap duration. However, napping can also have negative effects, one of which is the possible production of "sleep inertia" defined as (usually transient) performance impairment occurring during wakefulness following arousal from sleep. If this impairment is significant in degree and/or duration, it will decrease the "cost effectiveness" of naps. Sleep inertia is therefore an important factor to consider when planning a napping strategy for so-called sustained performance studies on clinical therapeutic applications.

In narcolepsy-cataplexy earlier studies employing performance measures were generally not supportive of sustained benefits for napping. However, performance was not tested with high frequency throughout the day but, rather, just prior to and immediately following naps (Billiard, 1976; Godbout and Montplaisir, 1986). In such studies any real benefits of napping could be obscured by sleep inertia, when results of subjects tested immediately or shortly after waking are averaged into those after sleep inertia has worn off. We have recently reported sustained benefits for napping when tests immediately upon waking were excluded from analysis (Mullington and Broughton, in press).

While sleep inertia in narcolepsy-cataplexy has not been systematically studied, there are some anecdotal reports and clinical observations suggesting that their naps, particularly involuntary "sleep attacks", are refreshing and apparently lack significant sleep inertia effects (Zarcone, 1973; Mitler et al., 1987; Broughton, 1989c). However, Valley and Broughton (1981;1983) found evidence for sleep inertia following brief episodes of drowsiness and light sleep inherent in "waxing and waning" EEG patterns during performance testing. These studies compared the performance of narcoleptic subjects on the Wilkinson (1970) auditory vigilance task during "sustained wakefulness" and "fragmented wakefulness", the latter defined as wakefulness which followed brief episodes of drowsiness patterns of slowed alpha (stage 1A) and deeper levels of sleep (stages 1B and 2). In fragmented wakefulness, performance on the task was significantly reduced, indicating existence of a "drowsiness inertia" effect.

In normal non-sleep deprived subjects, the process of awakening is typically gradual. Sleep inertia following afternoon naps has been studied in non sleep-deprived normals using the descending subtraction test (DST) and reaction time tests. A simple reaction time test found persistent sleep inertia effects lasting some 5 min following afternoon naps in normal subjects (Webb and Agnew, 1964). Dinges and colleagues (Dinges et al., 1981; 1985) found substantial levels of sleep inertia on the DST following 1 and 2 hour afternoon naps in non sleep-deprived normals which consisted of a 25-26% reduction from pre-sleep levels. These effects dissipated within 35 min following nap termination (Dinges et al., 1981). Sleep inertia as measured by the DST has been reported to increase following sleep deprivation, and to be most pronounced at the

circadian nadir (Dinges et al., 1987). The latter study also found that the performance decrement following naps was related to SWS awakenings and to the prior amount of SWS as has been found for nocturnal awakenings (cf. review, Broughton, 1985a).

In a study of normal subjects with reduced nocturnal sleep (to 4 hrs) and replacement naps of 20, 40 and 80 min duration (totalling 4 hrs), degree of sleep inertia was also related to nap duration (Stampi et al., 1990b). Sleep inertia was least apparent following naps of 20 min, was greatest following those 50 min in duration, and was intermediate following 80 min naps. Slow wave sleep was the most frequent stage at arousal for naps of 50 min duration, further corroborating the association between SWS awakenings and decreased performance.

The present study was designed both to investigate the efficacy of napping strategies to alleviate daytime sleepiness in narcolepsy-cataplexy, and to investigate sleep inertia effects associated with daytime naps. Results from parallel analyses documenting the sustained benefits of napping on reaction time performance sampled between naps have been reported elsewhere (Mullington and Broughton, in press). This paper reports our results concerning sleep inertia. Despite the commonly reported subjective experience of narcoleptics that naps are refreshing and lack lingering grogginess, we hypothesized that performance would be impaired following the daytime naps, based on the already cited objective existence of sleep inertia in this condition and on various reports with normal subjects. It was further postulated that performance would be highly

associated with SWS arousals and more severely impaired following awakening from long rather than short naps. In addition, time-of-day effects were expected; specifically it was anticipated that sleep inertia might be more pronounced for naps occurring around the midday period of increased sleep propensity.

Methods

Subjects

Eight narcoleptic patients, 4 male, 4 female, average age 42.7 years (range 19-55), participated in the study. All had a history of more or less irresistible sleep "attacks", excessive daytime sleepiness and cataplexy. All exhibited sleep onset latencies under 5 min and at least 2 REM sleep onset periods as determined by prior MSLT and/or 24h ambulant polysomnographic monitoring. All subjects were free of stimulant medications for at least 10 days prior to the commencement of the study. Three subjects were taking tricyclic medications to control cataplexy and were not required to stop; and one subject who was taking gamma-hydroxybutyrate (GHB), continued with this medication throughout the study period. More extensive patient details are provided elsewhere (Mullington and Broughton, in press).

Procedure

The study was carried out in a quiet rural setting at a bed and-breakfast inn. Four subjects participated at a time and remained on site for 8 consecutive days. The first two days were ad-libitium "adaptation" days during which subjects were free to sleep whenever they wished but were requested to do performance tests immediately prior to commencement of, and immediately following each nap. At other times, excluding mealtimes, subjects performed a test session every 30 min.

Following the adaptation days, three treatment protocols were administered in counterbalanced order, each maintained for 2 days with the first being a practice day, and the second a test day. For all three conditions individual sleep-wake schedules were based on the average total sleep time of each subject as determined from at least 5 days of stimulant free baseline sleep log data. In all schedules nocturnal midsleep time was maintained constant.

The three treatment protocols consisted of a no-nap condition, in which daytime naps were not permitted, and two napping conditions, both of which involved reducing nocturnal sleep time to 75% of the individual 24h average as determined by the baseline sleep logs. The remaining 25% of total sleep time was scheduled either as a single long afternoon nap or as 5 short naps spaced equidistantly throughout the waking period. In all three conditions total scheduled sleep time per 24h was held constant and equivalent

to the individual daily average as determined by the baseline sleep logs. The division of 75% nocturnal to 25% nap sleep was chosen because of results of a previous ad-lib home ambulant EEG study in which narcoleptic subjects were found on average to sleep for 76% during the nocturnal period and 24% during the day (Broughton et al., 1988).

The long nap was taken in the afternoon, because the well known period of mid-day sleepiness has also been demonstrated in narcoleptics (Broughton et al., 1988; Richardson, et al., 1978). Its precise timing was chosen as 180 degrees out-of-phase with the nocturnal midsleep time, since this has been found to be the time of most frequent napping in normal subjects (Dinges, 1989; Richardson et al., 1982; Lavie, 1986). The short naps were placed equidistantly throughout the day with the scheduled midsleep time of the third short nap also placed at 180 degrees out-of-phase with the nocturnal midsleep time. The mean scheduled mid-nap times (to nearest 5 min) were: for the long nap, 1540; and for the short naps 0950, 1245, 1540, 1835, and 2130 h. Subjects were continuously supervised outside of sleep periods. The group setting was beneficial in that subjects were able to help monitor and motivate one another.

Performance tests and sleep-wake schedules were administered by lightweight notebook computers. These were left running for the duration of the study and informed the subjects (by alarm) when to go to bed, when to get up and when to do a performance test. Software details are provided elsewhere (Rivers et al., submitted). The entire protocol took approximately 180 hours for each subject to complete and

resulted in totals of over 1,000 hours of physiological recordings and over 1,000 test sessions.

The performance tests were administered in a fixed sequence to keep constant their times from waking. Each test session lasted approximately 13 min and included (in order of presentation): the descending subtraction test (2 min) (Dinges et al., 1981, Dinges et al., 1985), a grammatical transformation test (2 min) (Wilkinson and Houghton, 1975), four-choice reaction time test (5 min) (computerized version after Wilkinson and Houghton), grip strength test (Aschoff et al., 1972), a measure of oral temperature, the Stanford Sleepiness Scale (Hoddes et al., 1973) and a number of additional subjective evaluation questions derived primarily from Thayer's (1978) activation-deactivation checklist. On the practice days, test sessions were administered at hourly intervals. Tests on nap treatment days were administered approximately 15 min prior to a nap, immediately following a nap, 20 minutes after nap termination and at regular half-hourly intervals thereafter until the next sleep period (excluding mealtimes). Subjects performed an average of 28.5 test sessions on test days and 20.2 on practice days.

At the start of test sessions (and bed periods) subjects were instructed to press both the event marker on a Medilog ambulant recorder and a designated computer key, so that physiological and performance data could be synchronized. Physiological data were recorded with the Oxford 9000 Medilog using a montage consisting of EEG from

C3-M2, C4-M1, O1-M2; left and right electro- oculogram (REOG-M1, LEOG-M2); and submental EMG. In addition, EKG and tympanic temperature were recorded. For each of the counterbalanced conditions, electrodes were applied between test sessions during the evening of the adaptation day and left on for approximately 36 hours. In this way, all nights and the test day of each condition were recorded. Recordings were printed out at 20 times real time using a Medilog 9000 playback unit and Siemens- Elma Mingograph polygraph. Paper records were scored using 30 sec epochs. Sleep was scored according to criteria of Rechtschaffen and Kales (Rechtschaffen et al., 1968) and wakefulness was divided into active and quiet wakefulness according to criteria of Volk et al., (Rechtschaffen et al., ,1968; Volk et. al., 1984). In addition, drowsiness consisting of slowing of the alpha rhythm with or without slow rolling eye movements (stage 1A) was scored according to criteria of Valley and Broughton (1981). Stage 1B was scored identical to stage 1 of Rechtschaffen and Kales (1968).

Performance testing for sleep inertia

The descending subtraction test was included in the test battery primarily for its known sensitivity to sleep inertia; it was therefore first in the sequence of tests. The DST ran for 2 min. In this test subjects were first presented with a randomly generated 3-digit number between 500 and 999. They were instructed to begin subtracting backwards starting with 9, enter the subtrahend into the computer and continue by subtracting 8 from the remainder, then 7, and to continue with the descending sequence

until 2, after which point they were to start the cycle of descending subtraction again. The cycle of subtraction was continued for the remainder of the test, when the computer automatically ended the session and calculated and stored the number completed, number and percent correct, and number of errors.

The four-choice reaction time test followed and continued for 5 min. The test consists of four diodes which illuminate randomly, the subjects being requested to press a corresponding button as soon as possible. The computer saved the following dependent measures: number completed and number correct per test session; overall mean reaction time and its standard deviation; number, mean and standard deviation of correct responses without gaps, of wrong responses without gaps; number of gaps and their mean duration and standard deviation.

Results

All subjects were able to sleep during each of the naps. There was some concern as to whether subjects would be able to sleep for 25% of their total sleep time in one long midday nap, but only one subject woke up more than 4 min before the buzzer sounded (15 min earlier). In the short naps condition, none of the subjects awakened in advance of the buzzer, however, 3 subjects continued to sleep through their awakening alarms, despite the fact that they continued to sound. Two of these instances occurred

following the fourth short nap, one by 7 min and one by 16.5 min and the other was after the 5th short nap, when one subject overslept by 14.5 min.

Sleep Architecture

Data from the multiple short naps condition were combined and compared with those from the single long naps. For percent stage data long naps had significantly greater stage 4 and SWS than short naps; and there was a trend towards reduced REM sleep ($p.<.10$). Stage data analyzed by duration in minutes revealed only trends towards greater amounts of SWS and stage 4 for the long nap compared with all short naps combined. Table 5.1 provides sleep stage data for each of the naps separately, analyzed as number of minutes and percent of total sleep time.

TABLE 5.1. *Nap sleep architecture*[a]

	LONG NAP		SHORT NAPS									
			FIRST		SECOND		THIRD		FOURTH		FIFTH	
MINUTES												
Stage 1B	11.1	(7.6)	1.6	(1.9)	2.6	(2.0)	3.2	(2.0)	2.8	3.0)	5.3	7.0)
Stage 2	22.6	(5.4)	1.8	(2.5)	5.0	(5.2)	5.3	(3.3)	3.6	(4.1)	4.1	(4.4)
Stage 3	6.3	(5.9)	0.9	(1.7)	1.4	(1.8)	0.7	(1.1)	2.4	2.7)	1.4	(2.0)
Stage 4	41.1	(13.5)	3.0	(5.6)	2.4	(4.3)	1.8	(4.8)	7.8	(10.6)	6.0	(9.7)
SWS	47.4	(14.6)	3.9	(7.3)	3.7	(5.8)	2.4	(5.6)	10.3	(12.8)	7.4	(10.7)
REM	35.9	(9.0)	16.6	(8.2)[b]	10.9	(8.6)[b]	13.0	(9.6)	9.3	(7.3)[b]	7.4	(4.8)[b]
PERCENT												
Stage 1B	9.4	(6.5)	6.6	(8.6)	11.5	(8.8)	13.9	(10.4)	13.4	(17.7)	22.3	(27.7)
Stage 2	19.6	(6.2)	7.8	(11.8)	22.2	(22.3)	23.4	(15.9)	15.0	(18.0)	17.3	(19.9)
Stage 3	5.5	(5.0)	3.8	(7.0)	6.2	(8.3)	3.3	(5.3)	8.8	(9.5)	5.4	(8.3)
Stage 4	34.8	(9.6)[c]	12.0	(22.3)	11.0	(19.9)	6.9	(18.3)[c]	23.1	(29.3)	18.9	(26.8)
SWS	40.3	(10.0)[c]	15.6	(29.2)	17.2	(27.2)	10.1	(21.7)[c]	31.9	(34.6)	24.3	(32.5)
REM	30.4	(6.1)	69.9	(33.1)	49.3	(37.7)	52.8	(36.1)	40.0	(36.4)	36.1	(30.1)
SE	92.6	(6.9)	93.6	(4.5)	88.4	(10.1)	92.5	(4.1)	89.1	(9.2)	87.0	(17.1)
REMeff	80.0	(20.3)	97.1	(2.8)	96.2	(5.1)	94.7	(10.4)	90.5	(12.1)	89.7	(21.0)

[a] Values are in means with standard deviations in brackets. REMeff=REM sleep efficiency.

[b] Minutes of REM sleep in the 1st short nap was greater than in naps 2, 4, and 5, p.<0.05.

[c] Stage 4 and SWS percent were greater in the long than in the 3rd short nap, p.<.02 (both mid-nap times matched 180° from nocturnal midsleep).

To investigate time-of-day effects with respect to sleep stage content, repeated measures analysis of variance was performed across multiple short naps and a significant effect was found for minutes of REM sleep ($F(4,28)=3.09$, $p<0.05$). Further testing found significantly more minutes of REM sleep in the first nap compared with to the second, fourth and fifth naps. No other stage comparisons reached significance. The means also indicated a non-significant trend towards higher amounts of SWS in the 4th and 5th naps.

Comparisons were made between the single long and the third short nap (matched at 180° out of phase with the nocturnal midsleep time) using percent data. The long nap had significantly more stage 4 and total SWS. No other comparisons reached significance.

Performance Results

Sleep inertia can be operationally defined as a decrement in performance tested immediately upon waking from a nap compared with pre-nap performance. Due to the inherent directionality of sleep inertia, one-tailed Student's paired t-tests were employed for the testing of performance measures with the alpha level of rejection set at .025.

Table 5.2 summarizes performance on the descending subtraction test for pre-nap, immediate post-nap, and 20 min and 50 min post-nap sessions. It also provides results of direct pre-versus post-nap statistical comparisons. Data is presented for all naps combined, for long naps, for all short naps combined, and for individual short naps. Tables 5.3 and 5.4

present reaction time data for pre-and post-nap testing comparisons. Data for all naps combined, long naps and all short naps combined are presented in Table 5.3; and data for the individual short naps are presented in Table 5.4.

TABLE 5.2. *Descending subtraction test results*[a]

	Pre-Nap		Post-Nap		+20 min		+50 min		Pre- vs Post-[b]
NUMBER COMPLETED									
ALL NAPS	18.5	(3.0)	17.1	(3.0)	18.5	(3.0)	19.4	(3.0)	p<.05
LONG NAPS	18.9	(2.7)	15.6	(2.9)	15.9	(3.2)	17.5	(2.8)	p<.05
SHORT NAPS COMBINED	18.4	(3.1)	17.4	(3.0)	19.1	(3.1)	19.8	(3.0)	ns
FIRST	18.1	(3.2)	20.1	(3.3)	20.1	(3.9)	20.9	(3.9)	ns
SECOND	17.5	(3.8)	16.4	(3.5)	18.9	(3.2)	20.8	(3.2)	ns
THIRD	20.9	(3.3)	18.1	(3.4)	17.9	(3.2)	19.4	(3.3)	ns
FOURTH	17.8	(3.6)	16.0	(3.0)	18.6	(2.9)	20.6	(3.1)	ns
FIFTH	17.8	(2.9)	16.1	(3.2)	19.9	(2.9)	17.5	(2.2)	ns
NUMBER CORRECT									
ALL NAPS	16.8	(3.1)	14.3	(3.0)	16.7	(3.2)	17.7	(3.1)	p<.025
LONG NAPS	16.5	(2.6)	12.8	(3.0)	14.0	(3.5)	15.1	(3.0)	ns
SHORT NAPS COMBINED	16.8	(3.3)	14.7	(3.0)	17.2	(3.3)	18.3	(3.1)	ns
FIRST	15.8	(3.3)	17.4	(3.6)	18.1	(4.5)	19.3	(4.0)	ns
SECOND	15.8	(4.1)	13.3	(3.5)	17.6	(3.2)	19.1	(3.5)	ns
THIRD	19.6	(3.4)	14.5	(3.5)	15.3	(3.4)	17.4	(3.1)	p<.025
FOURTH	16.5	(3.8)	14.9	(2.9)	17.3	(2.8)	19.5	(3.4)	ns
FIFTH	16.5	(3.1)	13.3	(3.1)	17.8	(3.2)	16.0	(2.3)	p<.01

[a] Values are in means with standard errors in brackets. Dur'n=average reaction time response latency; SD=average standard deviations; Gaps=responses with latency of 1000msec or more; Pre=pre-nap test session; Post-=post-nap test session; +20=test sessions 20min following end of nap period; +50=test sessions 50 min following end of nap period.

[b] P-values are for one-tailed paired t-tests, 7df, with alpha level of rejection set at .025; for pre-nap versus immediate post-nap comparisons. Results approaching significance (p<0.05) are also included in the table.

TABLE 5.3 (Part a). *Four-choice reaction time data for all naps combined, single long nap and multiple short naps combined*[a]

	ALL NAPS				
	Pre-		Post-		p[b]
OVERALL					
Total Completed	436.6	(18.2)	388.5	(22.3)	*.05*
Total Correct	406.5	(22.8)	361.6	(23.9)	*ns*
Dur'n.	517.2	(43.7)	663.2	(96.3)	*ns*
SD	526.5	(141.7)	1245.4	(615.1)	*ns*
CORRECT (No Gaps)					
No.	394.8	(25.7)	345.2	(26.9)	*ns*
Dur'n.	418.9	(17.7)	448.7	(16.0)	.01
SD	110.3	(13.4)	126.4	(13.2)	*.05*
WRONG (No Gaps)					
No.	27.2	(5.9)	24.5	(5.9)	*ns*
Dur'n.	381.5	(23.9)	423.3	(38.7)	*ns*
SD	147.1	(19.3)	164.6	(17.7)	*ns*
GAPS					
No.	15.7	(4.1)	18.9	(4.7)	*ns*
Dur'n.[c]	2137.9	(260.5)	2811.4	(628.6)	*ns*
SD[c]	1803.2	(481.6)	3514.9	(1820.1)	*ns*

[a] Values are in means with standard errors in brackets for 8 subjects (unless otherwise indicated). Dur'n=average reaction time response latency; SD=average standard deviations; Gaps=response with latency of 1000msec or more; Pre-=pre-nap test session; Post-=post-nap test session.

[b] Paired t-tests (one-tailed) were performed on pre- and post-nap performance data, with alpha set to $p<0.025$. Comparisons which approached significance ($p<0.05$) are also reported in the table.

[c] For all naps and for multiple short naps combined, N=6 for pre- post-nap comparisons of Gap Dur'n and Gap SD. For the single long pre- post-nap comparisons of Gap SD, N=7.

TABLE 5.3 (Part b). *Four-choice reaction time data for all naps combined, single long nap and multiple short naps combined*[a]

	SINGLE LONG NAP					MULTIPLE SHORT NAPS COMBINED				
	Pre-		Post-		P	Pre-		Post-		P
OVERALL										
Total Completed	387.8	(40.1)	422.1	(29.4)	*ns*	446.4	(18.9)	381.8	(26.1)	.025
Total Correct	364.1	(43.9)	408.8	(31.0)	*ns*	415.0	(23.5)	352.2	(27.5)	*.05*
Dur'n.	668.7	(137.2)	543.2	(63.5)	*ns*	486.9	(39.9)	687.2	(117.6)	*ns*
SD	890.4	(480.4)	538.4	(261.6)	*ns*	453.7	(121.7)	1386.7	(738.6)	*ns*
CORRECT (No Gaps)										
No.	346.5	(48.2)	392.6	(34.3)	*ns*	404.5	(26.4)	335.7	(30.8)	*.05*
Dur'n.	456.8	(21.3)	437.6	(12.9)	*ns*	411.4	(18.7)	450.9	(18.4)	.01
SD	120.0	(17.8)	117.7	(12.8)	*ns*	108.4	(13.2)	128.2	(13.8)	*.05*
WRONG (No Gaps)										
No.	19.8	(5.7)	12.6	(2.1)	*ns*	28.7	(6.1)	26.8	(6.8)	*ns*
Dur'n.	425.2	(28.6)	419.3	(32.0)	*ns*	369.8	(24.4)	426.1	(42.0)	*ns*
SD	148.2	(31.0)	158.7	(23.2)	*ns*	128.4	(18.5)	151.3	(24.5)	*ns*
GAPS										
No.	21.5	(7.5)	16.9	(3.8)	*ns*	14.6	(4.0)	19.4	(5.5)	*ns*
Dur'n.[c]	2173.7	(502.9)	1949.7	(344.5)	*ns*	2084.8	(260.4)	3031.7	(752.3)	*ns*
SD[c]	2075.5	(1032.7)	1516.8	(578.2)	*ns*	1714.4	(519.2)	4029.7	(2181.6)	*ns*

[a] Values are in means with standard errors in brackets for 8 subjects (unless otherwise indicated). Dur'n=average reaction time response latency; SD=average standard deviations; Gaps=response with latency of 1000msec or more; Pre-=pre-nap test session; Post-=post-nap test session.

[b] Paired t-tests (one-tailed) were performed on pre- and post-nap performance data, with alpha set to $p<0.025$. Comparisons which approached significance ($p<0.05$) are also reported in the table.

[c] For all naps and for multiple short naps combined, N=6 for pre- post-nap comparisons of Gap Dur'n and Gap SD. For the single long pre- post-nap comparisons of Gap SD, N=7.

Table 5.4 (part a). *Four-choice reaction-time data for all short naps*[a]

	FIRST					SECOND					THIRD				
	Pre-		Post-		P	Pre-		Post-		P	Pre-		Post-		P
OVERALL															
Total Completed	396.1	(41.7)	349.3	(46.0)	*ns*	449.3	(20.6)	358.2	(48.1)	*ns*	451.5	(18.6)	393.8	(37.1)	*.05*
Total Correct	346.4	(52.3)	321.1	(48.4)	*ns*	423.5	(26.2)	331.1	(50.0)	*ns*	416.3	(24.6)	359.8	(39.3)	*.05*
Dur'n	620.8	(106.7)	835.8	(250.8)	*ns*	475.2	(38.0)	912.4	(333.6)	*ns*	465.5	(30.2)	592.8	(90.4)	*ns*
SD	1060.1	(378.6)	2172.7	(1559.6)	*ns*	348.5	(97.7)	2994.3	(2244.3)	*ns*	335.3	(72.2)	621.0	(283.0)	*ns*
CORRECT (No Gaps)															
No.	331.6	(56.3)	304.5	(51.4)	*ns*	418.3	(30.6)	316.5	(51.4)	*ns*	402.0	(27.3)	340.8	(43.5)	*.05*
Dur'n	428.2	(22.1)	466.0	(23.1)	*.05*	410.9	(18.1)	434.4	(13.1)	*ns*	405.3	(20.2)	451.2	(23.8)	.025
SD	140.2	(18.2)	137.4	(16.2)	*ns*	102.0	(12.3)	130.7	(15.0)	.025	103.2	(14.9)	129.0	(15.1)	ns
WRONG (No Gaps)															
No.	43.8	(13.9)	24.3	(9.4)	*ns*	23.3	(7.2)	24.0	(7.1)	*ns*	32.0	(10.8)	30.8	(7.0)	ns
Dur'n.	347.8	(27.8)	478.4	(60.7)	*.05*	373.9	(27.0)	402.1	(39.0)	*ns*	401.0	(27.3)	402.2	(40.6)	ns
SD	130.6	(28.0)	163.0	(29.2)	*ns*	144.0	(28.2)	167.4	(28.8)	*ns*	135.0	(22.6)	150.2	(25.0)	ns
GAPS															
No.	20.8	(7.5)	20.5	(6.6)	*ns*	14.3	(5.2)	17.6	(4.2)	*ns*	17.5	(5.3)	22.3	(7.0)	ns
Dur'n.	2848.2	(693.4)	3775.6	(1444.1)	*ns*	1730.4	(188.6)	4727.8	(1970.1)	*ns*	1772.8	(194.1)	2111.7	(385.8)	ns
SD	3463.4	(1637.9)	5969.5	(4041.6)	*ns*	1070.4	(366.4)	8033.6	(6752.8)	*ns*	1256.2	(344.5)	1716.0	(721.0)	ns

[a] Values are provided in means with standard errors in brackets. Dur'n=average reaction time response latency; SD=average standard deviations of response; Gaps=responses with latency of 1000msec or more. Pre-=pre-nap test session; Post-=post-nap test session; P= p<.

[b] Paired t-tests (one-tailed) were performed on pre- and post-nap performance data, with alpha set to p<0.025. Comparisons which approached significance (p<0.05) are also reported in the table.

Table 5.4 (part b). *Four-choice reaction-time data for all short naps*[a]

	FOURTH					FIFTH				
	Pre-		Post-		P	Pre-		Post-		P
OVERALL										
Total Completed	472.5	(19.3)	404.5	(25.9)	.01	462.8	(15.9)	403.5	(29.7)	*.05*
Total Correct	450.3	(18.7)	371.3	(24.8)	.01	438.8	(20.4)	377.6	(32.0)	*ns*
Dur'n	432.0	(27.0)	540.8	(44.7)	.025	441.1	(28.1)	554.1	(61.5)	*.05*
SD	309.6	(77.4)	588.2	(165.1)	*ns*	214.9	(57.6)	557.5	(175.0)	.025
CORRECT (No Gaps)										
No.	440.8	(20.7)	356.3	(28.3)	.01	429.9	(22.5)	360.3	(37.0)	*ns*
Dur'n	401.0	(22.2)	454.9	(18.5)	.01	411.5	(20.4)	447.9	(25.0)	*ns*
SD	98.3	(12.6)	128.1	(13.4)	.01	98.2	(14.4)	115.8	(15.0)	*.05*
WRONG (No Gaps)										
No.	21.9	(6.3)	31.6	(10.0)	*ns*	22.5	(7.2)	23.5	(6.7)	*ns*
Dur'n.	368.8	(30.9)	417.2	(38.8)	*ns*	387.7	(30.5)	413.1	(31.6)	*ns*
SD	110.6	(21.8)	137.7	(17.8)	*ns*	109.7	(14.7)	112.6	(29.4)	*ns*
GAPS										
No.	9.9	(2.5)	16.6	(5.8)	*ns*	10.4	(3.7)	19.8	(7.0)	*ns*
Dur'n.	1782.9	(195.8)	5202.9	(2968.5)	*ns*	1660.2	(161.8)	2177.6	(368.2)	*.05*
SD	1655.4	(516.8)	1535.8	(659.6)	*ns*	563.2	(168.0)	1900.6	(685.4)	*.05*

[a] Values are provided in means with standard errors in brackets. Dur'n=average reaction time response latency; SD=average standard deviations of response; Gaps=responses with latency of 1000msec or more.
Pre-=pre-nap test session; Post-=post-nap test session; P= p<.

[b] Paired t-tests (one-tailed) were performed on pre- and post-nap performance data, with alpha set to p<0.025.
Comparisons which approached significance (p<0.05) are also reported in the table.

Descending subtraction test

The existence of sleep inertia was first tested for all naps (long and short) combined and as significant for the number of correct responses ($p < 0.025$). When performance tested 20 min after waking was compared with the pre-nap level, the difference was no longer significant. Sleep inertia on this test had therefore dissipated within the first 20 minutes following arousal.

Following the single long nap, sleep inertia was not significant for any of the measures; however, it did approach significance for the number of responses completed ($p < 0.05$). For short naps combined, the number completed and number correct were not significant; however, percent correct (pre-nap x = 85.9, 5.8(SE); post-nap x = 79.7, 4.9(SE) and number of errors (pre-nap x = 1.8, 0.4(SE); post-nap x = 2.7, 0.7(SE) both showed strong trends for sleep inertia which approached significance ($p < 0.05$, respectively).

Sleep inertia was also tested for each of the 5 short naps in order to investigate possible time-of-day effects. As seen in Figure 5.1, although descending subtraction number correct demonstrated a significant sleep inertia effect for only the 3rd and 5th naps, the pattern of reduced performance levels is very apparent in all but the first nap which in fact shows mild performance improvement upon awakening.

In addition to the data shown in Table 5.2, following the third nap, sleep inertia was also significant for percent correct on the DST: pre-nap x = 92.5, 4.5(SE); post-nap x = 75.7, 6.9(SE), which demonstrated a prolonged effect, with performance still significantly below pre-nap levels 20 min after waking (x=79.6; 5.6(SE) ($p < 0.025$). By 50 minutes following arousal, sleep inertia had dissipated. This prolonged sleep inertia is illustrated in Figure 5.2.

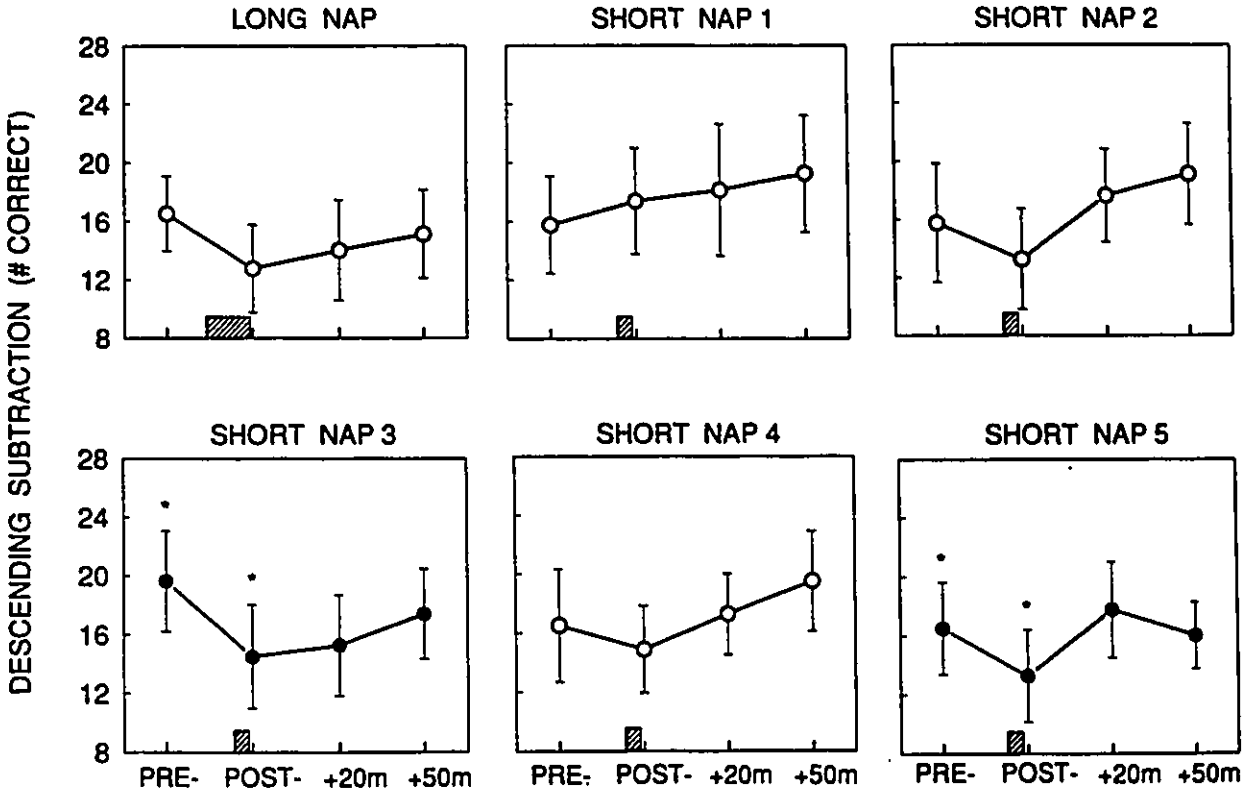

FIGURE 5.1: Descending subtraction test results (number correct). The graph in upper left corner presents across the x-axis, results from the test prior to the nap, immediately following the nap, 20 and 50 min following the single long nap. First to fifth short naps follow in order from left to right. The hatched boxes are schematic representations of scheduled sleep periods. Vertical bars indicate standard errors; significant pre- post-nap comparisons are indicated with asterisks.

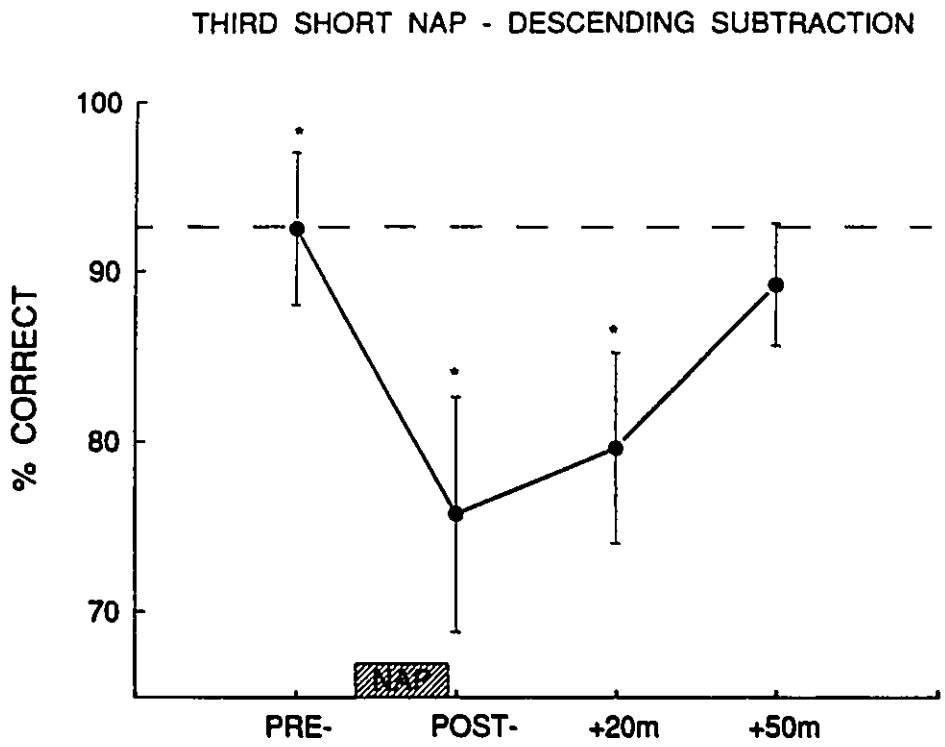

FIGURE 5.2: Persistent sleep inertia following the third short nap for percentage of correct responses made on the descending subtraction test. Test sessions are indicated along the x-axis from left to right: pre-nap, immediate post-nap, 20 and 50 minute following the end of a nap period. The nap is schematically indicated by the hatched box and vertical bars represent standard errors. Significant pre-post-nap comparisons are indicated with asterisks.

Four-choice reaction time test

For all naps combined, significant sleep inertia was present for the average reaction time of correct responses without gaps ($p < 0.01$). As with the descending subtraction results for all nap data, sleep inertia dissipated within the first 20 min following arousal. A trend was also evident for sleep inertia in the number of reaction time responses made during test sessions following naps ($p < 0.05$).

Contrary to our hypothesis that long naps would show greatest sleep-inertia effects, reaction time test results failed to demonstrate even a trend in that direction. In fact, as can be seen in Fig 5.3, a clear improvement was seen immediately following long naps for average reaction time involving correct responses without gaps, which continued to improve in subsequent testing. Using a .05 alpha level of rejection, post-hoc analyses found this improvement to be significant 50 min after waking compared to the pre-nap level ($p<0.02$, two-tailed Student's paired t-test).

For short naps combined, a strong trend for sleep inertia was present in the reaction time data which reached significance for number of reaction time responses per session ($p<0.025$) and for reaction time of correct responses without gaps ($p<0.01$). In addition, sleep inertia approached significance as measured by the overall total number of correct responses per session, the number of correct responses without gaps, and the standard deviations of correct reaction times without gaps (all $p<0.05$). As was found for all naps combined, sleep inertia dissipated within the first 20 minutes following the naps.

In the analysis of short naps, the variables which demonstrated significant sleep inertia for all five short naps combined, i.e., total number of responses per session and average reaction time of correct responses without gaps, both demonstrated significant sleep inertia following the 4th nap. The number of reaction time responses per session also demonstrated significant sleep inertia following the 4th nap ($p<0.01$); but this inertia was no longer significant 20 minutes following arousal. Average reaction time of correct

responses without gaps (Fig. 5.3) demonstrated significant sleep inertia following both the 3rd and 4th naps, ($p<0.02$ and $p<0.01$ respectively); and this inertia had also dissipated 20 min after the nap.

As seen in Tables 5.3 and 5.4, sleep inertia was also significant following the fourth nap for number of correct reaction time responses completed and for average overall reaction time, ($p<0.01$ and $p<0.02$, respectively). Standard deviation of overall average reaction time data showed sleep inertia effects for the 5th nap ($p<0.025$). Standard deviation of average correct reaction time responses showed significant effects for both the 4th and 2nd naps ($p<0.01$ and $p<0.025$), respectively. The number of correct responses

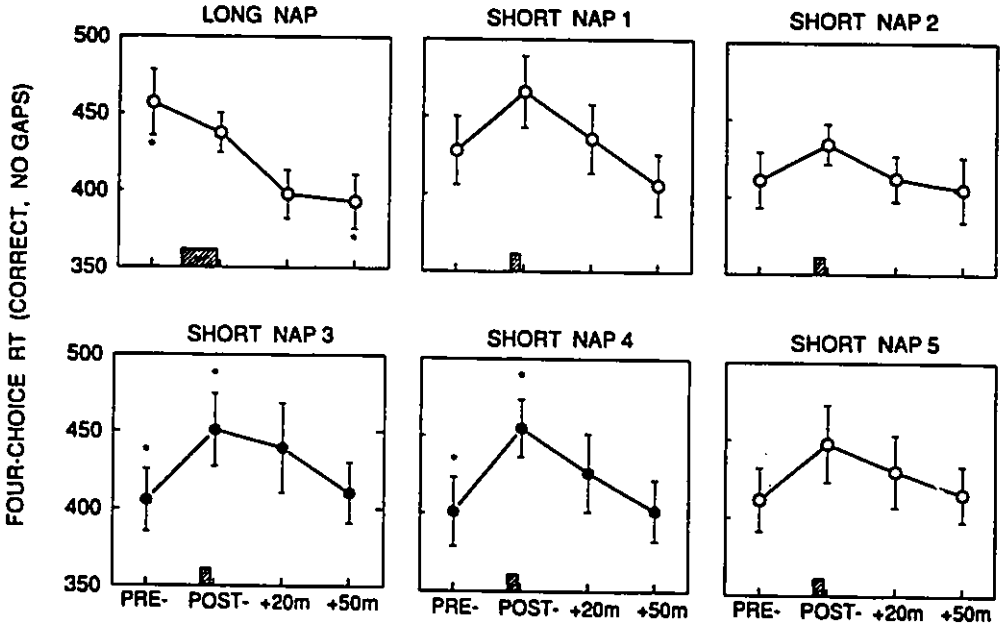

Figure 5.3: Four-choice reaction time (msec) for correct responses without gaps. As in Figure 1, the single long nap is in the upper left corner, followed from left right by the first to fifth short naps. Test sessions are indicated along the x-axis and include pre-nap, immediate post-nap and 20 and 50 min post-nap tests. Nap periods are schematically represented by hatched boxes. Standard error bars are included; significant pre- post-nap comparisons are indicated with asterisks.

made without gaps showed significant sleep inertia effects as well for the 4th nap. The overall greater sleep inertia associated with the termination of short naps three and four corresponded to mean phase angles (calculated clockwise from mid- nocturnal sleep) of 183° and 227°, and to mean clock times of 1555 and 1850h.

Long versus short nap sleep inertia

In order to test for differences in sleep inertia between long and short nap performance following naps was transformed to a percent of pre-nap levels (immediate post-nap/pre-nap x 100). This procedure created data reflecting relative sleep inertia. There were no differences in relative sleep inertia for long versus short naps for the descending subtraction variables. Relative sleep inertia was tested between the long nap and each of the 3rd and 4th short naps and was not significant for any of the descending subtraction measures. Relative sleep inertia for the reaction time data was also compared between the single long nap and each of the 3rd and the 4th short naps. When the long nap was compared with the 4th short nap, the average reaction time for correct responses without gaps approached significance ($p=0.05$).

Performance as a function of prior sleep stage

Since subjects did not have equal numbers of wakeups from each stage, one nap was randomly selected from each subject for both REM and SWS arousals, and paired t-tests

performed on relative sleep inertia data surrounding these naps. There were insufficient arousals from stage 2 to perform within-subjects comparisons, as only 3 subjects had wakeups from that stage and either REM or SWS.

Results of within-subjects comparisons are illustrated in Fig 5.4. Sleep inertia was significantly greater when subjects were awakened from SWS compared to REM (116 versus

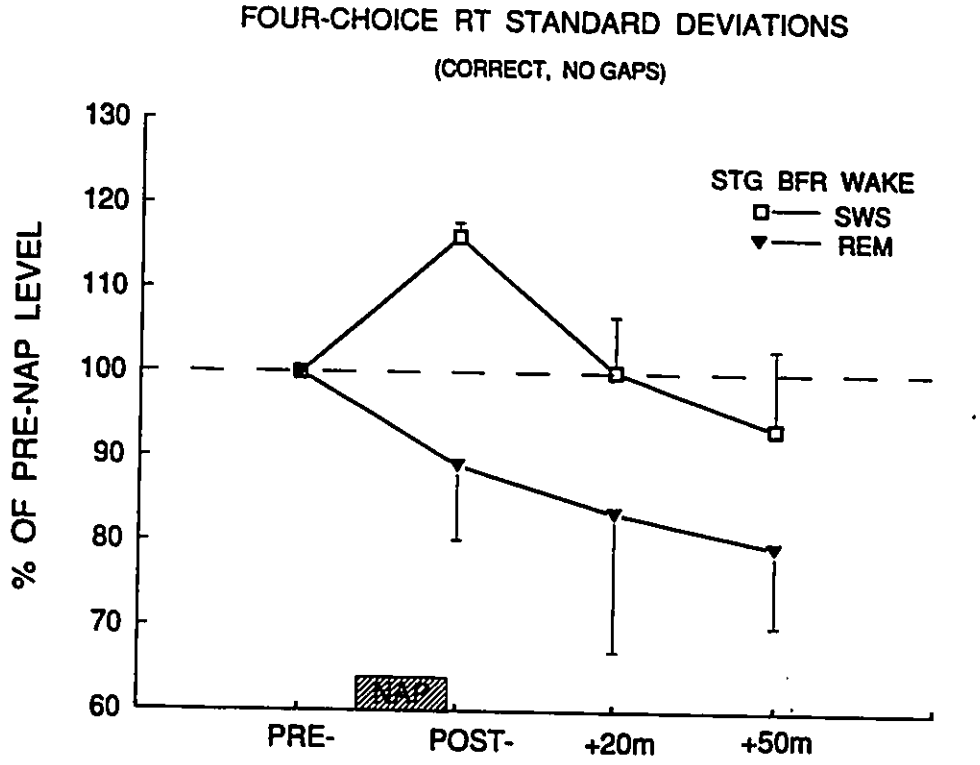

FIGURE 5.4: Four-choice reaction time standard deviations for correct responses without gaps. Date are plotted by stage at awakening, as a percentage of their pre-nap level. The hatched boxes schematically indicate the placement of a nap, and standard error bars are indicated. Performance results are plotted for tests prior to a nap, immediately following nap, 20 and 50 min after nap termination.

89.0%, $p < 0.025$). Although the trend for greater sleep inertia persisted in the subsequent two tests, these differences were not significant. However, because 3 subjects did not have both SWS and REM arousals, only 5 subjects contributed to these analyses.

Discussion

This is the first study to our knowledge which empirically demonstrates sleep inertia effects in narcolepsy. The present study demonstrates appreciable sleep inertia effects following naps of approximately 25 min, in narcoleptics. This finding contradicts those subjective and clinical reports which suggest that naps of narcoleptics lack sleep inertia. Our results for both the descending subtraction test and the reaction time task indicate that sleep inertia is, in fact, quite pronounced following short naps. The exception to this pattern was seen for the first short nap where an actual (non-significant) improvement was noted in the descending subtraction results for the first post-nap test. The additional finding that the first short nap contained by far the greatest amount of REM sleep is consistent with the finding of Broughton and Aguirre (1987) that REM containing MSLT naps have a preferentially refreshing effect (measured by the Stanford Sleepiness Scale) in narcoleptics compared with NREM naps. It is possible that the improvement following short morning (mainly REM containing) naps on the descending subtraction test may be so subjectively striking that this is the basis of the purported lack of sleep inertia in general. The fact that a trend for sleep inertia exists for the first nap on some reaction time measures indicates selective effects on different performance measures.

We found evidence for time-of-day effects. Sleep inertia was in general both greater and more persistent in the afternoon. Persistence was greatest following the 3rd short nap (average wake-up time of 1555h). The midafternoon third short nap showed sleep inertia on the descending subtraction task for the number of correct responses as well as for the percent correct responses; in addition, the third short nap was the only one to show significant sustained sleep inertia 20 min following the nap.

Sleep inertia effects, however, were not restricted to the third short nap. The four-choice reaction-time test results suggest an increasing sleep inertia until after the 4th nap, followed by a levelling-off. This circadian pattern is also supported by the fact that 2 subjects overslept following the 4th nap, and in another, the 5th nap. In addition, most of the SWS arousals occurred following the 4th and 5th naps.

The reaction time results suggest that those variables most sensitive to sleep inertia involve correct performance without gaps. This category in our breakdown of reaction time data most closely approximates the "optimal response range" of Dinges and colleagues (1987), and expresses the optimum of our subjects' response capacity. These results suggest that, following awakening from daytime naps in narcolepsy-cataplexy, performance impairment is not primarily one of post-arousal waxing and waning, microsleeps or sleep attacks, but rather represents a progressive awakening process. The optimal response improvement seen in the first 20 minutes following arousal from naps appears to represent the rallying of cognitive efficiency and the assembling of motor output control.

This study finds that both single mid-day long naps and early morning short naps produce minimal sleep inertia, which is consistent with the sustained performance improvement which was found to follow these naps (Mullington & Broughton, in press). On the other hand, the prevalence of significant sleep inertia under other nap conditions contradicts previous notions that nap sleep of narcoleptics is necessarily immediately refreshing. These data from narcoleptics are consistent with previous reports of normal subjects demonstrating that SWS arousals are associated with decreased perfcrmance (Dinges, Orne, Whitehouse, Orne, 1987; Stampi, et al., 1990a), and are also consistent with reports of sustained benefits of napping in normals.

CHAPTER 6

Conclusions

The studies described in the body of the thesis have brought new knowledge to bear on the organization of the sleep-wake patterns and the pathophysiology of narcolepsy-cataplexy. A phase-advance in the frequency of napping has been found in the ambulatory in-home study (Chapter 2), and seen again for unscheduled sleep in the no-nap condition of the study of the effects of napping (or not) upon performance in this condition (Chapter 4). As reflected in both of these methodological approaches, narcoleptics have an earlier daytime sleep tendency. As previously mentioned, since the time of publication of the phase advance of napping in narcolepsy (Chapter 2), there have been two replications of this finding using very different protocols. One was that of an ultrashort sleep schedule involving 20 min "days" (Lavie, 1991a) and the other using a temporal isolation approach, (Pollak, et al., 1992). It is of interest that illustrations in previous literature on the timing of sleep attacks (Passouant et al., 1968); sleep placement (Billiard et al, 1986) and sleep onset latency (Richardson et al., 1978) in narcolepsy, have also shown this trend, although these authors have not commented on it.

Whether the advance seen in the daytime napping tendency of narcoleptics is related to an alteration in a circadian or circasemidian rhythm of sleep/wake regulation, or to an impairment in the homeostatic mechanisms of sleep warrants further exploration. One way to investigate this issue would be to look at the napping patterns of other pathologically sleepy populations such as sleep apneics, where pathological sleepiness may be as severe as in narcolepsy, but REM-based symptoms are absent. If apneic subjects were found to show a circasemidean sleep propensity pattern similar in timing to the later afternoon sleep propensity of normals, this would be evidence in support of a circasemidian rhythm abnormality in narcolepsy-cataplexy. However, if daytime sleepiness was advanced in both patient groups, the alternative postulated hypothesis that the phase-advance is due to an impairment in the homeostatic regulation of sleepiness would be strengthened.

Daan et al., (1984) hypothesized, in their update of the homeostatic model, that the excessive sleepiness seen in narcolepsy may be attributable to reduced upper and raised lower thresholds for the onset of sleep and wakefulness. According to this conceptualization, narcoleptics would be unable to either accumulate nor deplete the same levels of process S as normals. The frequent naps and sleep attacks associated with the disorder would then be due to an inability to accumulate a sufficient level of process S during the day, and an inability to reduce it during sleep. This hypothesis is in keeping with the model of narcolepsy as a chronically sleep deprived, or at least insufficiently recuperated, state (Rechtschaffen et al., 1963).

The frequent sleep episodes distributed across the day suggests a narrowing of these upper and lower thresholds, with process S frequently reaching the pathologically low threshold for sleep onset. Moreover, the more even redistribution of SWS across the night suggests an abnormality of process S discharge and its time course in that it does not get sufficiently depleted. Residual sleepiness is therefore carried over into wakefulness expressed as shortened wakefulness and sleep periods in a matrix of daytime sleep and wakefulness patterns, repeatedly crossing narrow thresholds.

Another approach for investigating the circasemidian versus homeostatic issue would be to measure the quantified spectral EEG data of 24 hour recordings in normals, narcoleptics and apneics and compare the time course of the different spectral bands through nocturnal sleep and in daytime napping. As mentioned in the Introduction, Broughton and Mamelak (1980) observed a more even distribution across the night of SWS in narcoleptics compared to normals. The recent work of Tafti and colleagues (1992) has also demonstrated a relatively greater degree of delta activity in the latter part of the night in narcoleptics as compared with normal subjects. This may not, as these authors suggest, reflect a normal homeostatic process in narcolepsy; rather, this relatively elevated delta power in the latter part of the night may reflect an inability to fully reduce the accumulated process S in homeostatic terms.

Relevant to the Daan et al., (1984) hypothesis of a reduced threshold in the model is the apparent trend for an approximately 240-260 degree second entrance point to sleep

(Chapter 2) and also the 260 degree entrance point seen in the no-nap condition of the scheduled napping and performance study (Chapter 4). The second prominent napping peak is consistent with a phase time after the first peak from waking of about 90o-100o, i.e., some 6-6.5 hours after the earlier one. But, while this second peak of tendency for napping may reflect a lowered upper threshold, the narrowness of this second point is not obviously in keeping with their model, and warrants further exploration.

The phase advance of the most frequent nap time for narcoleptics can be explained by the phase-amplitude model (presented in Chapter 3) with respect to the endogenous circadian rhythm; more specifically its amplitude and area under the curve. According to this model, napping occurs at a point in circadian time where the metabolic load exceeds its coordinate phase-amplitude level. The amplitude and phase are genetically determined and then shaped or modulated to some extent by repeated associations through conditioning and adaptation effects which are reflected for instance, in morningness and eveningness (Horne, Ostberg, 1976). In the multiple napping studies of normal subjects in our laboratories, we have noted that subjects adapt to experimental sleep schedules, and have higher sleep efficiencies following this adaptational period. The cited works by Lavie which demonstrate sleep "gates" may indicate specific entry facilitation points, highly consistent for the individual, and may mark the conditioned ("learned") effect of sleep facilitation and wake maintenance.

In narcoleptics, the amplitude of circadian body temperature rhythm is reduced and its nadir phase advanced (Mosko et al., 1983). The phase advance may in fact be secondary to the reduced amplitude. According to the phase amplitude model, the capacity of the organism to accept further load varies along a circadian setpoint band, and the drive of the system is to maintain its circadian coordinates of phase and amplitude. Therefore, if the metabolic load is rising too fast, sleepiness will lower the output and both reduce the metabolic load and, if sleep ensues, further enhance this reduction. A reduced circadian amplitude of core body temperature as seen in narcolepsy will, by this construction, lead to an earlier onset of afternoon sleepiness (the phase advance) if metabolic load exceeds the combined phase and amplitude coordinate setpoint, as described in chapter 3.

Concerning the issue of REM versus NREM sleepiness, there were too few NREM sleep onset periods in the data set to further clarify the postulated qualitative or quantitative differences. While it is clear that REM pressure (or facilitation)is enhanced in narcolepsy, with SOREMPs occurring both during daytime and night sleep, and with REM pressure relatively greater in response to repeated arousals from nocturnal REM sleep (Spielman et al., 1986), REM sleepiness results in heightened post-nap performance with relatively little sleep inertia. Thus, while the pressure for REM sleep is certainly enhanced in narcolepsy, the nature of REM sleepiness in narcoleptics does not appear to be different from that of normals. SWS arousals have repeatedly been closely associated with greater impaired performance following nocturnal arousals (reviewed in Broughton, 1985a) as well as following naps (Stampi et al., 1990a;1990b); and the finding for narcoleptics are consistent with this. Conversely, REM arousals have not been associated with significant memory

impairment. The relatively small performance deficit following REM nap arousals in narcoleptics is therefore not surprising.

The prevalence of SOREMPs in this study (85% of naps) clearly demonstrates a pressure for REM sleep. While under standard MSLT conditions (Broughton, 1989) narcoleptics have tended to have about 50% of naps with SOREMPs, it is possible that the cognitive demands imposed by repeated performance tests increased the REM sleepiness pressure, since REM is also associated with cognitive functioning (reviewed in Smith, 1988). Interestingly, narcoleptics complain of memory impairment, but this impairment may be alleviated by frequent REM naps. It appears that for whatever reason, REM sleepiness is inherent in narcolepsy and is preferentially restorative. This is also supported by research of Broughton and Aguirre (1987) who found that narcoleptics fell asleep into REM almost twice as fast as into NREM naps. In addition, they were subjectively more sleepy prior to REM naps, and their higher subjective sleepiness was more reversed after REM versus NREM naps.

The time of day aspects of performance are also worthy of separate comment. It is of interest to compare the time of day pattern of results for 4-choice reaction time number correct data in the multiple naps condition (with post-nap results removed) (Chapter 4), to the sleep inertia results in short naps (Chapter 5). Performance between naps independent of sleep stage inertia effects shows a steady increase across the day with a slight drop before the 5th nap, which continued to decline after this nap prior to subsequent nocturnal sleep

(Chapter 4, Fig 4). Immediate post-nap performance (sleep inertia), on the other hand, is at its worst level following the first nap and improves in a linear fashion across the day, reaching its highest post-nap performance level after the 5th nap (Chapter 5, Fig 3.). This pattern of performance is therefore consistent with the earlier mentioned trends for normals.

Finally, with respect to the practical implications of this research, it is clear that napping can provide at least some alleviation from the symptom of excessive daytime sleepiness in narcoleptics, and if properly timed, that these naps can produce maximal benefits with minimal associated sleep inertia costs. It is clear from these data that narcoleptics are very much like normal subjects in that they have greater sleep inertia following SWS than REM sleep, attain maximal performance benefits from REM containing naps, and benefit from napping for sleepiness. These data hold promise for improving the management of excessive daytime sleepiness in narcolepsy by judicious napping, particularly when tailored to the individual's timing of nocturnal sleep.

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APPENDIX

A Program for Studies of Altered Sleep-Wake Schedules and Performance [1]

MARTIN RIVERS, JANET MULLINGTON and ROGER BROUGHTON [2]

Human Neurosciences Research Unit, Faculty of Medicine, University of Ottawa,
451 Smyth Rd., Ottawa,
Ontario, Canada
K1H 8M5
(tel) 613 787-6634
(fax) 613 738-3191

1. Acknowledgment: This work was supported by a grant (MT-3291) awarded to R.J. Broughton by the Medical Research Council of Canada. Claudio Stampi M.D. helped in early software development and assessment.

2. Address correspondence to : Dr. R.J. Broughton, Division of Neurology, Ottawa General Hospital, 501 Smyth Rd., Ottawa, CANADA, K1H 8L6

ABSTRACT

Studies designed to investigate the effects of variations in sleep-wake schedules on human performance tend to run for several days and involve extensive repeated testing in order to examine time of day and cumulative cross-day effects (Webb, 1982; Monk, 1991; Broughton and Ogilvie, 1992). Such research is typically designed to address issues pertaining to sustained operations and shift work and is often more appropriately conducted in the field. The present paper describes a computer automated system designed to administer sleep-wake schedules and performance tests, and to store results of such testing in file-formats easily accessed by commercially available statistical packages.

OVERVIEW

Various sleep-wake schedule protocols have been used to study performance (Lubin et at 1976; Carskadon et al 1977; Mullaney et al 1983; Tilley et al 1984; Lavie et al 1987; Webb 1987; Dinges 1986; Dinges et al 1987). Fluctuations in performance levels, like those associated with emergency and sustained operations, shift work, jet lag and disorders of excessive sleepiness, are a function of both time-of-day and sleep-wake patterns. In order to properly assess the alteration of sleep-wake schedules, performance testing must be frequent throughout the waking period.

Continuous testing paradigms often involve schedules spanning days or weeks. When several subjects are involved, a trade off exists between capacity for subject supervision and total running time of the experiment. If subjects are run concurrently, increased supervision is required; whereas, if subjects are run sequentially, the total experimental time can become excessive. Computer administration of sleep schedules and performance test sessions has the advantage of reducing the amount of individual supervision needed, thus allowing more subjects to be studied in less time.

The long protocols common in establishing altered sleep-wake schedules often involve some discomfort for the subject, due to sleep deprivation or sleep fragmentation. As a result, personality factors may impact significantly upon subject performance by their influence on the subject's mood and attitude towards the study. In these situations, administration by computer can be beneficial to a study by enforcing the protocol while freeing time for the maintenance of good rapport between subjects and experimenters.

The maintenance of precise timing becomes difficult in the establishment of sleep-wake schedules during multiple days and yet is essential for the investigation of both sleep and chronobiological phenomena. When measuring sleep inertia, it is critical to control test time after awakening, and to ensure that subjects do not fall asleep while performing test sessions (Dinges et al 1985). Accurate description of time of day effects requires the precise temporal placement of bed periods and execution of test sessions.

Traditional administration of performance and self evaluation batteries involves data collection from a variety of sources such as pen and paper or audio recording of oral responses. These methods necessitate the later transcription of data to computer for analysis. This has led a number of investigators to develop computer software to directly acquire and analyze

performance test data (Angus and Heslegrave, 1985; Bittner, Smith, Kennedy, Staley and Harbeson, 1985; Brand and Houx, 1992; Bremer, 1989; Kaplan, 1982; Mullaney, Fleck, Okudaira and Kripke, 1985; Popper, Dragsbaek, Siegel and Hirsch, 1988; Ryman, Naitoh and Englund, 1984). By allowing the computer to collect the data, the transcription phase can be eliminated minimizing errors and saving time. In addition, data contamination is reduced by using standardized computer instructions and by minimizing or removing the experimenter-subject social contact from the testing environment.

We describe here an automated schedule execution program (ASEP) developed to alleviate some of the difficulties described by both providing subjects with a sleep-wake protocol to be followed and administering performance tests and sleep quality and self-evaluation questions. To our knowledge this is the first program to combine sleep-wake scheduling with performance tasks chosen to be sensitive to such manipulations.

PROGRAM OPERATION

The ASEP program can be run on any IBM-PC compatible computer equipped with a hard disk and a math coprocessor. It was developed using C and assembly languages and uses approximately 110 kilobytes of DOS memory while running. Timing is based on the standard timer which maintains the DOS clock and therefore operates independent of processor speed. In our studies, subjects used a notebook computer running the ASEP software driven by a preprogrammed personalized schedule (see Fig. 1., here a Compaq LTE). Each system was equipped with a serial Four-Choice Reaction-Time device. An additional numeric keypad (not necessary for program operation) was also provided, simplifying the method of data entry on the notebook computers we used. For all tests, subjects are seated in a cubical area on a comfortable chair, the notebook computer on a desk with the screen some 40-45 cm from the eyes. Screen intensity was self-adjusted for comfort.

Place Figure 1 about here.

The program uses three system files in order to run: a "configuration", a "status" and a "schedule" file. All three are text files that can be viewed and modified with a text editor.

The configuration file 'as.cfg' provides subject information. This information includes the subject name and identification number, the data file prefix, the start date of the experiment and a schedule file name. A typical configuration file is shown below.

```
as.cfg
name:DD
number:1
start date:03/5/1991
data file:DD
schedule file:DD.SCH
```

The status file 'as.sts' is created and used by ASEP to record its running status when operation is to be suspended. It can be used to resume or begin execution at any point in the sleep-wake schedule defined by the schedule file specified in 'as.cfg'.

The schedule file specified in 'as.cfg' defines both the sleep-wake schedule and testing protocol for ASEP. The schedule file contains a list of tasks which initiate sleep periods and test sessions. A typical schedule file is shown below.

```
DAY 3        ; March 17
23:41:49 G   ;
;Short Nap Condition. (TEST DAY)
DAY 4        ; March 18
00:01:49 B   ;
06:20:54 A   ;
06:37:54 G   ;
07:07:54 G   ;
;Breakfast
08:07:54 G   ;
08:42:41 G   ;
09:02:41 B   ;
09:30:45 A   ;
09:47:45 G   ;
10:17:45 G   ;
10:57:45 G   ;
11:40:00 G   ;
12:00:00 B   ;
12:28:04 A   ;
12:45:04 G   ;
13:15:04 G   ;
;Lunch
14:40:19 G   ;
15:00:19 B   ;
15:25:23 A   ;
15:42:23 G   ;
```

Tasks before sleep periods are indicated by the 'B' (before-sleep episode session) following a specified time, and test- sessions tasks are indicated by the letters 'G' (general session) and 'A' (after-sleep episode session). Each line of the schedule file provides either a target task pus its corresponding time or an experimental day number. Tasks for different days are separated by 'DAY' specifiers; and the tasks following are initiated on that experimental day. Day and target entries must be listed in chronological order. Semicolons denote a trailing comment enabling the file to be documented.

As implied by the previous sample schedule file, our investigations involved the definition of three separate schedulable task sessions for ASEP to perform: a preparation session before a scheduled nocturnal sleep or nap bed period (B), a test-session after a bed period (A) and a general test-session (G) for sessions presented at other times between scheduled sleep periods. Each task is defined by the set of subtasks listed below:

'B' Session Tasks

i) two-part warning of upcoming sleep period
ii) instructions for synchronizing the computer with external devices
iii) instruction to turn out lights and go to sleep

'A' Session Tasks

i) alarm clock signal to wake subject from sleep period
ii) instructions for synchronizing the computer with external devices
iii) sleep and mood questions prior to performance testing
iv) the Descending Subtraction Test
v) the Grammatical Transformation Test
vi) the Four-Choice Reaction-Time Test
vii) the Grip Strength Test
vii) the Subjective Estimation Report Questions
viii) oral temperature reading
ix) sleep and mood questions after performance testing
x) report of mental experience for previous sleep period
xi) Stanford Sleepiness Scale

'G' Session Tasks

i) two-part warning of upcoming test session
ii) instructions for synchronizing the computer with external devices
iii) the Descending Subtraction Test
iv) the Grammatical Transformation Test
v) the Four-Choice Reaction-Time Test

vi) the Grip Strength Test
vii) the Subjective Estimation Report Questions
viii) oral temperature reading
ix) Stanford Sleepiness Scale

The B session task involves instructions to guide the subject through the preparations for a scheduled sleep period with the responsibility for subject compliance remaining with the experimenter. In our own applications involving various nap schedules, concurrent ambulatory physiological sleep-wake monitoring has been performed (Medilog 9000 recorders, Oxford Medical Systems). An alternative approach might be wrist actigraphy the patterns of which concord over 90% with sleep-wake state (Kripke et al 1978; Mullaney, Kripke and Messin, 1980; Sadeh et al 1989). Execution of each scheduled sleep period begins by presenting the subject with a two-part warning, one three minutes prior to lights out and the other warning one and a half minutes prior to lights out. Subjects are instructed to set event markers for synchronizing the computer with external devices and then to turn out their lights and go to sleep. The onset and offset times of each scheduled sleep period can be preset to an accuracy of 1 second. Any series of schedules of alterations of sleep length and timing (sleep reduction, sleep extension, changes in circadian sleep placement, various polyphasic sleep patterns) can be programmed.

The scheduled wake-up time for the subjects is marked by the execution of an A session task. Rather than the two-part warning, this task begins with an "alarm clock" signal consisting of tone bursts of three second duration followed by three seconds of silence. Consecutive tone bursts get increasingly louder until a maximum volume of 75 dB is reached.[1] The subject has only to hit any key on the computer keyboard to shut off the alarm and the reaction time to the key hit is measured. A battery of sleep and self-evaluation questions as well as selected performance tests are then administered.

Between the completion of the A session task and the next B session sleep period, ASEP collects data by administering G session tasks at scheduled intervals. A G session task begins with a two-part warning identical to that of a B session. The subject is then guided through a set of self-evaluation questions and performance tests similar to the A session but containing no sleep related questions. All input from the subjects is timed and the subjects are warned via the computer's buzzer when more than 30 seconds of inactivity has occurred. This aids the subjects in maintaining wakefulness during a test-session and ensures a timely completion of each test-session task. ASEP records the actual start time and duration of each session task performed as well as the start times and durations of all subtasks within a session.

PERFORMANCE TASKS

Currently 4 performance tests have been chosen and implemented because of their sensitivity to altered sleep-wake schedules, relatively low learning effects and overall reliability. They are: the Descending Subtraction Test (DST) (Evans and Orne 1975), Baddeley's Grammatical Transformation Test (GTT)(Baddeley 1968), the Four-Choice Reaction-Time Test (FCRT)(Wilkinson and Houghton 1975) and a Grip Strength Test (GRIP)(Aschoff et al 1972).

The DST measures information processing ability through repeated subtractions with decrementing subtrahends. Each occurrence of the test presents the subject with a randomly generated root number in the range of 500 to 999 from which they must subtract the number 9. From the difference, 8 is subtracted resulting in a new difference from which 7 is subtracted. This continues until a subtrahend of 2 has been used to generate a difference and then the process repeats using 9 as the subtrahend. Responses are entered using the numeric keys on the keyboard and the subject's previous difference response is continually displayed on the screen. The test runs to a maximum of 2 minutes or 150 responses. The responses are used to calculate the total correct, the errors and the percentage correct.[2] All three values are saved.

Baddeley's GTT provides a measure of logical reasoning ability requiring the subject to make true or false responses to logical relational statements such as 'A precedes B - BA'. A total of 64 relational statements are used with the order of presentation generated randomly for each occurrence of the test. Test items are displayed one at a time. The test's duration is set to a maximum of 2 minutes with total responses, total correct, errors and percentage correct computed at test completion.

The Four-Choice Reaction-Time test measures a combination of attentional capacity and response speed. It uses a box external to the computer which contains four stimulus lights and four response buttons each in a square formation (see Figure 1.). The computer controls and randomly generates the stimuli and monitors responses through the parallel printer port which is used to interface the box to the computer. Figure 2a illustrates the stimulus-response circuit for a single reaction-time element. Four separate stimulus-response circuit elements are present in the Reaction-Time device. Figure 2b identifies the pin interface for connecting the Reaction-Time device to the PC's parallel printer port. ASEP uses the PC's internal clock for timing but reprograms the clock to attain greater than millisecond resolution. The reaction time responses are measured to millisecond accuracy. The ASEP version of the FCRT test was developed at the

University of Ottawa's Human Neuroscience Research Unit but its specifications are derived from those outlined in Wilkinson and Houghton (1975). The start times of each trial's stimulus are recorded for intra-test analysis. The test runs for a maximum of 5 minutes or 800 responses with the total number of trials, the total correct, errors and percentage correct computed at test termination.

The Grip Strength performance test instructs the subject to perform three grip strength trials on a commercial hand-held dynamometer and prompts the subject to key in the results of each trial. Each value entered is checked to ensure that it lies in the valid range for the dynamometer. From the three trials, the mean, standard deviation and variance are computed for consistency of data treatment.

Place Figure 2 about here.

SELF-EVALUATION QUESTIONS

Self-evaluation questions are used to collect data concerning the subject's emotional and mental states and quality of sleep in the preceding bed period. Subjective evaluation subtasks are presented as either visual analog lines, numeric input scales or multiple choice questions. The visual analog scale is used to measure how subjects rate themselves with respect to a descriptive statement. The scale is presented as a horizontal line whose center, they are instructed, represents the value of how they would usually rate themselves; towards the right is a greater value than usual while to the left is less than usual. For example, for the variable 'sleepiness', the extreme right represents the most intense sleepiness ever encountered, the center represents average sleepiness and the extreme left, the maximum alertness ever experienced. Responses are given by moving a cursor along the visual analog line which contains 38 discrete levels. Cursor movement is controlled by the keyboard's horizontal arrow keys and a selection is made by pressing the enter key.

The subjective evaluation tasks include a subjective estimation report (SER) inventory which is a modified version of Thayer's Adjective Checklist (Thayer, 1967, 1978). It consists of 34 adjectives selected for known sensitivity to the multidimensional nature of sleepiness which are

scored on a visual analog basis. The Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973) is also administered. Seven levels of sleepiness are described and identified by the numeric value assigned to them. The subject indicates the appropriate level by selecting the corresponding number key.

OUTPUT

A total of 19 files are used to store the data resulting from the execution of targets with each test session generating just over 12,000 bytes of data. Variables are grouped according to subtask and to function and then stored in separate subtest files. Raw data files are binary, whereas processed data are stored in text format. Data file names are derived from the subject's data file prefix and subject number; and the extension reflects the task or the type of data contained in the file.

Text files containing processed data are created for all results of performance and self-evaluation tasks. These files are written in matrix format with each column representing an unique variable and each line containing data for a single test session. The first five fields of a text data file line contain test-session identification information. This consists of the subject identification number, session identification (type of test session), start time of target taken from the schedule file, actual start time of the target (useful in identifying delayed sessions), and a subtest identification number. The data variables occupy all remaining fields. This format was adopted for accessibility of data by commercially available statistical software packages such as BMDP and SPSS and for spreadsheet packages such as Lotus' 123, Borland's Quattro and Microsoft's Excel. The sample data file below contains results from the Descending Subtraction Test. The first column shows that this data belongs to subject number 6. Next is the type of session in which this data was collected where a general 'G' session is denoted by '0', an 'A' session by a '1' and a 'B' session by a '2'. The next two columns are the scheduled start time and actual start time of the session in seconds from the beginning of the study and the fifth column shows the DST's subtask ID of 1. The remaining four columns are the total number of responses, the number of correct responses, the number of incorrect responses and the percentage correct in that order.

sn	ses	sched	actual	tsk	n	c	e	%
6	0	298065	298065	1	17	16	1	94.1
6	0	301200	301200	1	17	16	1	94.1
6	1	304084	304084	1	12	11	1	91.7
6	0	305104	305104	1	13	12	1	92.3
6	0	306904	306904	1	18	17	1	94.4
6	0	312019	312019	1	16	16	0	100.0

Three of the performance tests, the Baddeley Grammatical Transformation test, Descending Subtraction test and the Four-Choice Reaction-Time test, all generate the same four processed variables: the total number of responses, the number of correct responses, the number of incorrect responses and the percent correct. The redundancy was introduced for the ease of further analysis. Processed variables from each grip strength test are also stored. Visual analog self-evaluation results are transformed from 38 discrete levels into a value between 1-100, while multiple choice and numeric inputs (such as the Stanford Sleepiness Scale) are stored in their immediate form.

Binary files are used to store raw performance test data as well as 'seed' values used in random number generation. The 'seed' values used to initialize the random number generator are saved so that specific task runs can be reproduced. The actual DST and GTT responses for each session are saved so that the pattern of errors can be examined. Raw data from each FCRT stimulus-response trial, consisting of the particular stimulus light, the actual response button depressed, the stimulus-response reaction time and the trial start time are saved. This data is used for off-line analyses of individual reaction times and patterns of response errors.

APPLICATIONS

ASEP has gone through three versions. The first version operated solely as a sleep-wake and performance schedule administration program, alerting experimenters and subjects upcoming test sessions. It was used in our laboratory's studies of the efficacy of different daytime nap schedules following 4 hours of 'anchor sleep' (Stampi et. al. 1990a, 1990b, 1990c). Although the DST, GTT, FCRT, and subjective evaluation subtests were included, they were not administered by computer, but were carried out by means of written and taped oral responses. Data was later transcribed for analysis and compared to prior and concomitant sleep-wake state objectified by ambulatory physiological monitoring.

The next version of ASEP was used in a polynap study of 60 minute "days" in which subjects slept for 20 minutes at a time followed by 40 minutes of wakefulness (unpublished data). During the 40 minutes of wakefulness subjects were required to do performance testing immediately upon waking and 20 minutes after waking, continuously around the clock for several consecutive days. The physiological monitoring and performance tests were the same as those listed above, with the exception that the FCRT had not yet been implemented into the ASEP, and

there were fewer subjective estimation items. Four subjects were run simultaneouslv in this protocol.

The current third version of the software was developed for use in a study of the efficacy of scheduled naps in the management of excessive daytime sleepiness in narcolepsy-cataplexy (Mullington & Broughton, in press-a, submitted). This study had 3 experimental conditions. In one condition, subjects received their full habitual total sleep time per 24 hours (as determined by sleep logs kept for 5 stimulant-free days just prior to entry into the study) in one major bed period. In the other two conditions, 25% of habitual total sleep time per 24 hours was given as either a single long nap in the middle of the waking period or as 5 short naps spread equidistant throughout the day. Eight subjects were run through the experimental conditions in 2 groups of 4 subjects. Scheduling was complicated by the fact that the subjects had differing pre-study total sleep times which needed to be divided into percentages for the protocols. Thus, every subject was on an individually tailored sleep-wake and performance testing schedule.

In all studies, learning sessions were programmed prior to experimental manipulations of the sleep-wake schedule. Typically it has taken 4-8 sessions on the DST and GTT tasks and 3-5 on the FCRT for learning to be complete. This is similar to the tests when done manually. Subjects have not sensed any significant differences between approaches and post-learning session baseline data in rested normals have been similar. There is no doubt however that computerization has increased efficiency of data gathering. All of the protocols described above would have been exceedingly difficult to conduct in a completely manual environment.

DISCUSSION

A number of available software programs for performance testing have been developed for non-portable computers which are unusable in the field (Bittner et al., 1985; Brand and Houx, 1992; Mullaney et al. 1985; Ryman et al. 1985) and are restricted to applications in the laboratory. Those developed for portable or pocket computers (Bremer, 1989; Popper et al. 1988) have generally not chosen tests for their sensitivity to sleep-wake manipulations and do not have software for scheduling of sleep-wake status or timing of performance tests. Other software packages can only be run on less common hardware (Bremer, 1989). Unlike other software, the ASEP program was developed specifically for computer controlled sleep-wake and performance

test scheduling using performance tasks selected for sensitivity to sleep-wake manipulations with a format usable on virtually all DOS-based PC-compatible portable and notebook computers.

ASEP's utility has increased with each successive version of the program. The progression has been towards increased automation and decreased demands on direct experimenter supervision of the sleep-wake schedule and associated test sessions. The benefits of this reduced interaction between experimenter and subject are threefold. Firstly, the use of computers enables the standardization of instructions and test administration conditions. Secondly, and related to this, the reduction of personal contact in the testing process minimizes the influence of the experimenter's personality and mood fluctuations on performance results via their effects on the subject's mood and motivation. Thirdly, the experimenter becomes free to attend to other duties involved in running the experiment.

The automatic storage of results enables more economical data processing. In the first version of this program, subjects were awakened by telephone, given their DST number and required to perform the test aurally over the phone. The responses were tape recorded and later transcribed for computer. On average, transcription took twice the time it took to perform the test. With protocols having DST lengths of 5 minutes and averaging 25 tests per day, transcription involved over 4 hours of analysis time per experimental day per subject. For tests such as the GTT and subjective estimation reports, the automated data storage protected against loss of test sheets or possible alteration of results by subjects after the allotted test time had passed.

As well as improving efficient use of human resources, the automated system has helped to improve data collection and ensure accurate timing of test sessions and bed periods. This is of considerable importance for the quality of data gathered in studies of sleep inertia and circadian (and ultradian) rhythms in performance. The timing information stored in the files is useful in the investigation of phase relationships between performance and such physiological measures as EEG and temperature. It also enables the experimenter to verify that tests were done at the prescribed times, and to pinpoint any unusual delays between individual subtests within a test session. The system records time in seconds from the beginning of the study and so can be used to analyze performance on "days" different than 24 hours (i.e. ultrashort "days" or extended "days" lasting more than 24 hours), or of length specified by the scheduled protocol.

There are limitations to any computer system in such studies of which experimenters need to be aware. For example, subjects can unplug a component (such as the 4-choice box or the

numeric keypad) or turn the computer off in an act of automatic behavior brought on by extreme sleepiness. This occurred during the third study in which the program was used. A narcoleptic subject turned the computer off in response to a "press any key" prompt made by the computer. Luckily the experimenter was standing close by and was able to reenter the program at the right time in order to continue the scheduled test with minimal time loss.

Another limitation is that the computer can do nothing beyond beeping at a subject who is unable to wake up or, as can occur in pathological sleepiness, who has fallen asleep on the computer keyboard. A human experimenter is able to shake the subject and call his or her name repeatedly to force an arousal. It is extremely useful to have both experimenters and subjects keep a careful record of the occurrence and timing of anything that goes wrong. By replacing the experimenter with the computer, there is otherwise no way of knowing when an error was made that the subject was unable to correct, or when the subject stopped performing in the middle of a test for reasons other than being asleep. Using computers to administer tests makes it all the more important for subjects and experimenters to keep record of human and technical factors that create difficulties.

It might be thought that computer presented performance tasks would be inherently less motivating than manual tasks. This has not proven to be the case in laboratory application. In both approaches, even after the test has been fully learned, the experimenter remains nearby the subject. In field testing outside the laboratory and without such direct supervision this might pose a problem, although there is no inherent reason why reduction of motivation under such conditions would be greater than for manual tasks.

This use of computers has been very well received by subjects participating in experiments conducted with ASEP. Computers are becoming more and more an indispensable everyday tool for the general population, and their increasing portability make them a real asset for field research. The experimenter need only be aware of the limitations of using the technology and it will facilitate increased productivity and developments in areas of research requiring repeated testing and altered sleep-wake schedules.

Hardware Requirements and Program Availability

To run the ASEP program, it is necessary to use an IBM-PC AT compatible computer with at least a 12MHz 286 processor, 640Kbytes of conventional memory, a 287 math coprocessor, a

40MByte hard disk, and DOS version 4.0 or greater. Persons interested in obtaining a copy of ASEP can do so for a nominal fee to recapture development costs by contacting Dr. Roger Broughton, Division of Neurology, Ottawa General Hospital, 501 Smyth Rd., Ottawa, Canada, K1H 8L6.

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Notes

1. Since the PC's speaker sounds with different intensities at different frequencies, a sound pressure meter was used to measure intensity at a distance of 3 ft. for different frequencies for each computer. The alarm signal was constructed by presenting different frequencies in an order that resulted in increasing volume.

2. Subjects were given standard instructions for performing the DST. They were also instructed that in case of forgetting the subtrahend (the number being subtracted), they were to select one between 2 and 9 and continue with the test. The first step in scoring the DST is to generate a list of differences, D_i ,by subtracting consecutive responses (the total number of responses is the maximum value for 'i'). When all responses are correct, the resultant sequence of differences should be: 9 8 7 6 5 4 3 2 9 8 7 6 5 4 3 2 9 8 ... D_i is scored correct if $D_i + 1 = D_{i-1}$ (or $D_{i-1}=2$ when $D_i =9$). When D_i is not in sequence with the D_{i-1} term, it is compared with the sequence starting with the D_{i-2} term. D_i is correct if $D_i + 2 = D_{i-2}$ (or $D_{i-2}=2$ when $D_i =8$ or $D_{i-2} =3$ when $D_i =9$). If D_i is not correct with respect to the D_{i-1} or D_{i-2} terms it is checked through a similar method to the D_{i-3} term. When the D_i term is not in agreement with the sequence beginning with any of the 3 previous terms, the response is considered incorrect.

Figure Caption

Figure 1. The portable notebook computer running the ASEP program assists subjects in maintaining sleep-wake schedules and administers performance tests. Also shown are a serial Four-Choice Reaction-Time interface and external numeric keypad.

Figure 2. The Four-Choice Reaction-Time Device. (a) shows the circuit schematic for one of the four stimulus-response elements in the Reaction-Time device. (b) shows the pin connections between the computer's parallel printer port and the four stimulus-response elements in the Reaction-time device.

Figure 1.

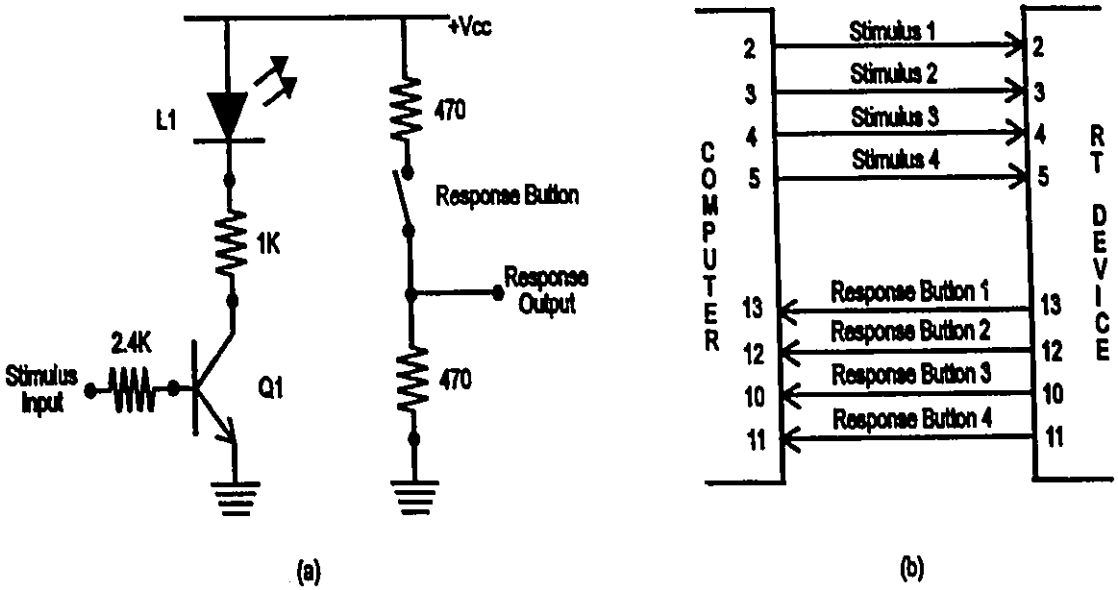
+Vcc
L1
470
Response Button
1K
Response Output
2.4K
Stimulus Input
Q1
470
(a)
COMPUTER
RT DEVICE
2
3
4
5
Stimulus 1
Stimulus 2
Stimulus 3
Stimulus 4
2
3
4
5
13
12
10
11
Response Button 1
Response Button 2
Response Button 3
Response Button 4
13
12
10
11
(b)

Figure 2.