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BEHAVIOURAL AND PHYSIOLOGICAL INDICES OF NORMAL AND PATHOLOGICAL SLEEPINESS.

Marisa Mayela Aguirre Gutiérrez

Thesis presented to the School of Graduate Studies of the University of Ottawa in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Ottawa, Canada, 1984

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ABSTRACT

A comparison of subjects with normal and pathological sleepiness was carried out with narcoleptic patients as representative of the latter population. Fluctuations of alertness through the day were observed using both subjective (SSS) and objective measures (reaction time, P3, CNV). In addition, a comparison of data recorded prior to REM and NREM naps was carried out.

The narcoleptic group reported subjective feelings of more intense sleepiness. They also showed significantly shorter sleep onset times to stages 1B and 2. No between groups differences were observed in total time spent in these stages. This suggests that healthy subjects, although less subjectively sleepy than narcoleptics, have an underlying pressure for sleep that is activated under conditions that encourage sleep. Narcoleptics reported a larger increase of alertness after naps as compared to controls. This increase in alertness might be related to the time spent in REM sleep or to the release of their larger pressure for sleep.

No between groups differences were found in the N1 amplitude. However, a significant time of day by group interaction was observed. While controls showed a reduction of N1 through the day with a significant decrease at 1400, the N1 for narcoleptics was significantly attenuated in the morning, increasing in amplitude through the day, with a significant increase in amplitude being observed at 1400. This increase was interpreted as an overcompensation of attentional effort.

The amplitude of P3 was significantly attenuated in narcoleptics. This may have resulted from a low level of confidence in decision making, or equivocation.

The contingent negative variation amplitude was similar in both types of sleepiness. A significantly greater negativity was observed in the slow wave recorded after S2 in narcoleptics, perhaps reflecting a larger processing effort during the task.

Comparison of REM vs NREM data showed that narcoleptics who later fell into REM sleep were significantly more drowsy than those later falling into NREM sleep. A significant increase in alertness was reported after REM naps. A significantly larger P2 was recorded prior to REM in the P3 paradigm. The interpretation of this finding is uncertain but a slower shift from positivity to negativity is a possible explanation. The second half of the CNV interval was significantly reduced over frontal areas prior to REM naps, which might reflect the lower level of alertness experienced by narcoleptics prior to this stage of sleep. It is also possible that a larger degree of depolarization of the cortex recorded during REM sleep precedes the actual onset of REM, thus increasing the baseline for maximal cortical depolarization and resulting in a CNV of smaller amplitude.

CURRICULUM STUDIORUM

Marisa Mayela Aguirre Gutiérrez was born on December 23, 1954 in Torreón, Coah., México. She received the Baccalaureate of Arts in Psychology (Honours) from the Universidad de Monterrey, in Monterrey, Nuevo León, México in 1977.

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INTRODUCTION

Sleep and wakefulness are different states of consciousness. During wakefulness a person's awareness or consciousness of his environment is very high. During sleep it is limited to selective and specific events. This has led to sleep being defined as a state of unconsciousness. However, research findings suggest that both information processing and awareness of the environment are present during sleep. A series of studies have shown that external stimuli presented during REM sleep are often incorporated into the dreams reported by the subject when he is awakened from REM sleep (Dement & Wolpert, 1958; Berger, 1963; Koulack, 1969) and that sensory stimuli delivered to the subject cause K complexes to be generated during stage 2 sleep (Loomis et al. 1938; Roth et al. 1956; Rechtschaffen & Kales, 1968). Some subjects have the ability to awaken themselves at a chosen hour (Cohen, 1979) and subjects can be awoken from deep stages of sleep when presented with significant stimuli, such as their name being called (Koella, 1968; Poitras et al. 1973).

From later childhood through adulthood, sleep and wakefulness interact at two levels. They occur sequentially in each succeeding 24 hour period (circadian in distribution) (Williams & Karacan, 1974; Williams et al. 1964) and also interact in ultradian fluctuations in daytime alertness (cycle duration less than 24 hours) (Carskadon & Dement, 1977, 1979; Broughton 1975). Low levels of alertness, experienced as sleepiness, are more intensely felt very early in the

morning and early in the afternoon (Carskadon & Dement, 1977, 1979). Studies have shown that while the general level of sleepiness is directly related to amount and quality of the prior night's sleep (Webb & Agnew, 1974; Carskadon & Dement, 1981) fluctuations of alertness that occur in a 24 hours period occur independent of these factors. For example, although sleep deprived subjects report being much sleepier than normals, they still show decreases of alertness at critical times (early morning and early afternoon) (Carskadon & Dement, 1977, 1979; Richardson et al. 1982). Decreased levels of alertness lead to a state characterized by a desire to sleep. This state known as sleepiness is essentially a motivational state whose consummatory response is to go to sleep. In situations which are inappropriate to sleep, the individual must fight their low functional level and continue to perform.

Excessive daytime sleepiness is experienced by healthy people under certain conditions such as sleep deprivation or jet lag and during the initial adaptation to a new sleep-waking schedule (Dirken, 1966; Glenville & Broughton, 1979; Herscovitch & Broughton, 1981; Verhaegen et al. 1981). This sleepiness is easily reversible by adequate sleep during the accustomed circadian cycle.

Excessive daytime sleepiness is also the major disabling symptom of sleep disorders such as narcolepsy, sleep apnea and idiopathic central nervous system hypersomnia (Guilleminault & Dement, 1974; Coleman et al. 1982). It also accompanies the symptomatology resulting from closed head injury and metabolic disorders (Guilleminault & Dement, 1974, 1977). Clinical reports indicate that the sleepiness

experienced by patients with sleep disorders is of a much more intense nature than that experienced by healthy people (Ganado, 1958; Dement, 1976). However, specific features that differentiate the two types of sleepiness have not been defined. The intense sleepiness experienced by those with sleep pathology has been described as 'excessive daytime sleepiness' (EDS) (Guilleminault & Dement, 1974; Dement, 1976, 1979). However, since healthy people can experience excessive daytime sleepiness (see above), the term 'pathological sleepiness' (PS) seems to be more appropriate and will therefore be employed in this thesis.

Pathological sleepiness is distinguished from normal sleepiness by its chronicity and intractable nature (Guilleminault & Dement, 1974; Broughton & Mamelak, 1979, 1980). Medication does not seem to alleviate the intensity of the sleepiness experienced by patients with PS. Unlike normal sleepiness, the sleepiness experienced by patients with sleep disorders is not solely a function of quantity and quality of night sleep. Hypersomniacs, for example, sleep for very prolonged periods of time (9 to 12 hours) and still feel chronically sleepy (Roth, 1980). The sleepiness of other patient populations, such as narcoleptics, decreases for short periods of time following a nap only to return to its previous intensity shortly afterwards (Ganado, 1958).

In the last decade, clinicians have approached the study of sleepiness mainly from two perspectives; a clinical one that has investigated methods for the diagnosis of sleepiness and the evaluation of its treatment (Dement et al. 1978, Hartse et al. 1980; Roth et al. 1980) and a more theoretical one that has studied the nature of sleepiness by establishing its determinants and fluctuating rhythms

(Carskadon & Dement, 1979, 1981, Carkadon et al. 1981, Richardson et al. 1982).

The first measure introduced to quantify subjective sleepiness was the Stanford Sleepiness Scale (Hoddes et al. 1972). This scale has since been widely used in evaluating the sleepiness of healthy people and that of people suffering from pathological sleepiness. In normal populations, the scale has proven sensitive to the effects of phasic sleep deprivation (Glenville & Broughton 1979; Carskadon & Dement, 1975, 1977; Herscovitch & Broughton, 1981). However, its sensitivity to the effects of chronic sleepiness has been questioned. (Friedman et al. 1977, Herscovitch & Broughton, 1981). While it was found to be successful in differentiating normal from pathological sleepiness by Valley & Broughton (1981), it was sometimes unreliable in differentiating chronically sleepy patients from controls in the study of Dement et al. (1978).

Dement et al. (1978) found that patients with PS tended to deny the extent of their sleepiness, rating themselves as alert on the SSS when visual observation indicated they were falling asleep. Similarly, Roth et al. (1980) found no difference in SSS ratings between a population of non-complaining normal subjects and a population of upper airway sleep apnea patients with pathological sleepiness. It has been suggested that chronically sleepy people are so infrequently alert that they no longer have a frame of reference for judging their own lack of wakefulness (Dement et al. 1978). While the SSS scale provides useful information regarding the phenomenological experience of the subjects, there is a need to look for objective

measures to better define their true level of sleepiness and the accompanying functional states.

Performance measures are an objective means of assessing the impairment associated with sleepiness. Few studies have investigated the difference in performance between normal subjects and those with PS. Guilleminault et al. (1975) using three different tasks, a signal detection task (Light Stimulus Vigilance Test), a serial counting task (Serial Alternation Test) and an addition task (Wilkinson Addition Test) reported that patients with PS made a larger number of errors than normals, many being errors of omission or non response resulting from microsleeps. Billiard (1976) reported that perseverative errors seemed to characterize the performance of pathologically-sleepy people in the Wilkinson Addition Test. Neither of these studies investigating performance deficits carried out statistical comparisons between the control and patient groups. Valley & Broughton (1981) found that both a long repetitive task (Wilkinson Auditory Vigilance Test) and a short test which required mental tracking and focused attention (Four Choice Serial Reaction Time Test) distinguished between normal and PS subjects. However, they observed that short tests such as the Knox Cube, Digit Span of the WAIS and Paced Auditory Serial Addition Test were unsuccessful in discriminating between the groups. The more challenging and motivating nature of these tests may have made it easier for the patients to sustain alertness.

Valley & Broughton (1983) observed that performance errors were not only associated with microsleeps but also with lower levels of alertness monitored during wakefulness with EEG methods. Narcoleptics

in this study made a larger number of errors of omission and showed longer RTs than controls. This emphasizes the potential usefulness of short performance tests in which reaction time and detection levels are measured.

More recently, researchers (Mitler et al. 1982) have employed short tests such as the Digit Symbol Substitution of the WAIS and the Wilkinson Addition Task in the evaluation of treatment for pathological sleepiness. They found that while these tests were sensitive to the positive effects of treatment, they did not always statistically differentiate between individuals with PS and normals, although performance differences were observed. A large amount of variability was possibly responsible for the lack of statistical significance.

The limitations of the clinical application of performance tests are evident. Short tasks have proven to be unreliable in measuring the effects of sleepiness (Williams et al. 1959, Mitler et al. 1982), possibly as a result of the large degree of variability that has been reported to be associated with them. A large variability in performance levels is probably related to the fact that motivational influences affect performance. For example, if the subjects perceive the task interesting and challenging they may exert more effort and thus perform better than if they perceive it as easy or boring. This suggests that only long repetitive tests can measure the stable effects of sleepiness after the initial motivation dies out. However, the time consuming nature of such tests and the effects of fatigue place limitations on their usefulness.

A different approach to the study of sleepiness has been provided by electrophysiological techniques. The EEG makes it possible to measure brain activity through electrodes placed on the scalp. Wakefulness is described as electrical wave activity of mixed fast frequency and low amplitude. Standard procedures have been established for the measurement of activity during sleep (Rechtschaffen & Kales, 1968), these include the recording of at least the EEG, muscle tonus (EMG) and eye movements (EOG).

The EEG pattern has also been used to define sleepiness. Armington & Mitnick (1959) found that alpha rhythm was absent in the EEG of subjects who had been awake more than 100 hours. These findings were later confirmed by other researchers (Johnson et al. 1965). The EEG pattern of drowsiness prior to sleep has been described as a slowing and fragmentation of the alpha rhythm accompanied by the appearance of medium voltage mixed frequency activity and slow rolling eye movements (Stage 1A)(Simon & Emmons, 1956; Oswald, 1962; Gastaut & Brougton, 1965). As the arousal level decreases further this pattern is replaced by medium voltage 4–7 cps theta activity and sharp waves (Stage 1B of Gastaut & Broughton, 1965). Some researchers have classified this pattern as stage 1 and have considered it to be the onset of sleep (Rechtschaffen & Kales, 1968). Others have asserted that spindles must be present for unambiguous sleep to occur (Johnson 1973). Evidence which supports this comes from studies showing that people do not normally perceive themselves as asleep until spindles appear in the EEG (Gastaut & Broughton, 1965). It seems that stage 1A

and 1B patterns alternate in a moment to moment interchange until alpha disappears.

Electrophysiological studies of subjects with sleep pathologies, i.e. narcolepsy and hypersomnia (Pond, 1952; Gastaut & Roth, 1957; Roth, 1964) have reported that drifting and vacillatory EEG states appear in their routine clinical EEGs. Studies in which EEG recordings were done while patients with PS performed a task have reported that their failure to respond was due to microsleeps consisting of short-lasting bursts of stage 1 (loss of alpha) and/or the synchronized theta activity of stage 2 (Guilleminault et al. 1975), which were recorded during periods of inadequate performance and inappropriate speech. Valley and Broughton (1983), on the other hand, observed performance deficits associated with higher levels of vigilance in which alternation of stages 1A and 1B were recorded. Neither Guilleminault et al. (1975) nor Valley & Broughton (1983) ever noted microsleeps in normal alert subjects. Valley and Broughton did record stage 1A in normal controls but it appeared with much less frequency than in narcoleptics. It seems that while extremely low levels of arousal (stage 2) do not characterize the drowsiness of normal healthy people, fluctuations of alertness (alternations of stage 1A and 1B) accompany the drowsiness state of both normals and patients with PS.

Another EEG procedure employed as a clinical tool in diagnosing PS is the Multiple Sleep Latency Test (MSLT) developed at Stanford. The MSLT records EEG-defined sleep onset latencies at different times throughout the day. Based on the premise that the sleepier the sub-

ject, the faster they will fall asleep, the MSLT provides a measure of sleepiness independent of the patient's subjective estimates. Several studies have demonstrated that the latency to sleep onset during the day is shortened when subjects are placed on a restricted sleep schedule (Carskadon and Dement, 1981; Carskadon et al. 1981) or deprived of sleep (Carskadon & Dement, 1977; Carskadon & Dement, 1979). Conversely, sleep onset latencies are increased when the number of hours of night sleep are increased (Carskadon & Dement, 1979). The changes in sleep latencies parallel changes in subjective estimates of sleepiness as measured by the SSS. The correspondence between self reported sleepiness and MSLT sleep latencies that have been found in sleep deprived normal subjects is not always observed in patients who complain of EDS and exhibit nocturnal sleep pathology. While Dement et al. (1978) reported that sleep apnea patients showed much longer sleep latencies and described a marked improvement in daytime alertness following treatment, Roth et al. (1980) found no difference between pre- and post-treatment sleep latencies despite patient reports that daytime sleepiness was dramatically reduced.

It may be that treatment improves the ability of the patient to remain alert without affecting their propensity to fall asleep under adequate conditions. Hartse et al. (1980, 1982) modified the MSLT to test the ability of the subjects to stay awake. Subjects were instructed to attempt to stay awake while in bed. This did result in overall longer sleep latencies, but the test still proved an insensitive measure of changes in alertness in patients treated for PS (i.e., they were unable to stay awake longer although they reported increased

alertness). As can be seen, the MSLT test has some shortcomings: 1) A large overlap has been reported between the sleep onset times of normals and people with pathological sleepiness, 2) The test is unable to differentiate between degrees of extreme sleepiness which limits the information regarding the intensity of sleepiness and, 3) The MSLT is not sensitive to increases in alertness resulting from treatment (Roth et al. 1980; Hartse et al. 1982). These limitations suggest that other methods for the assessment of sleepiness should be investigated.

A different electrophysiological approach to the study of alertness is to measure the latencies and amplitudes of cerebral evoked potentials recorded during the processing of sensory stimuli delivered to the subject. While the usual EEG records electrical activity related to different events (internal and external), averaging techniques make it possible to record potentials evoked by a specific stimulus such as clicks and tones (Davis, 1964; Picton et al. 1971). An auditory stimulus can elicit up to 15 separate wave components which can be extracted, as mentioned above, from ongoing neocortical activity by computer averaging techniques (Picton et al. 1971). Of the 15 waves, the initial components seem to correspond to cochlear nerve, to brainstem nuclei and to thalamic nuclei activity. These components have been reported to be insensitive to levels of alertness, as their amplitudes do not change with level of arousal of the subject or the level of attention paid to the stimuli (Mendel & Goldstein, 1971; Amadeo & Shagass, 1973; Picton et al. 1974). Because of their dependence on the physical qualities of the stimulus and their

independence of the psychological state of the subject, these short latency components have often been labeled as "exogenous". Long latency AEP components appearing 30 to 50 msec. after the presentation of the stimuli have been reported to vary with the level of attention of the subject (Hillyard et al. 1973, Picton et al. 1974, Schwent et al. 1976a, Hink & Hillyard, 1976).

The long latency auditory evoked potential components have been classified into mesogenous and endogenous components. The former include a negative-positive complex (often called N1-P2) having peak latencies at approximately 100 and 200 msec respectively. The components are known to be sensitive to the physical characteristics of the stimuli such as frequency rise and fall time, intensity and rate of presentation of the stimuli. For example, larger amplitudes are obtained with larger intensities and slower rates of presentation (Butler, 1968; Callaway, 1973). These components are also sensitive to psychological manipulations such as the level of attention paid to the stimulus. The N1, for example, has been known to increase in amplitude whenever the subject attends to the stimuli in one ear and ignores the stimuli in the other (Picton & Hillyard, 1974). The N1 has been observed to decrease in amplitude during divided attention tasks when the subject attends to stimuli presented to both ears and to increase when the subjects attends to stimuli presented to only one ear (Hink & Hillyard, 1976).

Two types of recordings have been reported in the AEP-alertness literature. In one, AEPs are recorded when subjects are detecting specific target stimuli. In the other, subjects listen to the stimuli with the eyes closed while lying down, or while lying or sitting in

the dark (Weitzman & Kremen, 1965; Hakinnen & Fruhstorfer, 1967; Fruhstorfer & Bergstrom, 1969). The AEPs have also been recorded as the subjects fall asleep, or during sleep with the recording being done through the night (Williams et al. 1962; Suzuki & Taguchi, 1968; Mendel & Goldstein, 1969, 1971, Anch, 1977). Williams et al. (1962) observed that as the EEG changed from wakefulness to sleep the waveform of the evoked response changed consistently; the amplitude of wave P1 increased, while those of waves N1 and P2 decreased. Other studies that have recorded the AEP of subjects sitting in a dark room with the eyes open or while lying down reported decreases of P1, N1 and P2 to 25% of their waking size (Fruhstorfer & Bergstrom, 1969). Other researchers have not reported decreases in AEP amplitudes from wakefulness to sleep (Buschaubam et al. 1975). It is possible that the differences in results among these studies can be explained on the basis of methodological differences. Exogenous components, as previously stated, are quite sensitive to stimulus parameters such as intensity, frequency, physical characteristics and rate of presentation. Because the different AEP-alertness studies have used different stimulus parameters, comparison of results is, then, somewhat problematic.

The interpretation of AEP components in relation to alertness poses a problem when subjects are asked only to listen to the stimuli. In view of the ambiguous instructions in which a subject is asked to simply lie still or to passively listen to or look at stimuli, one can never be sure precisely what the subject was doing. They may have been almost asleep or they may have been quite attentive. This may

explain some differences between studies. For example, Pressman et al. (1982) reported increases in N1-P2 amplitudes in a group of sleep deprived subjects as they listened to clicks prior to falling asleep. They interpreted the N1-P2 augmentation as reflecting increases in the amount of attention paid to the stimuli although no specific attentional requirements had been made to the subjects.

Studies that have used signal detection tasks to investigate the relationship between AEP components and levels of alertness report that the N1 and P2 are negatively correlated with reaction times (Wilkinson & Morlock, 1967; Bostock & Jarvis, 1970) with a decrease of amplitude reflecting a low level of alertness and/or inability to sustain attention. However, not all studies have reported decreases of amplitudes in these components. Campbell et al. (1980) had sleep-deprived subjects engage in a signal detection task in which subjects were asked to detect occasional 'targets' occurring infrequently among a train of regularly presented 'standard' stimuli. The count of the number of hits was used as behavioural evidence that the subject was attentive. They did not record N1-P2 decreases in these subjects. They suggested that subjects were able to allocate compensatory effort and hence maintain satisfactory levels of attention.

The endogenous auditory evoked potential components consist of a negativity occurring at approximately 250 msec (N2) and a positivity occurring at approximately 300 msec (P3). The components are called endogenous because they vary with the psychological significance that the stimulus has to the subject rather than with its physical characteristics. For example, varying the rate of intensity or frequency of

the task-relevant stimulus has no effect on the amplitude of P3. Similarly changing the modality of the stimulus has little effect on P3. N2 and P3 can also be elicited in the absence of any external stimulus when a subject is asked to detect occasional omissions in a regular train of stimuli (Hillyard et al. 1973; Picton et al. 1974; Ford et al. 1976; Ruchkin & Sutton, 1980). The latencies of these components are increased with decreasing stimuli discriminability (Ford et al. 1976, Ritter et al. 1979; Naatanen et al. 1980). Because both components occur in signal detection tasks they are often referred to as the N2-P3 complex.

Two different types of N2 components can be recorded depending on whether the subjects are only listening to the stimuli or are detecting specific target signals. The N2 component recorded under the former circumstances has repeatedly been found very sensitive to decreases in alertness. It has been reported to increase consistently in amplitude during the progression from wakefulness to sleep (Ornitz et al. 1967a; Picton et al. 1974; Williams et al. 1962). Ornitz et al. (1967b) determined that increases in N2 amplitudes were related to onset of sleep. They observed this increase at both the initiation of sleep and at sleep onsets after awakening from sleep during the night. Campbell et al. (1980) observed a tendency for increases in N2 amplitudes as the number of hours of sleep deprivation increased. Pressman et al. (1982) also recorded signficant N2 amplitude increases in a group of sleep deprived subjects as compared to a group of normal controls. However, they did not record similar significant

increases in a group of pathologically sleepy people in whom extreme low levels of alertness and difficulties in sustaining attention are present. Broughton et al. (1981), however, found significantly smaller N2 amplitudes in a group of narcoleptic subjects in association with low detection levels and significantly longer reaction times. It appears that failure to record an increase in N2 amplitude does not necessarily reflect a high level of alertness, and that the N2 amplitude might behave differently in sleep deprived subjects (Campbell et al. 1980) than in people with PS (Broughton et al. 1981). Furthermore, the N2 recorded in signal detection studies might be very different from that in which subjects are not engaged in decision-making tasks.

The P3 component is among the most widely researched endogenous components (Picton et al. 1978, Donchin et al. 1978). Researchers have been interested in determining the cognitive processes that underly changes in its latencies and amplitudes. It is difficult to define the process reflected in the P3 as its amplitude has been manipulated in a variety of paradigms. The P3 has been said to reflect active and passive attention processes (Roth & Kopell, 1973; Roth et al. 1976; Squires et al. 1975; Ford, et al. 1976), stimulus evaluation (Squires et al. 1977), the hit rate of the subjects (Squires, et al. 1975), the information value of a stimulus derived from its probability of occurrence (Tueting et al. 1971, Campbell et al. 1979) and the feedback value of the stimulus (Donchin, et al. 1973). It has also been stated that P3 reflects a comparison with memory models or templates (Hillyard et al. 1973; Donchin et al. 1978).

P3 has on separate occasions been reported to reflect active and passive attentional processes. Based on results of studies showing P3 of large amplitude when stimuli are detected and an absence of P3 when they are undetected (Hillyard et al. 1973), it has been concluded that P3 indexes active attentional processes. On the other hand, some researchers have recorded P3 under ignore conditions in which the subjects are told to ignore the stimulus. However, it is difficult to assess the extent to which the subjects actually ignored the stimuli (Roth, 1973; Roth et al. 1976). It is possible that they were in fact unable to ignore the low probability target signals. Squires et al. (1975) have noted the existence of two different types of positivities in the latency range of the P3 component. A positive wave can be recorded over frontal areas at shorter latencies when deviant stimuli (stimuli with different physical characteristics than the standards) are presented under ignore conditions to the subject. A positivity of larger amplitude and later latency can be recorded over parietal areas when the subjects are instructed to actively detect the deviant target signal.

The P3 component has been recorded in a multiplicity of paradigms. It seems that the common element in all of these paradigms is the identification of a target. Thus, it can be stated that in a target detection task, P3 reflects selective attentional and perceptual processes for identification of relevant stimuli and that this identification occurs in relation to the subjects expectancies of different stimulus categories (Hillyard et al. 1973, Hillyard & Woods, 1979). The P3 appears to represent a common, modality non-

specific process having a similar scalp distribution for detection of signals in auditory, visual and somatic modalities (Snyder et al. 1980).

Recently, Campbell et al. (1980) recorded long latency AEP's in a group of sleep deprived subjects and observed decreased P3 as the number of hours of sleep deprivation increased. They observed that the P3 amplitude after sleep deprivation tended to decrease from 0:00 to 8:00 hours and then return to baseline from 0800 to 1200. Under control conditions of normal sleep, no significant P3 decrements were recorded. The same finding of P3 amplitude reduction was confirmed in a second experiment in which an easier task and longer interstimulus interval were used. The decline in amplitude of P3 over the sleep deprivation night was observed to be independent of ease of target detection or rate of stimulus presentation. The authors concluded that the decrease in P3 could be interpreted in general terms as reflecting perceptual and attentional difficulties associated with sleepiness.

Studies that have been carried out to determine the usefulness of AEP components in the evaluation of PS have reported conflicting results. Pressman et al. (1982) showed that the amplitudes of the N1-P2 and P2-N2 omponents recorded from normal subjects listening to clicks were similar to those of people with PS. Broughton et al. (1981), on the other hand, reported reduced N1, P2, N2 and P3 amplitudes in narcoleptics compared to controls during a one hour vigilance test. Because normal controls spent most of the time in wakefulness, it was not possible to record AEP's during drowsiness. It is dif-

ficult to know if the results of these two studies reflect differences in the degree of engagement of the subjects or simply different stimulus parameters. In Pressman et al.'s study subjects were asked to remain alert, while Broughton et al.'s subjects were engaged in a signal detection task. Further research is needed to determine the usefulness of AEPs in measuring level of alertness. A paradigm requiring an optimal level of attention, such as a signal detection task, might be helpful since lower levels of performance observed during sleep deprivation conditions have been attributed to the subjects inablity to sustain attention (Williams et al. 1959; Wilkinson et al. 1966; Guilleminault et al. 1975).

Another event related potential that is sensitive to the subject's level of attention is the contingent negative variation (CNV). The CNV was first reported in 1964 (Walter et al. 1964) as a slow negative shift occurring in the EEG. This slow negative wave develops between a warning stimulus (S1) and a subsequent imperative stimulus (S2), to which the subject must respond. The CNV is most commonly recorded with maximal amplitude from frontocentral scalp electrodes (Loveless & Sanford, 1974a, 1974b; Gaillard, 1976). As the interval between the warning and the imperative stimulus is increased the contingent negative variation separates into an early slow negative wave following the warning stimulus and a later negative wave preceding the imperative stimulus (Loveless and Sandford, 1974a, 1974b; Gaillard, 1976). Loveless and Sandford (1974) have suggested that these early and late negative waves represent respectively the orientation to the warning and the expectancy of the required response.

Another two component view has been advanced by Gaillard (1976) who distinguishes an early orientation wave following S1 (O wave) and having a frontocentral distribution and a later, pre-S2, expectancy wave (E wave) recorded pre-centrally. These studies have underlined the differential involvement of various cortical areas during progressive stages of preparatory processes. However, Donchin et al. (1978) warn that replacing one diffuse generalized effect with two localized more specific effects would seem to be of dubious merit since it implies that the different functions described are subserved by differently located neuronal aggregates, whose activities overlap and summate. They consider it more likely that cortical slow potential changes reflect a depolarizing process in a complex mosaic of neuronal domains that have been activated by subcortical mechanisms (Gazzaniga & Hillyard, 1973).

When Walter et al. (1964) first reported the CNV, they described it as an "expectancy wave", which resulted from the association of two stimuli (S1 followed by S2). Later studies showed that expectancy per se was not the unique psychological correlate of the CNV. Experiments in which intention to act (Low et al. 1966); motivation (Irwin et al. 1966, Rebert et al. 1967); attention (Tecce & Scheff, 1969; Tecce, 1972); arousal (Tecce, 1972, Tecce et al. 1976); readiness (McAdam 1969); anticipatory response (Low & McSherry, 1968); and phasic alertness (Posner, 1978) were manipulated all produced CNVs Hillyard (1973) classified the different paradigms in which CNV was recorded into four general types: a) holding a motor response in readiness, b) preparing for a perceptual judgment, c) anticipation of

a reinforcer and d) preparation for a cognitive decision. Attempting to describe the psychological processes being reflected he stated: "...either the CNV can be differentiated into a family of task specific event-related slow potentials each having a different brain mechanism and functional role or it is a manifestation of a unitary process (e.g. arousal) common to all such preparatory acts". Hillyard recognized that the concept of arousal itself is too vaguely defined and probably too multifaceted to be precisely understood.

As the CNV appears to reflect an activity that is focal to the processing of information from the environment, some researchers have invoked "selective attention" as the psychological correlate of the CNV (Tecce & Scheff, 1969; Tecce, 1972; Hillyard, 1973), using RT as an external index of attention. Some researchers have reported negative correlations between CNV amplitudes and RT, i.e., larger CNVs, shorter RTs, suggesting that larger amplitudes correspond to greater degrees of attention (Hillyard, 1969). Others reported that increases in the level of difficulty produced a decrease in the amplitude of the CNV (Debecker & Desmedt, 1974). This may contradict the selective attention hypothesis which in difficult tasks should call for greater attention and therefore larger CNV amplitudes. Tecce's proposal (Tecce et al. 1976) that increased task difficulty might result in increased levels of autonomic arousal (increase heart rate, increased eye blinking, etc.) causing distraction and in turn decreased CNV amplitude (Tecce & Hamilton, 1973) suggests the possibility that the CNV does indeed reflect attentional processes. It is apparent that the relationship of the CNV to psychological phenomena such as RT is

not a simple one. A rise or fall in the CNV could be associated with either fast or slow RTs, depending on the experimental context.

Posner (1978) more recently has suggested that CNV is one of the many physiological indicators of the alert state. He wrote: " . . . much of the reason for believing in the relationship between CNV and alerting is the fact that the CNV appears in every paradigm where subjects are told to get ready to attend closely to external events. Thus it appears to be closely related to the process by which subjects prepare for external events". It can be stated, then, that CNV reflects the preparedness of the individual to attend to a specific stimuli. It is logical to expect that the CNV is sensitive to the level of efficiency of the organism in attending to the environment.

Naitoh et al. (1971) reported that a reduction in CNV amplitude was observed after one night of sleep deprivation and that after a second night of sleep deprivation, the CNV was almost completely abolished. A more recent study (Peeke et al. 1980) did not observe changes in CNV amplitude after sleep deprivation conditions. This later study used a fairly challenging paradigm in which the subject had to remember data of the preceding trial in order to respond to the present one. Therefore, it is possible that the demands of the task were such as to force the subject to compensate for any deficits present in their functional efficiency for its successful completion. The CNV recorded in a simple RT paradigm might reflect, as Naitoh et al. (1971) reported, the low levels of alertness that accompany sleepiness. At the moment, however, very little is known of how chronic sleepiness might affect the mechanisms of phasic alertness of subjects and/or how this might be reflected in CNV amplitudes.

Knott & Irwin (1968) recorded the CNV of highly anxious and low anxious control subjects. They found CNV's of lower amplitude in highly anxious individuals. They explained these data by assuming that persons with high anxiety have a higher baseline of cortical negativity than low anxiety groups. Thus, under stress, a maximum ceiling for cortical depolarization (hypothetical state) is reached earlier by the highly anxious group. Subsequently, Low & Swift (1971) measured the CNV of low and high anxiety subjects during easy and difficult tasks. They found similar results to those of Knott & Irwin, highly anxious subjects showed CNV of smaller amplitudes than did low anxiety subjects. It was observed that magnitudes for both high and low anxiety subjects progressively decreased in the more difficult conditions. These data were interpreted as further support for the existence of an effective ceiling for negative slow potential changes within the brain. The CNV is believed to rise toward this ceiling from a variable baseline, which is partly determined by anxiety or stress. These authors believed that the ceiling effect (maximum cortical excitation associated with a negative shift in the baseline DC level) exists and proposed that the maximum amplitude (upper limit) of the CNV results from an increasing tonic cortical inhibition rather than from a physical incapacity of the cortex to shift negatively beyond some fixed level.

Broughton (1975) suggested that the decreased CNV amplitude recorded in sleep-deprived subjects could be the effect of the increased depolarization of the cortex related to continuous wakefulness. This depolarization would elevate the baseline of cortical

negativity allowing less opportunity for increase in the CNV before the ceiling of maximal negativity is reached and would thus result in decreased CNV amplitude. Neither the "maximum ceiling effect" nor the "maximal cortical inhibition" are, however, easily testable hypotheses.

Researchers have also approached the study of sleepiness from a biorhythmic perspective. Based on data provided by the MSLT, a picture of the diurnal variation of sleepiness has emerged in which sleep tendency exhibits a biphasic pattern, minimal both in the morning and evening and maximal in the very early hours of the morning and early afternoon (Carskadon & Dement, 1975, 1977; Richardson et al. 1982). These same fluctuations in sleep onset latencies have been confirmed in studies that found sleep deprived subjects to have shorter latencies in the early morning and afternoon. These studies showed decreased latencies at certain times and longer latencies at others independent of hours of sleep deprivation. Richardson et al. (1978) reported a decrease of sleep onset times in the early afternoon in narcoleptics (patients with PS) and controls, which suggests that similar fluctuations may be present in both normal and pathological sleepiness.

Fluctuations of alertness through the day are accompanied by fluctuations in ability to sustain attention (Froberg, 1975). As mentioned, the different components (P1, N1, P2, N2, P3) of the auditory evoked potentials have been conceptualized as reflecting both attentional and perceptual processes (Hillyard et al. 1973; Donchin et al. 1978; Ritter et al. 1979). Fluctuations in biorhythmic pro-

cesses may therefore be mirrored in fluctuations in AEP components. Fluctuations in AEPs have indeed been reported but no agreement exists as to the trend that these fluctuations follow over the day. Henninger (1969) failed to observe significant changes in AEPs across time. Davis et al. (1978) reported lower amplitudes of somatosensory EPs during the morning than during the afternoon. Others (Browman & Sullivan 1980; Kerkhof, 1982) have reported larger amplitudes in the auditory evoked potentials in the morning compared to the evening. Recent studies have considered the possiblity that differences in amplitude through the day might be related to individual differences in diurnal arousal patterns (Kerkhof et al. 1980; Kerkhoff, 1982). It has been reported that the N1-P2 components of morning persons are larger during the morning than during the evening while the opposite seems to occur in evening persons. The existing evidence suggests that the AEP technique might provide a useful and objective measure of fluctuations of alertness and the ability to sustain attention through the day. If differences in fluctuations of alertness through the day are present in normal and PS, they should be mirrored in the AEP waveforms.

Sleepiness (pressure for sleep) state preceding REM and NREM sleep

Through observation of the EEG, Dement & Kleitman (1957) observed five different and distinctive stages which they subdivided in two main sleep states; rapid eye movement sleep or REM sleep characterized by rapid ocular movements and NREM which includes all sleep in which these eye movements are absent.

REM sleep is qualitatively quite distinct. It consists of an EEG with low voltage mixed frequencies and occasional superimposed bursts of so called "sawtoothed waves". In addition, absence of tone in the midline axial muscles of the body, usually monitored by a submental EMG; increases in heart rate, blood pressure and respiratory rate and, especially increased variability of autonomic functions are noted. Furthermore positive transient motor phenomena including twitching movements of the extremities and facial regions and rapid eye movements can be recorded. The presence of penile erections in males and increased vaginal blood flow in females have been recorded.

The main biological characteristics of NREM sleep are progressive slowing and increase in amplitude of EEG, decreasing muscle tone, slowing of heart and respiration and relative body quiescence. The EEG is used to divide this continuum arbitrarily into four stages according to the predominant brain wave activity in a given time epoch (usually 30 secs). These are: stage 1 (involving loss of waking 8-12 Hz alpha rhythm, presence of low voltage mixed frequency, mainly 4-7 Hz theta activity); stage 2 (presence of 12-15 Hz sleep spindles on a low voltage background activity with less than 20 per cent of the epoch containing high voltage (over 75 uV) delta activity of 3 Hz or less frequency; stage 3, (20-50 percent such delta activity) and stage 4 (greater than 50 percent delta) (Rechtschaffen & Kales, 1968). Stages 3 and 4 are often considered together as "slow wave sleep" or "delta sleep".

From later childhood and continuing into adulthood, sleep usually recurs only once a day and thus is circadian in distribution

(Williams & Karacan, 1974; Williams et al. 1964). By late childhood, most of the SWS is present in the first third of the night. NREM sleep normally precedes REM sleep for 60 to 120 minutes. During the night, NREM sleep becomes lighter and the REM periods tend to increase in length from the second to the third cycle and then stabilize such that the last third of sleep is about 50 per cent in REM and 50 percent in NREM sleep. Of the usual 6.5-8 hours sleep in young adults, stage 1 represents about 5 percent of total sleep time; stage 2, 50-55 percent; stage 3, 10 percent; stage 4, 10 per cent and REM sleep 20-25 per cent. Probably the most stable characteristic of sleep for a given individual or age group is the duration of the NREM/REM alternation, the cycle lengthening from 40-45 min in the neonate to approximately 90-100 min in the adult (Roffward et al. 1966).

Another distinctive characteristic of both types of sleep is the type of mental ativity that accompanies each. Mental activity of dream type largely occurs within the REM sleep state, being reported after some 70-90 percent of awakenings in REM sleep and after only 7-9 percent of NREM awakenings (Goodenough et al. 1965; Cohen, 1974). Other studies have found dream reports following up to 35 percent (Goudenough et al. 1965) and 54 percent (Foulkes, 1962) of NREM awakenings. It is now certain that dream-like reports can follow awakening from either type of sleep but are more common in relation to REM sleep (Cohen, 1974). Although dreaming can no longer be equated exclusively with REM sleep, there remain important differences in mental activity during sleep. The dreams reported after NREM (usually stage 2) awakenings tend to be less vivid and less bizarre than those

following REM awakenings. Thought-like mentation is more frequent in NREM sleep (Foulkes, 1967, Cohen, 1974; Gardiner et al. 1975).

Further evidence that REM and NREM are quite distinctive is provided by the fact that pressures for REM or NREM sleep exist under different circumstances. For example, pressure for REM exists when the normal circadian sleep-wakefulness cycle is altered either by submitting people to short sleep waking cycles (60 minutes wakefulness 30 minutes sleep) for prolonged periods of time, or by depriving them selectively of REM sleep (Webb & Agnew, 1974; Vogel, 1975; McGrath & Cohen, 1978). Pressure for REM also occurs when patients are withdrawn from medication such as tricyclic antidepressants (Lewis & Oswald, 1969; Nakazawa et al. 1975). Pressure for NREM, on the other hand, occurs under conditions of phasic, chronic or total sleep deprivation conditions (Johnson, 1973; Johnson et al. 1974). An increase of NREM sleep is also observed during conditions of starvation and hyperthyroidism (Oswald, 1973, 1974; Webb & Agnew, 1974) which provides support for the hypothesis that NREM sleep is involved in metabolic restoration (Karacan et al. 1971; Oswald, 1973, 1974).

Electrophysiological studies that have recorded EEG DC potential shifts, measured by subcortically placed electrodes, during these states also support the theory that REM and NREM are distinctive entities (Kawamura & Sawyer, 1964; Tabushi et al. 1966). DC shifts during the transition into REM have been shown to vary in the positive direction (Evarts, 1965, 1967; Noda & Adey, 1970) while DC shifts that occur as the subjects fall into NREM vary in a negative direction

(Caspers, 1965). DC shifts that have been recorded during REM sleep are negative-going (Tabushi et al. 1966) and during NREM sleep are positive-going (Kawamura & Pompeiano, 1969). Such pre-REM or pre-NREM DC baseline biases may have possible implications for the CNV. As already mentioned, it is subject to "ceiling effects", perhaps due to an already existing negative DC bias.

Based on the evidence that REM and NREM sleep are quite distinctive states, Broughton (1982) proposed that the states preceding them might also be considered distinctive physiological states. He suggested that the sleepiness experienced by a person might reflect impairment of waking arousal mechanisms, pressure for NREM or pressure for REM. The electrophysiological processes and the qualitative characteristics accompanying pressure for either type of sleep could well be different. The difficulty in testing this hypothesis stems from the fact that because of the order of succession between these states (NREM appears prior to REM in natural sleep) it is not possible to study REM without the interference of NREM sleep. Carskadon & Dement (1975, 1977, 1979) altered the sleep-waking cycles of individuals for 5 and a half days subjecting them to a 60 minutes wakefulness 30 minutes sleep cycle and observed that REM sleep occurred at onset instead of following NREM sleep. Subjects were asked to fill in the Stanford Sleepiness Scale and rate their level of alertness before and after their sleep. They observed that pre-sleep SSS rating were directly correlated with amount of REM sleep (higher scores associated with more REM sleep) while uncorrelated with SWS. They also observed that sleepiness decreased more following naps containing greater

amounts of REM sleep. It is possible that the beneficial arousing effects of REM sleep are related to a larger degree of sleepiness being present prior to this state. Apart from this study, very little investigation of pre-REM and pre-NREM behaviour has been attempted. An alternative approach to the study of the qualitative and quantitative aspects of the states prior to REM and NREM sleep is to study a group of patients, narcoleptics, who have the characteristic of sometimes falling directly into REM sleep.

Narcolepsy is a disorder that falls into the diagnostic classification of Disorders of Excessive Sleepiness (DOES) established by the Association of Sleep Disorders (1979). Narcolepsy, was first described as a discrete disease entity by Gelineau in 1880 as a "rare, little known neurosis characterized by an imperative need to sleep, of sudden onset and short duration, recurring over more or less close intervals" (p. 1156) For many years narcolepsy was synonymous with hypersomnia. It is now known that the condition rarely, if ever, is characterized by excessive sleep within a 24-hour period (Rechtschaffen & Dement, 1969; Kales & Kales, 1974). Yoss and Daly (1960) established the criteria for diagnosis of narcolepsy which included four major symptoms, termed the narcoleptic tetrad. These are irresistible sleep attacks, usually the first symptoms to appear, and three auxiliary symptoms: cataplexy, sleep paralysis and hypnagogic hallucinations. Of these, one or more usually appears as the disease progresses (Sours, 1963, Guilleminault & Dement, 1974, Carskadon, 1976). The symptoms tend to be unremitting once they occur. A major complaint in this patient population is the presence of chronic

daytime drowsiness.

The incidence of narcolepsy in the general population is not known with certainty, but it is believed to range from 0.02% to 0.05% (Bruhova and Roth, 1972). Prevalence studies conducted in the San Francisco (Dement et al. 1972) and Los Angeles (Dement et al. 1973) areas, showed that the incidence may be as high as .09 percent. Narcolepsy characteristically begins at a point of maturational crisis such as puberty or pregnancy. The common age of onset is between 25 and 35 years, although approximately 5% of the cases seem to begin before the age of 10 and 18% after the age of 30 (Roth, 1957; Zarcone, 1973).

Narcolepsy can appear in association with CNS dysfunctions, brain tumours, metabolic disorders, encephalitis or vertebral artery insufficiency (Roth, 1980). Idiopathic narcolepsy is, on the other hand, unrelated to any of the above mentioned disorders. Two types of sleep attacks have been delineated and are associated with two different categories of narcolepsy (Dement et al. 1966; Roth et al. 1969). Independent narcolepsy (characterized by sleep attacks alone) involves NREM sleep attacks in which the patient gradually goes from drowsiness to NREM sleep. Compound narcolepsy (characterized by auxilliary smptoms -cataplexy, sleep paralysis, etc.- most often involves sleep onset REM periods (SOREMP) which tend to be more abrupt in onset (Guilleminault & Dement, 1974).

Narcoleptics in general can have both types of sleep attacks, those in which they experience REM sleep, either at onset or following NREM epochs and those in which they spend time exclusively in NREM

sleep. This population then provides the opportunity to study the waking state immediately preceding REM sleep without the interference of NREM sleep.

Pressman et al. (1982) have recently measured AEP components in a group of narcoleptic patients just prior to an onset of either REM or NREM sleep. The state prior to NREM naps in narcoleptics was associated with larger N1-P2 and P2-N2 than that prior to their REM naps and prior to NREM naps in non sleep-deprived controls. No differences were found between the state pre-REM in narcoleptics and non-sleep deprived controls or the state pre-NREM in narcoleptics and sleep deprived controls. These findings suggest that the neurophysiological state of narcoleptic subjects just prior to REM sleep is different from the state just prior to their NREM sleep. These results, therefore support the proposal that two different types of sleepiness exist (Broughton 1982). Research should be carried out to further investigate the states that appear prior to REM and NREM sleep. That REM and NREM sleepiness (the pressure for sleep prior to these states) might be quite distinct should be researched by studying the diverse aspects of sleepiness; its subjective, attentional and electrophysiological characteristics.

PURPOSES AND HYPOTHESES OF THE PRESENT RESEARCH

The purposes of the study described in the following reports were:

1) To investigate the characteristic differential features of normal and pathological sleepiness, and the similarities and differences of fluctuations through the day between both types of sleepiness.
2) To test the hypothesis that the pressure for sleep preceding REM and NREM sleep stages constitute two types of sleepiness states, each one with specific and distinctive characteristics.

Measures were employed that investigated the different aspects of sleepiness. Subjective aspects were measured through a self-rating sleepineess questionnaire, the Stanford Sleepiness Scale (SSS). Mental aspects were studied through a signal detection task which required sustained attention. Detection rates and reaction times were considered indices of attentional levels. Electrophysiological states were investigated by measuring sleep onset times through the day using the standard EEG recording (Multiple Sleep Latency Test). Another index of the electrophysiological states accompanying the different types of sleepiness was obtained by the measurement of brain potentials evoked by auditory stimuli delivered to the subjects in the context of paradigms of attention. Auditory evoked potentials and the contingent negative variation paradigms were employed.

HYPOTHESES RELATED TO DIFFERENCES BETWEEN NORMAL AND PATHOLOGICAL SLEEPINESS

Related to SSS

The clinical literature suggests that the sleepiness experienced through the day by people with PS, is of a much more intense nature (Ganado, 1958; Dement, 1976) than that experienced by . . . healthy people. On the other hand, some studies have shown that SSS is not a particularly sensitive measure for estimating the degree of subjective sleepiness of this patient population since the chronicity of their sleepiness cause them to lose their frame of reference for judging their own lack of wakefulness (Dement et al. 1978; Roth et al. 1980). Because of the functional level of the patient population used in the present study (actively employed and remaining active in their social and family life) it can be assumed that the degree of severity of the illness in this population was not so extreme to prevent the patients from subjectively evaluating their own level of sleepiness. Therefore,

> It was hypothesized that PS would be characterized by significantly higher SSS scores (greater sleepiness) compared to normal controls.

Based on clinical reports (Daniels, 1934; Ganado, 1958; Dement, 1976) indicating that sleepiness is chronically present in people

with sleep disorders (suffering PS) thereby lessening their sensitivity to fluctuations of subjective alertness,

> It was expected that the fluctuations of PS as reflected in SSS ratings (averaged scores over different periods during the day: morning (0930-1230), early afternoon (1300-1630) and late afternoon (1630-1830) would be smaller than those observed in normals.

Reports in the literature (Yoss and Daly, 1960) indicate that narcoleptics report their day naps to be very refreshing. Considering that the relief provided by sleep would be of much larger magnitude when the pressure for sleep was larger, (as could be expected in PS)

> It was hypothesized that narcoleptics' change of alertness scores after the naps (SSS scores after naps minus SSS scores prior to naps) would be significantly larger compared to to the changes observed in normal control subjects.

Related to Multiple Sleep Latency Test

Assuming that sleepiness is a reflection of a very real biological need for sleep (Carskadon & Dement, 1982) it appears that this need is particularly great in PS:

> It was hypothesized that PS would show significantly shorter sleep onset latencies and longer sleep times than controls.

The literature also suggests (Richardson et al. 1978) that both narcoleptics and normal control subjects show similar increases of sleepiness, (as expressed by shorter sleep onset latencies) in the afternoon (1400 and 1600 hrs) as compared to the morning (1000 and 1200) and late afternoon (1800). Therefore,

> It was expected that both groups would show significantly shorter sleep onset times and longer sleep times in the 1400 and 1600 MSLT recording sessions.

Related to Auditory Evoked Potentials

The latencies and amplitudes of AEP mesogenous components (P1,N1,P2) have been reported to be sensitive to levels of alertness (Weitzman & Kremen, 1965; Fruhstrofer et al, 1969) and to the degree of attention paid to the stimuli (Picton & Hillyard, 1974). Endogenous components (N2-P3) have been shown to reflect discriminatory, recognition and perceptual processes (Picton & Hillyard, 1974; Donchin et al. 1978; Ritter et al. 1979). It has long been established that sleepiness is accompanied by difficulties in sustaining attention (Williams et al, 1959), and in lower levels of efficiency in perceptual processes (Wilkinson et al. 1966). It could be expected that a direct relationship exist between intensity of sleepiness and levels of difficulty in maintaining attention and mental efficiency. It is logical to expect that the larger intensity of sleepiness present in people with PS is accompanied by larger difficulties in attentional and perceptual processes, and that these latter would be differently

expressed in the amplitudes of the AEP's recorded during normal and pathological sleepiness. Therefore:

> It was expected that significantly larger decreases in N1 and P3 amplitudes would be recorded in PS patients than in controls.

It has been reported (Browman & Sullivan, 1980; Kerkhof, 1982) that fluctuations of alertness are reflected in increases and decreases in N1-P2 AEP amplitudes from morning to afternoon. Therefore:

> It was expected that significant decreases in amplitudes of P1, N1 and P2 would be recorded from morning to afternoon in controls and that the already significantly decreased AEP components of narcoleptics would decrease further through the day.

Based on scalp distribution studies showing that the different AEP components are maximally recorded over specific areas (Picton et al. 1974; Simson et al. 1976, 1977a).

> It was expected that in both groups N1 and N2 would be maximally recorded over frontocentral areas (Fz and Cz), P2 would display a more posterior distribution, and P3 was expected to be maximal over parietocentral areas.

Related to Contingent negative variation

CNV increases in amplitude may reflect the larger attentional level or larger degree of phasic alertness of the subject (Tecce 1972, Tecce et al.1976; Posner, 1978). Considering that sleepiness is usually accompanied by lowered levels of alertness,

It was hypothesized that CNV amplitude recorded in patients with PS would be significantly smaller than those of control subjects.

Studies have shown that in long intervals, the early and late negativities are maximally recorded over different areas (Loveless & Sanford, 1974; Gaillard, 1976, 1977; Simson et al. 1977). Therefore,

It was expected that in both groups the average magnitude in the first half (AMFH) of the CNV interval would show a maximal amplitude over frontal areas (Fz) and the second half (AMSH) would be maximally recorded centrally (Cz) with reduced magnitude frontally (Fz) and parietally (Pz).

HYPOTHESES RELATED TO DIFFERENCES BETWEEN REM AND NREM SLEEPINESS

Related to SSS

The study of Carskadon & Dement (1975) carried out with normal control subjects suggested that the state preceding REM sleep (from wakefulness to REM sleep directly) is accompanied by larger pressure for sleep or larger feelings of sleepiness. Therefore,

It was hypothesized that pre-REM SSS scores would be higher than pre-NREM scores.

Related to Multiple Sleep Latency Test

Based on the premise that there is a large positive correlation between subjective sleepiness and sleep onset times (Carskadon & Dement, 1981, 1982)

It was expected that REM sleepiness would be accompanied by significantly shorter sleep onset times as compared to sleep latencies recorded prior to NREM sleep

Related to AEP's

As mentioned above mesogenous components reflect levels of alertness (Weitzman & Kremen, 1965), and degree of attention paid to the stimuli (Picton & Hillyard, 1974). Based on the premise that larger levels of sleepiness precede REM sleep as compared to NREM and that lower levels of alertness are accompanied by larger difficulties in sustaining attention.

It was hypothesized that the N1 and P3 components recorded prior to REM would be of smaller amplitude than those recorded prior to NREM.

No apriori hypotheses were set regarding the differential scalp distribution to be recorded prior to REM or NREM sleep.

Related to CNV

Research findings indicate that DC potential shifts recorded in the transition from REM to NREM sleep are negative-going (Tabushi et al. 1966; Kawamura & Pompeiano, 1969) while those recorded in the transition from NREM to REM sleep are positive-going (Tabushi et al. 1966, Kawamura & Sawyer, 1964; Kawamura & Pompeiano, 1969). Negative potential shifts have been recorded as the subjects drifts into NREM sleep (Caspers, 1965), though these findings have not always been confirmed (Rossi et al. 1961). Because the CNVs in this study were

to be recorded prior to the transition from wakefulness to either REM or NREM sleep it was assumed that different DC potential shifts might occur prior to these states. Due to lack of available information in the literature regarding these states,

> No apriori hypothesis were established regarding size and scalp distribution differences of the amplitudes to be recorded prior to these two sleep states, although, differences were expected.

FORMAT OF THE PRESENT THESIS

The present thesis consists of two separate reports. The first describes a study carried out to evaluate the usefulness of AEP's in defining pathological sleep and differences in the daily fluctuations of normal and pathological sleepiness. The second report describes results of statistical comparisons of the data recorded prior to REM and NREM sleep. The format of the thesis follows the style of the Journal of Electroencephalography and Clinical Neurophysiology to which a revised manuscript will be submitted.

EVENT-RELATED POTENTIALS AS A METHOD OF DIFFERENTIATING NORMAL AND PATHOLOGICAL SLEEPINESS

INTRODUCTION

In the past, the study of sleepiness has been of indirect interest to researchers studying sleep functions through sleep deprivation (Froberg et al. 1972; Dement & Mitler, 1974; Friedman et al. 1974; Glenville & Broughton, 1979). Its study has recently been pursued more extensively in clinical settings (Carskadon et al. 1981; Zorick et al. 1982; Valley & Broughton, 1982), possibly because excessive daytime sleepiness is now recognized as a primary disabling symptom (Coleman et al. 1982).

Sleepiness seems to result from a combination of amount of prior sleep (Carskadon & Dement, 1981; Carskadon et al. 1981) and circadian effects (Carskadon & Dement, 1977, 1979; Broughton, 1975). However, there is evidence that other factors affect the sleepiness of those with sleep pathologies who experience intense sleepiness independent of the amount of night sleep. For example, hypersomniacs sleep from 10 to 14 hours and still experience excessive daytime sleepiness (pathological sleepiness) throughout the day (Roth et al. 1969; Roth, 1980).

Clinical researchers have been interested in determining the similarities and differences between normal and pathological sleepiness. The greatest difficulty involved in such an undertaking is the lack of available methods for its quantitative study. A method that has recently been employed to evaluate the neurophysiological correlates of the lower alertness levels of pathological sleepiness (PS)

involves the use of auditory evoked potentials (AEPs). This technique consists of the electroencephalographic recording of brain responses to auditory stimuli usually delivered to the subjects through earphones. AEPs have been shown to be sensitive to levels of attention (Hillyard et al. 1973; Picton et al. 1974; Schwent et al. 1976a, 1976b), lower levels of arousal (Weitzman & Kremen, 1965; Fruhstorfer & Bergstrom, 1969) and fluctuations of alertness through the day (Browman & Sullivan, 1980, Kerkhof et al. 1980, Kerkhof, 1982).

No definite conclusions have been made regarding the neurophysiological correlates of PS as reflected by the AEP components (Pressman et al. 1982, Broughton et al. 1981, Broughton, 1982). Recently, Pressman et al. (1982) recorded long latency evoked potentials prior to Multiple Sleep Latency Test (MSLT) naps (Carskadon & Dement) in sleep deprived controls, non-sleep deprived controls, and narcoleptics. Narcolepsy is a sleep disorder characterized, amongst other symptoms, by sleep attacks in which the patient falls directly into NREM or REM sleep (Guilleminault & Dement, 1974). Pressman and his colleagues (1982) observed that sleep deprived subjects showed larger N1-P2 and P2-N2 amplitudes than did narcoleptics. The AEP amplitudes recorded in narcoleptics did not differ from those recorded in nonsleep deprived subjects. The data were then analyzed according to the type of sleep into which narcoleptics subsequently fell (REM or NREM). It was observed that EPs recorded prior to NREM naps in narcoleptics had significantly larger amplitudes than those of both non-sleep deprived subjects and those recorded prior to REM naps in narcoleptics. The pre-NREM nap amplitudes were as large as those

recorded in sleep deprived subjects. Based on these findings, the authors concluded that due to the presumed influence of an underlying REM pressure during behavioural wakefulness in narcoleptics, the AEP would not be useful as an independent measure of sleepiness in this patient population.

Broughton et al. (1981), on the other hand, recorded significantly decreased N1, P2, N2 and P3 amplitudes in narcoleptics in the presence of a waking EEG pattern during a focused attention task (Wilkinson Auditory Vigilance Test). It was not possible to obtain a recording of evoked potentials from controls in a state of drowsiness since they remained awake most of the time. Broughton and colleagues (Broughton et al. 1981; Broughton, 1982) have suggested that the AEP approach might prove a more sensitive measurement of PS than the visual analysis of the EEG.

The differing conclusions of these two research groups may perhaps be explained by methodological variances. Firstly, there was a difference in stimulus type, intensity and rate of presentation, each of which has a marked effect on N1 and P2 morphology. While Pressman and his group delivered clicks just prior to a nap and asked the subjects to remain alert, Broughton's group measured AEP's to tones during a one hour vigilance task. It appears that further research should be done to determine if AEP measures can in fact identify PS and therefore be used as a rapid method of quantitative assessment.

It is widely believed that extreme sleepiness will lead to impaired performance (Carskadon & Dement, 1975, 1977; Glenville & Broughton, 1979). Guilleminault et al. (1975) have reported that performance decrements in narcoleptics take the form of lapses accompanied by microsleeps consisting of short bursts of stage 1, synchronized theta activity, or stage 2 sleep. Valley & Broughton (1983) have shown that low performance levels in narcoleptics occur during electroencephalographic wakefulness, but at reduced levels of alertness. Since performance deficits, in general, seem to be related to the inability to sustain attention (Williams et al. 1959; Wilkinson et al. 1966), the study of attentional engagement can provide useful information regarding differences between normal and pathological sleepiness. Three types of event related potentials have been associated with attention and may be useful in the evaluation of sleepiness. These are the AEP components N1 and P3 (Hillyard et al. 1973; Picton et al. 1974; Ford et al. 1976; Picton et al. 1978), and the contingent negative variation (CNV) (Walter et al. 1964; Loveless and Sanford, 1974a, 1974b; Gaillard, 1976).

In an odd-ball paradigm, "target" stimuli are presented which differ in some physical characteristics from a train of non-target stimuli. As the subject listens to each stimulus, a negative wave is recorded at approximately 100 msec (hence the label N100). This N100 component increases in amplitude when a larger degree of attention is paid to the stimuli (Picton et al. 1974; Parasuraman et al. 1980). However, this is highly dependent on stimulus parameters such as

intensity and rate of presentation (Scwent et al. 1976a, 1976b, 1976c). When the subject detects the target stimuli a late negative-positive complex, occurring after approximately 200 msec., is recorded. This complex (N2-P3) is said to reflect further cognitive processing subsequent to the analysis of the physical characteristics of the stimuli (Donchin et al. 1978; Picton et al. 1978). The sensitivity of this paradigm to the effects of sleepiness associated with sleep deprivation which has been reported recently (Campbell et al. 1980) suggests it may be useful as a tool in the evaluation of pathological sleepiness.

The CNV is a slow negative potential that can be recorded from the scalp after the presentation of a warning stimulus and prior to the presentation of a second stimulus (imperative stimulus) which the subject is asked to detect (Walter et al. 1964). Naitoh et al. (1971) found this paradigm to be more sensitive than performance measures (reaction time) to the effects of phasic sleep deprivation. Peeke et al. (1980) found no CNV amplitude differences between sleep deprived and non-sleep deprived subjects in a CNV paradigm which required the subjects to remember information from the previous trial and compare it to S1 before being able to respond to S2. The cognitive demands of this paradigm may have forced the subjects to increase attentional effort which compensated for their low level of alertness. The sensitivity of the CNV in the evaluation of pathological sleepiness has yet to be determined.

Another issue of interest is the fluctuation of sleepiness through the day. Carskadon and her colleagues (Carskadon et al. 1981,

1981a) have shown that sleepiness is accentuated in the very early hours of the morning and again in the early to mid-afternoon. They also found that sleepiness is decreased in later hours of the morning and early evening independent of the amount of hours of prior sleep (Carskadon & Dement, 1975, 1977; Carskadon et al. 1981a).

Very little is known about the fluctuations of pathological sleepiness (PS) which accompany sleep disorders and are experienced by the patients as excessive daytime sleepiness. It seems that normal sleepiness is felt intensely only at certain times during the day (Richardson et al. 1982), and pathological sleepiness is chronically present (Dement, 1976, 1979). Richardson et al. (1978) showed that narcoleptic patients and their controls had faster sleep onset times in the early afternoon, a time of day at which controls have been known to increase their sleepiness (Blake, 1967; Richardson et al. 1982). Shorter sleep latencies in the early afternoon seem to be a common characteristic of both types of sleepiness (Richardson et al. 1978). These findings suggest that similar fluctuations of physiological sleepiness may exist in normal and pathological sleepiness. The nature of the fluctuations in both types of sleepiness are not known and should be researched further.

The purpose of the present study was two-fold: 1) to further investigate the usefulness of ERPs (AEPs and CNVs) in the evaluation of PS and 2) to determine fluctuation differences between normal and pathological sleepiness, which are known to be reflected by AEP's (Kerkhof, 1982).

METHODS

Thirteen right-handed patients with a history of narcolepsy-cataplexy, with or without further accessory symptoms, participated in the study. Data from one of the patients were not analyzed, as she slept during most of the performance testing sessions. Of the 12 remaining narcoleptics, 5 were female and 7 were male. Their ages ranged from 22 to 63 years (mean= 46.3 SD= 13.2). Duration of illness ranged from 1 to 30 years. Because very few narcoleptics had durations of illness less than 10 (3 subjects) or between 10 and 20 years (2 subjects), it was not possible to subdivide the population to permit a study of the effects of duration of illnes. Five narcoleptics were not under treatment at the time of the study. The remainder were withdrawn from all tricyclic medication for at least three weeks and from stimulants for at least one week prior to the study. A patient who had been taking gamma-hydroxy-butyrate was withdrawn from the medication three weeks before the study. Although all narcoleptics experienced cataplexy, all remained functional, able to work and participate in active social and family lives. Each of the narcoleptics were given a polysomnogram in the six month period prior to the study. They all showed disturbed nocturnal sleep characterized either by multiple awakenings (11 cases) or leg myoclonus (2 cases). Seven were found to have coexistent sleep apnea (3 obstructive, 3 central and 1 mixed type) with an average of 2.4 sleep apneas per hour.

Thirteen normal controls were recruited from different clubs and centres in the city. They were interviewed prior to inclusion in the study. Criteria for exclusion were as follows: irregular sleep

habits, problems falling or staying asleep, frequent drug or alcohol ingestion, habitual daytime naps, and major medical or psychiatric disorders. During experimentation, one of the controls showed sleep onset REM periods in 9 of the 10 naps, despite the absence in his personal or family history of any sleep disorders. This subject's data was replaced by that of another normal control. Controls were paid $50.00 for their participation.

Narcoleptics and controls were matched as closely as possible for sex, age, education (narcoleptics mean 16.8 years, controls 17.1) and IQ (narcoleptics mean 122, controls 124), as measured by the Wechsler Adult Intelligence Scale (Wechsler, 1955). Recent studies (Kerkhof et al. 1980; Kerkhof, 1982) show that AEP fluctuations through the day are related to the personality type of the individual (morning type people show larger EP amplitudes in the morning and evening type people show larger EP amplitudes in the evening). To control for this, each narcoleptic was matched to his/her respective control for their diurnal personality (morning or evening types), based on scores from the Horne & Ostberg (1976) version of The Ostberg Swedish Morningness Eveningness Questionnaire (Ostberg 1973). Narcoleptics obtained on the questionnaire an average score of 56.9 (SD= 12.5) and controls 56.6 (SD= 11.30). Each group was comprised of 4 moderately morning type, 3 definitely morning type, 2 moderately evening type and 3 that did not fit any classification.

Subjects were screened for normal hearing at 20 dB ISO for 1000 and 2000 Hz pure tones. All controls had normal hearing. One of the narcoleptics had a moderate hearing loss (30 dB) for the 1000 Hz frequency. Female subjects participated during the luteal phase of their menstrual cycle.

Both narcoleptics and controls were requested to go to sleep at their regular bedtime for at least three nights prior to the experimental period. They were told that the purpose of the experiment was to measure their brain activity throughout the day and that it was important that they should not be unusually tired.

General Paradigm

Each subject was tested over two consecutive days. SSS forms were completed at intervals of approximately 30 min. throughout both days. Subjects were asked to take naps 5 times a day, at 1000, 1200, 1400, 1600 and 1800 as part of the MSLT (Richardson et al. 1978). Prior to each MSLT, one of two different ERP paradigms was applied. On one day, the P3 paradigm was employed and on the other, the CNV (Walter et al. 1964) was recorded. Half of the narcoleptic patients and their respective controls were randomly selected to receive the P3 paradigm during the first day, and the other half during the second. During the testing sessions EEG, EOG and submental EMG were monitored to assess the subjects' sleep/waking state.

The subjects arrived at the laboratory at 0800 hrs. and electrodes were applied. At approximately 0900 hrs they were given a

short practice trial of the paradigm they would receive that day. They spent the time between ERP tests and MSLT naps reading or talking to the experimenter. After the 1800 testing session, the electrodes were removed and the subjects went home, returning the next day at 0800 hrs. Due to equipment problems, two of the control subjects and one narcoleptic were not studied on consecutive days. One of the controls and the narcoleptic were tested for the second time one week later; the other control was tested after a three week interval.

Subjects were not permitted to ingest alcohol or coffee during the day. They had lunch at approximately 1230 hrs.

MSLT

Following the ERP testing session, subjects were asked to lie down on the bed and to try to fall asleep. Electroencephalographic signals were recorded from the standard Cz and O1 locations of the International 10-20 System (Jasper, 1958), using Beckman Ag/AgCl electrodes which were connected to the scalp with Beckman saline paste, collodion, gauze and adhesive collars. Right and left mastoid electrodes were linked and served as reference for the EEG recordings. Vertical and horizontal eye movements (electroculogram EOG) were recorded from electrodes placed directly above and below the left eye and on the outer canthi of the eyes, respectively. The interelectrode impedances were below 3 kOhms. The EEG, EMG and EOG signals were amplified by a Beckman R-611 polygraph. Due to the 8-channel oscillograph limitation of the Beckman polygraph, the output of these signals as well as stimulus and response indicators were fed into the

chart drive of a 13-channel Nihon Kohden polygraph. Chart speed was set at 15 mm/sec and calibrated at 70 uV/cm for EEG, 100 uV/cm for EOG, and 20 uV/cm for EMG.

The MSLT was terminated after a maximum of 20 minutes in bed or following 10 consecutive minutes of sleep. The data were scored by one person in 20 sec epochs using standard criteria (Rechtschaffen and Kales, 1968). Twenty percent of the records were scored by a second person in order to get a coefficient of reliability. Fluctuations in EEG activity during the naps were investigated by scoring a state designated by Gastaut & Broughton (1965) as stage 1A. This stage was scored when more than 50% of an epoch contained either or both of the following EEG events: a) slower alpha rhythm (defined as at least 1 cps slower than the individuals waking or baseline alpha rhythm) and b) alpha rhythm having an irregular or fragmented appearance i.e. intermixed with a medium voltage mixed frequency pattern. Eye movements were important cues for scoring. During this stage they often occurred as low amplitude or definite slow rolling eye movements lasting at least 3 secs.

Sleep onset latency was considered to be the interval between the beginning of the test and either six consecutive epochs (2 minutes) of stage 1B or one epoch of stage 1B followed by stage 2 or REM. Stage 1B corresponded to stage 1 according to Rechtschaffen & Kales (1968) scoring criteria. The REM latency was taken as the interval between the start of the test and the first epoch of REM sleep. Sleep efficiencies (total sleep time/total time in bed) were calculated together with number of arousals and time awake after sleep onset.

To determine if there were any differences in the degree of sleepiness experienced between day 1 and 2, as expressed in sleep onset times and total sleep times, an analysis was done of latencies to stages 1B and 2 and sleep time spent in these stages.

Sleep latencies and total sleep times were subjected to a two factor (groups by sessions) ANOVA with repeated measures on the sessions factor. Alpha level was set at $p < .05$.

SSS

To obtain a measure of subjective sleepiness, all subjects filled in SSS forms at approximately 30 minutes intervals. They also completed the forms before and after each ERP testing session (just prior to each MSLT nap) and within 2 minutes following the MSLT session.

In order to assess subjective diurnal fluctuations of alertness, SSS ratings of narcoleptics and controls were averaged over 3 time periods, morning (0900–1230), early afternoon (1300–1630) and late afternoon (1630–1830).

Changes of alertness resulting from both ERP testing and napping, were measured by subtracting the SSS scores prior to ERP testing sessions from those after the sessions and by subtracting those prior to MSLT naps from those after the naps. The resultant change of alertness score would indicate a decrease in the level of alertness if negative and an increase in alertness if positive.

The comparisons between narcoleptics and controls averaged SSS scores and change of alertness scores were done by using the Mann-

Whitney Test (Spiegel, 1956). SSS fluctuations of alertness scores were analyzed by a Friedman two-way analysis of variance by ranks (Spiegel, 1956).

P3 ERP Study

All subjects had long latency auditory evoked responses recorded during wakefulness immediately prior to each of the 5 naps of the day. Each recording session lasted about 6 min. The subjects sat on a bed in a sound-attenuated and electrically shielded room. Their backs were supported by a removable wood back rest placed against a wall. During the recording, they were instructed to keep their eyes fixed on a point approximately 1.5 m in front of them and to blink as little as possible.

EEG signals were recorded from standard Fz, Cz and Pz locations and referred to linked mastoids. EOG derivations were the same as in the MSLT recording.

The inter-electrode impedances were below 3 kOhms. The EEG and EOG signals were passed to the computer for averaging following amplification by the Beckman R-611 polygraph. The amplified EEG and EOG signals were digitized by a MINC-11 computer using dwell times of 4.5 msec over a 900 msec sweep time beginning 50 msec prior to stimulus onset. Digitized single trial data were coded and stored on a disk or magnetic tape for subsequent off-line averaging.

The magnitude and vector contributions of eye movement potentials were measured on each day just prior to the 1200 hrs ERP testing session. Subjects were instructed to blink and move their eyes verti-

cally and horizontally. The movements were recorded on the different EEG and EOG channels and were stored by a MINC PDP-11 computer. Later, these data were used to subtract the effects of eye movements from the ERPs.

The stimuli were 50 msec tone bursts with rise and fall times of 5 msec. They were delivered through Telephonics TDH-49 headphones to the right ear at an intensity of 90 dB SPL and at a rate of 1/1.1 sec. Ninety percent of the stimuli were "standard" tones of 1000 Hz and the remaining ten percent were "target" tones of 2000 Hz. The targets were randomly interspersed during each trial. The subjects were asked to press a button with their preferred hand in response to each target stimulus. One block of 300 stimuli was presented in each session. Reaction times (RTs) in msec were recorded and stored automatically by the computer.

During stimulus presentation, the experimenter monitored the electroencephalographic activities on the polygraph. If the EEG (Cz and O1) activity showed a stage 1B pattern for three consecutive epochs (60 secs) and the subject also failed to respond to target stimuli during that period, the experimenter would stop the program delivering the stimuli and awaken the subject. The program would then be reinitiated and stimulus delivery would continue. This was necessary for only one subject, a narcoleptic who fell asleep in the 1400 hrs session.

Data Analysis

Five separate peaks of the ERP were identified in the vertex recordings: P1 was the maximum positive peak between 30 and 70 msec, N1 was the maximum negative peak between 50 and 150 msec; P2 was the maximum positive peak between 120 and 250 msec; N2 was the maximum negative peak between 150 and 350 msec; and P3 was the maximum positive peak between 250 and 700 msec. Once the component peak latency was defined at Cz, the amplitude at that latency was measured at all electrode sites using a baseline-to-peak approach.

The averaged EEG data were corrected for eye movement artifacts using an eye movement compensation program. The EEG and EOG data collected prior to the 1200 testing session (see above) were used. For each EEG channel, ratios measuring the effects of vertical and horizontal movements were calculated. The deviation of the EEG channel from its baseline was divided by the deviation of each of the EOG channels from their baselines during the various eye movement periods. The ratio for horizontal eye movement was derived from periods of horizontal eye movement. The ratio for vertical eye movement was derived from both blinking and vertical eye movement periods. Correction of eye movement effects on the EEG data was then accomplished by subtracting from each EEG channel the horizontal eye movement ratio times the horizontal EOG data plus the vertical eye movement ratio times the vertical EOG data.

The latencies, performance levels (targets missed and number of signals falsely detected) and RT's were submitted to a two factor (sessions x group) ANOVA with repeated measures on the sessions factor

(Kirk, 1968). The amplitudes were submitted to a three way ANOVA, with sessions and electrodes as the within group factors and groups (narcoleptics, controls) as the between group factor. The alpha level was set at $p < .05$.

CNV ERP Study

This ERP was recorded prior to each nap on the alternate day. In order to later subtract the contribution of eye movements, the measurement of eye movement potentials was done prior to the 1200 hrs session (see above).

Subjects were tested in the same environment as described before. They were trained to suppress eye movements during the interstimulus interval. In order to further reduce eye movements, subjects were instructed to fixate their vision on a point situated approximately 1.5 m in front of them. Because of excessive eye movements, the data of one of the narcoleptic subjects and his respective control were omitted from analysis.

Two auditory stimuli were delivered binaurally through the TDH-49 earphones. The first stimulus (S1) a 90 dB SPL 2000 Hz tone had a duration of 50 msec with a 5 msec rise and fall time. This stimulus was followed 3 sec later by a 90 dB SPL buzzer (S2), with a duration of 3 secs.

Both stimuli (S1 and S2) were generated by a Wavetek 159 waveform function generator. The trigger and timing of signals and the measurement of reaction time in msec was done by a MINC PDP-11 computer. Each subject received 30 computer initiated trials at random

8-10 sec intervals. Subjects were instructed to turn off the buzzer by pressing a button.

The EEG and EOG derivations were identical to those used in the P3 ERP recording. EEG and EOG signals were amplified by a Beckman R-611 polygraph set for a 6.6 sec time constant and a high frequency cut-off of 30 Hz. The amplified EEG and EOG signals were digitized over a 5000 msec sweep time beginning 500 msec prior to the S1 stimulus. A/D conversion was 100 samples/sec. Those trials in which the subjects did not press the button to turn off the buzzer were not recorded and were removed automatically. Data that were not rejected were saved on disk or magnetic tape and averaged off-line.

Data Analysis

The following measures were obtained:

1) Latencies and amplitudes of N1 (range 60-150 msec) after S1 (N1S1) and S2 (N1S2).
2) Latencies and amplitudes of P2 (range 120-250 msec) after S1 (P2S1) and S2 (P2S2).
3) AMFH, the average magnitude in the period 350-1500 msec after S1. This early component of the CNV has been interpreted as reflecting an orienting or reactive response to S1. It appears to have a frontal dominant distribution whenever auditory stimuli is used (S1) (Loveless and Sanford, 1974; Gaillard, 1976; Simson et al. 1977).

4) AMSH, the average magnitude in the period 1500-3000 msec after S1. This late component has been associated with anticipation processes involving S2. Its amplitude has been seen to increase with motor responses. It is recorded maximally centrally with reduced magnitude frontally and parietally (Loveless and Sanford, 1974; Rohrbaugh et al. 1976).

5) Post-CNV; the average magnitude between 3300-4500 msec after S1.

All measures were with respect to the pre-S1 baseline, which was the average potential within the period 0-500 msec before S1.

Since the records of narcoleptic subjects contained a large amount of eye movements which are usually present in periods of intense sleepiness, it was decided to use all the trials of the sessions and to compensate for eye movement artifact through an eye movement compensation program (see above).

ERP latencies as well as performance data (anticipatory responses and no responses) and reaction times were subjected to a two factor (group x sessions) repeated measures ANOVA. Amplitudes were subjected to a 3 way ANOVA (time of day x groups x electrodes). Results were considered significant at the $p < .05$ alpha level.

FURTHER STATISTICAL ANALYSIS

Significance levels for all the interactions were determined using the conservative Geisser-Greenhouse method (Kirk, 1968). Analysis of interaction comparisons was carried out using simple main

effects procedures. Post-hoc comparisons were made using Tukey's Test (Kirk, 1968). Correlations were calculated between ERP change of alertness scores and reaction times of both ERP paradigms and between ERP change of alertness and N1 and P3 latencies and amplitudes.

RESULTS

Raw data of each of the variables described below is found in Appendices 1 to 13.

MSLT

Interjudge reliability was established with a second rater based on twenty percent of the records, chosen pseudorandomly to include difficult to score records. An overall 89% agreement was reached (narcoleptics 82%, controls 96%).

Two of the 12 narcoleptics had only sleep onset REM naps, one had only NREM naps and the remaining 9 had both REM and NREM naps. Narcoleptics experienced a total of 35 REM and 25 NREM naps the first day and 36 REM and 24 NREM naps the second day. More detailed findings regarding REM naps will be reported separately (see next report).

Intragroup Comparisons

No differences emerged among narcoleptics or among controls in sleep onset latencies or total sleep time in day 1 as compared to day 2 (Tables I to IV).

Narcoleptics showed a significant session effect in stage 2 latency (Table I). It took them longer (Figure 2) to fall into stage 2 in nap 1000 than it did in nap 1400 ($F=2.71$, $df=4,88$, $p < .04$). They also showed a session effect for time spent in stage 1B (Table II). They spent significantly less time in this stage in nap 1800 than in nap 1400 ($F=2.48$, $df=4,88$, $p < .05$).

A significant session effect was observed in controls in latencies to stage 1B and 2 (Table III). The latency to stage 1B in the last nap (1800 hrs) was significantly longer ($F=3.65$, $df=4,88$, $p < .02$) than the latencies in the naps at 1200, 1400 and 1600 hrs (Figure 1). The latency to stage 2 in the nap at 1800 hrs was also significantly longer ($F=6.60$, $df=4,88$, $p < .001$) than the latencies in the 1200, 1400 and 1600 hrs naps (Figure 2). A session effect also appeared in controls for total time spent in stage 2 (Table IV). In the 1800 hrs nap, they spent significantly less time in this stage ($F=6.28$, $df=4,88$, $p < .0007$) than they did in naps at 1400 and 1600 hrs (Table IV). No REM sleep was recorded in controls.

Intergroup Comparisons

Latencies There were no significant differences in latencies to stage 1A between narcoleptics and controls (Table V). A significant difference between groups appeared in MSLT latencies to stage 1B and stage 2 (Table V). It took narcoleptics a mean of only 5.1 min to fall into stage 1B while it took controls 10.3 min ($F=14.86$, $df=1,22$, $p < .001$). There was a significant main effect of session. Post-hoc analyses indicated that the latency to stage 1B at 1800 was much

longer than at 1000 ($F=4.56$, $df=4,88$, $p < .006$) (Figure 1).

A significant between groups difference was observed in stage 2 latency. It took narcoleptics 11.5 min to fall into stage 2 while it took controls 15.5 min ($F=5.26$, $df=1,22$, $p < .04$). A significant session effect was observed in both narcoleptics and controls. (Figure 2). Post-hoc analyses revealed that the groups entered stage 2 much faster at 1400 than they did at 1800 ($F=5.09$, $df=4,88$, $p < .001$).

Sleep Time in Stages Controls spent significantly more time in stage 1A ($F=9.50$, $df=1,22$, $p < .005$) than narcoleptics (Table VI). This was due to the fact that the controls took longer to fall asleep and spent more time awake after sleep onset. Stage 1A was not considered a sleep stage but it is described in table VI because it occurred intermixed other stages of sleep. Both groups spent about the same amount of time in stages 1B and 2 (Figure 3). A significant session effect was observed in stage 2. Both groups spent less total sleep time in stage 2 at 1800 than at 1400 and 1600 ($F=6.16$, $df= 4,88$ $p < .0004$). The longer time spent in stage 2 in these early afternoon MSLT naps was expected, since the shortest latencies to stage 2 were observed at these times (Figure 2).

Two narcoleptics spent some time in stage 3 (40 sec) and stage 4 (120 sec). Controls' longer sleep latencies and longer times spent awake after sleep onset resulted in their having lower sleep efficiency (.40) than narcoleptics (.81) during the nap sessions.

SSS

Subjective sleepiness of narcoleptics as reflected by SSS

scores was significantly greater than that of the control group (U=25, p <.02). There were no significant differences between narcoleptics SSS scores in the morning (0900-1230), early afternoon (1300-1630), and late afternoon (1630-1800) (F=.79, df=2, p <.70). Although controls' subjective reports fluctuated more through the day, (late-afternoon scores were smaller than in the morning) no significant differences among sessions were observed (Table VII).

SSS scores taken before and after ERP and MSLT sessions revealed significant differences. Reduction of alertness after ERP sessions was much greater in narcoleptics (-.69, SD= 52) than in controls (-.28, SD= 1.59) (U=28, p <.01). MSLT nap periods were associated with increases in subjective alertness. This effect was greater in narcoleptics (.63 SD= .31) than in controls (.09, SD= .29) (U= 17, p <.002).

A comparison of change of alertness scores after REM naps (naps containing REM and NREM sleep or only REM sleep) versus NREM naps (containing only NREM sleep) showed that narcoleptics reported significantly larger increases of alertness (+.87) after REM naps as compared to NREM naps (+ .39) (t=3.48, df=58, p <.01).

P300 ERP Study

Performance

Stimuli Detected No significant differences between groups emerged in the number of targets missed or in the number of false

positives (Table VIII), although narcoleptics made more errors than controls.

Reaction Time There were no significant differences between narcoleptics and controls (Table VIII), although narcoleptics showed lower reaction times than controls in every session (Appendix VII). Non-significant low correlations were found between hit rates and P3 amplitudes in both groups.

Intergroup Comparisons

The different AEP components across the day can be observed for both groups in Figure 5.

N1 (latency= 108 msec) was largest at Fz, declining by 0.05% i.e. effectively no attenuation at all at Cz and 44% at Pz. P2 (latency 179 msec) showed a central locus, declining by 1.4% at Fz and 36% at Pz. N2 (latency= 235 msec) was maximum at Fz and was attenuated by 0.06%, hardly nothing at Cz and 21% at Pz. The distribution of P3 (latency = 353 msec) was different between narcoleptics and controls. For controls, it showed a parietal maximum being reduced by 15% at Cz and 31% at Fz. For narcoleptics, P3 was maximum at Cz and was attenuated by 18% at Pz and 40% at Fz.

Latencies and Amplitudes There were essentially no differences between groups in P1, N1, N2 and P3 latencies (Table IX). There were no intergroup differences in N1, P2 and N2 amplitudes (Table X). P1 amplitude was significantly larger in narcoleptics than controls ($F=5.03$, $df=1,22$, $p < .04$). However P3 amplitude was significantly smaller in narcoleptics ($F=4.69$, $df=1,22$, $p < .04$) (Figure 6).

A significant group x session interaction effect was observed for N1 amplitude (Figure 7). At 1000, controls showed a significantly larger N1 amplitude than narcoleptics at this session ($F=3.95$, $df=1,22$, $p < .05$) whereas at 1400 controls showed a significantly smaller N1 amplitude than narcoleptics at 1400 ($F=6.48$, $df= 1,22$, $p < .02$). There was a fluctuation of N1 amplitude through the day in both groups. The amplitude of N1 in controls at 1400 was significantly smaller than at 1000 ($F=6.48$, $df=4,44$, $p < .0001$). In narcoleptics, N1 amplitudes at 1400, 1600 and 1800 were all significantly larger than at 1000 ($F=3.77$, $df= 4,44$, $p < .0001$) (Figure 7).

Apart from the N1 interaction, there was no significant time of day effect, it was therefore decided to collapse all the data, across sessions and submit them to a two way ANOVA (group x electrode) to increase the power of our test. The P1 amplitude of narcoleptics was found to be significantly larger than controls at $p < .004$ ($F=8.58$, $df=1,118$). P3 amplitude remained significantly smaller in narcoleptics at $p < .001$ ($F=18.99$, $df=1,118$), but a significant electrode x group interaction was observed ($F=4.09$, $df=2,236$, $p < .02$). This indicated that while the P3 amplitudes of narcoleptics and controls were similar at Cz, the narcoleptic P3 at both Fz and Pz was significantly attenuated ($F=12.89$, $df=1,118$, $p < .001$) and ($F=15.84$, $df=1, 118$, $p < .001$ respectively). In addition, it was also observed that the N2 amplitude of narcoleptics was significantly smaller than that of controls ($F=9.31$, $df=1,118$, $p < .003$).

CNV ERP Study

Performance

Narcoleptics showed overall significantly slower reaction times

(F=6.68, df=1,20, p <.02). No session differences were observed (Table XI). Narcoleptics also made a larger number of anticipatory responses (responses before S2 presentation) than controls (F=6.11, df=1,20, p <.02). Only 2 narcoleptics made errors of omission (no response).

The average magnitude of the second half of the CNV interval did not correlate significantly with RT at any of the electrode sites in either narcoleptics or controls. The latency and amplitude of N1 after S2 also did not correlate with reaction time in either group.

Intergroup Differences

N1S1 (latency=117 msec) was largest at Cz declining by 19% at Fz and 55% at Pz. P1S2 (latency=220 msec) was largest at Cz declining by 26% at Fz and 17% at Pz. N1S2 (latency=113 msec) was largest at Cz decreasing by 25% at Fz and 50% at Pz. P2S2 (latency=232 msec) was largest at Pz declining by 18% at Cz and 56% at Pz. The distribution of AMSH was different between narcoleptics and controls. For controls it showed a central maximum, being reduced by 60% at Fz and 62% at Pz. In narcoleptics AMSH was maximum at Pz declining by 7% at Cz and 48% at Fz. Post-CNV was recorded negatively at Fz and positively parietally.

Latencies The only significant intergroup differences were found in N1 latencies to both S1 (p <.0003) and S2 (p <.0007) (Table XII). A session by group interaction was observed in P2 latencies. Controls had longer P2S1 latencies than narcoleptics in the 1000 hrs session (F=7.02, df=1,22, p <.02). The P2S1 of controls showed a

longer latency at 1000 than at 1200, 1600 and 1800 hrs (F=5.23, df=4,40, p <.002) (Table XII).

Amplitudes No significant differences between groups were observed in either the EP components (Table XIII) or in the CNV amplitude measures (Figure 8). Opposite trends were observed in N1S2 amplitude variations through the day. The N1S2 amplitude decreased through the day in narcoleptics and increased in controls which resulted in a significant group x session interaction. The narcoleptics' N1S2 amplitude at the 1000 hrs session was larger than at 1800 hrs (F=3.5, df=4,40, p <.05). Controls' N1S2 amplitude at 1000 was significantly smaller than at 1800 (F=2.5, df=4,40, p <.01) (Figure 9).

Narcoleptics showed a significantly greater Post-CNV negativity in the 3300–4500 msec period after S2 than controls (F=4.86, df= 1,20, p <.04). The pattern of resolution of this component was quite different in both groups. Narcoleptics showed a much larger negativity at Fz (-2.5 uV) than controls (-.4 uV) and showed a negativity at both central (-1.9 uV) and parietal sites (-.2 uV) whereas controls showed a positivity at both the Cz (1.27 uV) and Pz (3.82 uV) electrodes.

A significant group x electrode interaction was observed in the average magnitude of the second half of the CNV interval (AMSH). While narcoleptics' AMSH amplitude at Cz was significantly smaller than the Cz amplitude of controls (F=6.27, df=1,20, p .<03). The AMSH amplitude of narcoleptics at Pz was significantly larger than controls' amplitude at Pz (F=8.02, df=1,20, p <.01). The maximal negativity recorded at Cz in the second half of the interval in controls agrees with past reports of amplitude distributions of this late CNV negativity (Gaillard, 1976, 1977; Rohrbaugh, et al. 1976).

DISCUSSION

MSLT and SSS

As there were no significant differences between day 1 and day 2 in the sleep latencies or total sleep times of either the narcoleptics or the controls, the data of both days were collapsed.

We recorded significantly shorter sleep latencies in narcoleptics that have been reported in the past (Richardson et al. 1978, Hartse et al. 1982). This is congruent with the significantly larger degree of subjective sleepiness narcoleptics reported (higher SSS scores). We did not observe a marked reduction of sleep onset times at 1400 and 1600 hours in either group (Figure 1) even though a more lax sleep onset criteria was used (first epoch of stage 1B) (Richardson et al. 1978). Shorter sleep latencies in the early afternoon (Carskadon & Dement, 1975, 1977; Richardson et al. 1982) have been interpreted as reflecting an increase in sleepiness intensity as part of the circadian rhythm. In our study, the indexes of circadian fluctuations of sleepiness (increase) were shorter sleep latencies to stage 2 and longer times spent in this stage in both groups. These similarities suggest that both types of sleepiness, normal and PS may be affected by the same biological clock which controls fluctuations of alertness.

Shorter sleep latencies and longer sleep times in stage 2 in the early afternoon have been reported previously in people without sleep disorders (Webb & Agnew, 1977, Lavie & Scherson, 1981). An

ultradian effect on deeper stages of sleep might explain these findings (Agnew et al. 1968), as would the proposal for a 12 hour slow wave sleep rhythm with pressure for NREM sleep in the early afternoon (Broughton, 1975; Gaghon & de Koninck, 1984). The number of REM naps in narcoleptics at 1000 hrs was much larger than at any other session. The appearance of REM sleep in normal subjects in the early morning has been considered a prolongation into wakefulness of a circadian effect (Webb et al. 1966; Webb & Agnew, 1966, 1977). This circadian distribution characterized our narcoleptic group, although it was not found by Mitler et al. (1979). Our results provide additional support for the presence of relatively normal distribution of sleep stages in narcoleptics in 24 hour periods (Baldy-Moulinier et al. 1976; Hishikawa et al. 1976).

Controls occasionally showed nap latencies that were as short or even shorter than those of narcoleptics. This great variability and overlap in sleep onset latency measures for both patients with sleep disorders and normal controls has been reported in the past (Hishikawa et al. 1976; Zorick et al. 1982; Hartse et al. 1982). However, controls rarely reported excessive daytime sleepiness (SSS scores). There thus appeared to be a dissociation between subjective (SSS) and objective (MSLT) measures of sleepiness in controls. In narcoleptics higher SSS scores (greater subjective sleepiness) corresponded with shorter sleep onset latencies (greater objective sleepiness). Dissociation of objective and subjective measures of sleepiness in narcoleptics, though, were observed in relation to fluctuations of their sleepiness. Narcoleptics rated themselves as equally

sleepy throughout the day despite the fact that their sleep latencies in the latter part of the afternoon were significantly longer than at other times. Although controls' SSS scores also showed non significant fluctuations of sleepiness, they did tend to rate themselves as more alert at the end of the afternoon, which was consistent with their longer sleep latencies at that time.

The longest sleep latencies were present in both groups at 1800. This has been reported in the last session in other studies (Dement et al. 1978; Hartse et al. 1980, 1982; Zorick et al. 1982) and has been interpreted as either a reduction of the circadian sleep tendency in the early evening (Carskadon & Dement, 1975; Richardson et al. 1982) or as an improvement effect of the preceding naps (Carskadon & Dement, 1979). However, the longest latencies have also been recorded in studies (Hartse et al. 1983, Zorick et al. 982) where the last nap was at a time (1600) when others have reported much shorter latencies (Richardson et al. 1978; Mitler et al. 1978) when later naps were to follow. This suggests that increased sleep latency in the last session might result from an interaction between the physiological tendency to sleep and the alerting effect of psychological factors related to the relief of knowing that the experiment would soon be over (Carskadon & Dement, 1982). It is interesting to note that in controls both the subjective feeling of sleepiness and the physiological state were affected. In narcoleptics, subjective sleepiness did not change although the ability to stay awake longer did increase. This supports suggestions that the chronicity of PS makes those that experience it less sensitive to fluctuations of

sleepiness (Dement et al. 1978; Roth et al. 1982).

Narcoleptics spent less time than controls in stage 1A. This is in part due to their short sleep onset latencies, which allowed for fewer fluctuations of vigilance before descent into sleep. While narcoleptics showed a much larger mean number of awakenings after falling asleep than controls, they spent significantly less time awake after sleep onset, tending to fall asleep immediately after each arousal. Fragmentation of sleep has been previously reported in the nocturnal sleep of narcoleptics (Montplaisir, 1976; Broughton & Mamelak, 1979, 1980). The narcoleptics' sleep fragmentation during MSLT naps did not affect their sleep efficiency during MSLT naps (time asleep/time in bed) which was much higher (.81) than that of controls (.40).

The significant decrease of alertness in narcoleptics after ERP sessions confirms clinical reports that their sleepiness is significantly increased in non-stimulating circumstances (Ganado, 1958). It could also be that the demands for constant vigilance during the ERP tests caused excessive fatigue in the narcoleptics. Narcoleptics showed significantly greater increase of alertness after MSLT sessions than controls which confirms past reports on the refreshing effect naps have upon narcoleptics (Yoss & Daly, 1960; Rechtschaffen & Dement, 1969; Zarcone, 1973). A comparison of changes of alertness in narcoleptics following either REM or NREM naps showed that those who spent some time in REM sleep increased their alertness much more than their respective controls, while those who spent time in NREM sleep did not. The presence of REM sleep appears to be the element that

contributes to the larger recuperative quality of narcoleptics sleep.

The SSS scores did not correlate significantly with the detection levels, RTs, latencies or amplitudes of the P3 or CNV components. A lack of correlation between performance levels and subjective alertness ratings of narcoleptics has been previously reported (Valley & Broughton, 1981). A lack of significant correlation has also been reported for studies of subchronic sleep deprivation in normals (Friedman et al. 1977; Herscovitch & Broughton, 1981). This may reflect the many factors that can affect performance independent of the state of alertness of the subject, i.e. motivation, overcompensation etc. (Naitoh, 1976). It may also be that in subchronic or chronic forms of sleepiness, subjects lose the ability to accurately self-assess their impairment (Dement et al. 1978; Roth et al. 1982).

P3

The EEG pattern recorded in both narcoleptics and controls during performance of the P3 paradigm was that of wakefulness. In other test situations, brief microsleeps (Guilleminault et al. 1975) or fluctuations of alertness described as stage 1A (Valley & Broughton, 1983) have been recorded in narcoleptics. We observed neither of these patterns. The briefness of our tests (about 6 min) may not have allowed sufficient time for fluctuations of alertness to occur (Malmo, 1959). Similar sustained waking patterns were observed for the shorter tests in the Valley & Broughton (1981) study.

No significant intergroup latency differences were observed for

the different components. This is similar to the findings of Pressman et al. (1982) and (for P1, N2, P2 and N2) of Broughton et al. 1981, 1982). No latency fluctuations were observed as a function of time of day either in narcoleptics or in controls. Similar findings have been reported in normal subjects (Heninger et al. 1969). Campbell et al. (1980) also observed no latency fluctuations in a group of sleep deprived normals. Browman & Sullivan (1980), on the other hand, have reported an increase in N1-P2 latency from the morning to the evening. Our mixed sample and differences in recording times might explain the differences in findings.

The narcoleptics' N1 amplitude generally increased through the day, while controls'decreased. This opposite pattern of fluctuation resulted in an interaction effect in which narcoleptics' N1 amplitude at 1000 was significantly smaller than controls' at this session. Conversely, narcoleptics' N1 amplitude recorded at 1400 was significantly larger than that of controls at this time.

We observed a reduction of N1 amplitude in controls in the middle of the day, as reported by Kerkhof (1982). The smaller N1 amplitudes recorded in controls in the afternoon session suggest a decrease in the level of alertness in this group over the course of the day (Browman, 1979; Kerkhof et al. 1980; Browman & Sullivan, 1980). This reduction might also represent what has been described as slow habituation (Callaway, 1973; Picton et al. 1976; Ohman & Ladder, 1972) resulting from test repetition. The fact that N1 amplitude increases were recorded in narcoleptics in the afternoon suggests that factors other than habituation produced the decreased N1 amplitude of

controls. Controls' decreased sleep onset latencies to stage 2 in the afternoon suggest that the smaller N1 amplitude reflects a lower ability to sustain phasic alertness related to a reduced tonic arousal level (Kerkhof, 1982; Browman & Sullivan, 1980).

The large number of errors made by narcoleptics in the afternoon, their slower reaction times at 1600 and 1800 and the shorter sleep onset times and longer total sleep times in stage 2 at 1400 and 1600, indicate that they were sleepier in the afternoon than in the morning, although this was not reported subjectively. These data do not agree with their significantly larger N1 recorded in the afternoon, as an increase in N1 amplitude has been reported to reflect a greater level of alertness and higher attentional level (Schwent et al. 1976a). We suggest that the increased N1 of narcoleptics in the afternoon, particularly at 1400, reflects the overcompensation made to offset their lower levels of arousal and greater difficulties in sustaining attention (Naitoh, 1976). The significantly increased P1 recorded in narcoleptics is also congruent with our interpretation that narcoleptics were making a large attentional effort in order to perform (Wilkinson & Morlock, 1967). An increase in muscle tension caused by the effort to remain alert has been found to affect very early components (Davis, 1964; Picton et al. 1971) and may be responsible for the enlarged P1. That narcoleptics were making a great attentionl effort is supported by clinical reports which emphasize the constant struggle of narcoleptics to overcome sleepiness in order to function (Ganado, 1958; Zarcone, 1973). Our results, (no N1 amplitude differences between narcoleptics and controls) agree with those of

Pressman et al. (1982). The absence of N1 amplitude differences may be the result of a cancellation effect of amplitude fluctuations during the day that results when all data are collapsed, as it was the case in Pressman et al's. study. The statistical analysis we performed (3-way ANOVA group x session x electrode) allowed to consider possible amplitude fluctuations over the course of the day. We observed that the lack of N1 differences between groups was due to the latter. Broughton et al's. (1981) decreased N1 and P2 amplitudes could be related to their long testing time (one hour) which allowed for a true reflection of the difficulties in sustaining attention experienced by people with PS (Valley & Broughton, 1983).

The lack of agreement between the behavioral (detection levels) physiological (sleep onset latencies and time asleep) attentional (reaction times) and electrophysiological (AEP amplitudes) measurements reflects the dissociation that can occur between different indices of alertness or attention. As a result of this dissociation, different conclusions can be arrived at depending on the measure or index of attention employed (Lacey & Lacey, 1970). In this particular study, the dissociation may have occurred under conditions in which an effort was exerted to sustain a high level of alertness when a low tonic arousal level was overriding (Gostnell, 1976; Naitoh, 1976).

Comparison of our N2 amplitude measures to those reported by Pressman et al. (1982) is probably inappropriate due to procedural differences. Pressman et al. recorded AEPs in subjects who were passively listening to stimuli while we recorded them in subjects who

were actively engaged in a signal detection task. The N2 recorded during signal detection is probably related to task difficulty and subjective effort, whereas the N2 observed by Pressman et al. (1982) may be related to alertness.

We did not record in either group the enlarged N2 amplitudes previously recorded in normal subjects (Wilkinson et al. 1966; Wilkinson & Morlock, 1967) and in sleep deprived subjects (Campbell et al. 1980), during signal detection tasks. This enlarged N2 has been previously associated with low levels of alertness (Wilkinson et al. 1966; Wilkinson & Morlock, 1967) and, more recently, with increased cognitive effort (Fitzgerald & Picton, 1983). We also did not find the significantly decreased N2 that has been recorded in the past in narcoleptic subjects during prolonged signal detection tasks (Broughton et al. 1981). However, when the data were collapsed accross time significant N2 amplitude differences emerged. Narcoleptics showed much smaller N2 amplitudes than controls (figure 10). Similar fluctuations were observed in N1 and N2 amplitudes. If the fluctuations in N1 amplitude reflect biorhythmic changes in alertness (Kerkhof, 1982) then the decreased N2 amplitude in controls at 1400 could be explained by a decreased cognitive effort due to a lower level of alertness. In the narcoleptic group, the augmentation of N2 may be a manifestation of increased effort. The overall smaller N2 amplitude in narcoleptics compared to controls sugggests that in general less cognitive effort was being made by this group (Fitzgerald-

and Picton, 1983).

We recorded significantly smaller P3 amplitude in narcoleptics. P3 has been found to be directly related to hit rate (Squires et al. 1975) and to the level of confidence with which a decision is made (Squires et al. 1973; Parasuraman et al. 1980). In our paradigm, the P3 amplitude does not correlate in either group with hit rates. The smaller P3 amplitude of narcoleptics may reflect a lower level of confidence in decision making (Squires et al. 1973) or equivocation (Ruchkin & Sutton, 1978). The generally smaller P3 amplitudes observed in narcoleptics might be interpreted as reflecting the narcoleptics' greater difficulty in making signal discriminations due to a relatively low level of effort (low N2 amplitude). This in turn might lead to a lack of confidence or equivocation with respect to target discrimination (attenuated P3).

It is quite important to note, as well, that there were no significant group differences in P3 latency, although a 100 msec difference was noted in RT. Kutas et al. (1977) and Duncan-Johnson & Donchin (1982) have pointed out that while both RT and P3 latencies are affected by processes involved in the evaluation of the stimuli, processes involved in response selection and execution affect only RT and not P3. Pachella (1974) has observed that when accuracy is relatively high, very small individual or group differences in error rates may be associated with significant RT differences. Although RTs of narcoleptic patients were about 100 msec longer than the controls, their accuracy rates tended to be very high (nearly 100%). The P3-RT

results therefore suggest that the groups primarily differed in processes involved in response selection and execution. Amongst the possible response biases are equivocation (as reflected in P3 amplitude) and/or an emphasis on accuracy rather than speed. The important consideration is that stimulus evaluation processes occurred at essentially the same time in both groups (similar P3 latencies). Thus, even if narcoleptics, in general, made less effort, this had little detrimental effect on their performance of this relatively easy task (accuracy rates were high, P3 latency was similar to controls).

Finally, the smaller P3 amplitude in narcoleptics might be a result of averaging individual P3's varying in time ('jitter'), rather than a true amplitude decrease. The instability of alertness of narcoleptics, which was not necessarily recorded in the normal EEG record, might accentuate the phenomenon (jitter) and lead to lower P3 amplitude. Ruchkin and Sutton (1978) recorded significantly smaller P3 amplitudes when subjects were uncertain of correct detections of stimulus omissions as compared to when they were certain. After using correction procedures in which P3 amplitudes were adjusted for latency variations, it was observed that the P3 amplitude related to uncertain trials increased in amplitude but this amplitude was still smaller than those recorded in trials in which subjects were certain about correct detection of stimuli omissions. Ruchkin and Sutton (1979) have shown that reduction in P3 amplitude cannot be entirely ascribed to jitter effects. Thus, while our results may in part be due to this phenomena, other factors must also be involved.

While similar P3 amplitudes were recorded at Cz in both of our

groups, significantly smaller amplitudes were recorded in narcoleptics at Fz and Pz. Studies on topographic distribution of AEP components have reported P3 to be maximally recorded in areas overlying the parietal lobes. Simson et al. (1977a) suggested that the P3 distribution is compatible with either a single source extending into a central region from the inferior parietal lobule or with two spatially distinct parietal and frontal sources. Our own results favor the existence of two distinct frontal and parietal sources (Simson et al. 1976, 1977a, Squires et al. 1975).

Subcortical-cortical connections have been found between mesencephalic reticular formation structures and frontal and parietal lobes (French et al. 1955; Astruc, 1971). Electroencephalographic arousal are mediated by such connections. Cortico-cortical connections have also been reported between the inferior parietal lobule and frontal regions (Nauta, 1964; Pandya & Kuypers, 1969) whose lesions can result in the inattention syndrome (Brain, 1944; Critchley, 1966; Heilman & Watson, 1977; Damasio et al. 1980) in which impairment of the arousal and orienting system is present (Heilman & Valenstein, 1972; Watson et al. 1973, 1974, 1977). It is possible that a low level of efficiency of the arousal and orienting system, in which frontal and parietal lobes seem to be involved, are reflected in the decreased P3 recorded at the Fz and Pz electrodes in our group with PS. The bilateral distribution of the P3 component and its modality nonspecificity has led some authors to suggest the mesencephalic reticular formation (MRF) as its source generator (Desmedt et al. 1979). Feedback control of the MRF by the efferent connections of the

prefrontal granular cortex has been documented in cats (Bremer, 1977; Hugelin and Bonvallet,, 1957). It might be possible that the reduced P3 in narcoleptics is reflecting the inhibitory effects of the frontal cortex over MRF which in turn inhibits transmission to parietal areas, resulting in a decreased P3. The decreased P3 over frontal areas is the result of either decreased transmission through anatomical connections from parietal association to frontal cortex (Nauta, 1964) or of the same inhibitory mechanisms of MRF by frontal cortex (Hugelin and Bonvallet, 1957). Recent evidence suggests that limbic structures, specifically the hippocampus are possible source generators of the P3 component (Halgren et al. 1980; Wood et al. 1980; Perrault & Picton, 1984). MRF-Septo-hippocampal connections have been reported (Valenstein & Nauta, 1959; Raisman, 1966, 1969). Single neuronal discharge studies have documented the existence of excitatory and inhibitory discharges between these structures (Grantyn et al. 1972; Mok & Mogenson, 1974; McLennan eta l. 1974, 1975). The hippocampus is known to be interconnected with the temporal lobes (Hjorth-Simonsen et al. 1971a 1971b; Deadwyler et al. 1975). Temporal and frontal lobes are reciprocally connected with each other and with the inferior parietal lobe (Nauta, 1964; Pandya & Kuypers, 1969). It might well be possible that all these structures influence each other and form part of a circuit involved in the generation of the P3 component.

The significantly decreased P3 amplitude may not be exclusive to narcolepsy. This is suggested by the findings of Campbell et al (1980) that showed a similar P3 decrease in subjects during a 24 hour sleep deprivation paradigm. Decreased P3 amplitudes have also been

reported in patients suffering from hyperactivity (Loiselle et al. 1980) and schizophrenia (Beribeau-Braun et al. 1983) in whom attentional deficits are present. A decreased P3 has also been reported to be present in the aged (Picton et al. 1984).

Past research has reported significantly lower performance in narcoleptics (Billiard, 1976; Valley & Broughton, 1983; Guilleminault et al. 1975). An attentional deficit has been proposed as the cause of their lower detection efficiency. It can be hypothesized that narcoleptics' lower performance in attention tasks could be due to either: a) a low level of sustained alertness, b) a deficit in the evaluation of stimuli or c) a deficit in the processes related to selection of responses. The evidence suggests that, in general, narcoleptics had a similar level of sustained alertness as controls (average N1 amplitude) although they were less able to compensate their lower level of arousal in the morning which reduced their ability to sustain high phasic alertness. Our results strongly suggest that narcoleptics' lower performance levels are not related to deficits in evaluation of stimuli (narcoleptics and controls showed similar N2 and P3 latencies) but to uncertainty and to deficits in the processes related to selection and mobilization of responses (slower RTs of narcoleptics).

CNV

The CNV amplitude in the present study did not reveal differences between narcoleptics and controls. Peeke et al. (1980) also found the CNV to be insensitive to the effects of sleep deprivation.

Naitoh and colleagues (1971), however, reported a decrease in the CNV amplitude after one night of sleep deprivation and abolition of the CNV after 2 nights. Our negative results could be due again to a compensatory effort on the part of the narcoleptic patients to sustain attention.

Narcoleptics showed significantly longer N1 latencies following both S1 and S2. Similar results were reported by Peeke et al. (1980) with sleep deprived subjects. These researchers also observed a significantly longer P2 latency. Longer latencies have been recorded with increased difficulty in stimulus discriminability (Schwent et al. 1976a). The possibility that increased latencies in narcoleptics are related to an increase in the subjective perception of task difficulty should be considered. The significantly longer N1 latencies of narcoleptics in the CNV paradigm contrast with the lack of N1 latency differencies in the P3 paradigm. The slower rate of stimulus presentation in the CNV paradigm might explain these N1 latency differences (Campbell et al. 1980). An interaction between the stimuli being delivered and the different psychological processes involved in the CNV and P3 paradigms might also explain the different N1 latencies recorded (Peacock, 1965).

A time of day effect was observed for the amplitude of N1S2. The amplitude in controls at 1000 was much smaller than at 1800 and in narcoleptics it was much larger in the morning than it was at 1800. An opposite pattern was observed for the N1 measures in the P3 paradigm. The narcoleptics' N1 was much smaller in the morning than it was in the afternoon and the controls' N1 amplitude decreased

throughout the day. This decrease of N1 amplitude in controls was interpreted as expressing reduction of alertness and the increase in narcoleptics as reflecting higher phasic alertness. The CNV results would contradict this interpretation. Both groups showed a significant positive correlation (Table XV) between the amplitudes of the second half of the CNV interval (1500 to 3000 msec) and N1S2 during the test session when the amplitude of N1S2 was the largest (narcoleptics at 1000, controls at 1800). This could well be due to a superimposition of the already existing negativity onto N1S2. It should be recalled that N1S2 was measured relative to the baseline established prior to S1 (not S2) and would thus be affected by the DC shift associated with the CNV.

Both groups showed maximal negativity in the first half of the CNV interval (350 to 1500 msec.) over the frontocentral areas as has been reported in the past (Naatanen and Gaillard, 1974; Gaillard, 1976; Grunewald et al. 1979). However, a shift towards maximal central negativity in the second half of the interval was recorded only in controls (Sanford & Loveless, 1974b, Gaillard, 1976; Simson et al. 1977b). Narcoleptics showed their largest amplitude equally spread over parietal and central electrodes, while maximal negativity was recorded in controls over central areas. These results agree with past reports (Gaillard et al. 1976; Rohrbaugh, 1976). The equal spread of negativity over central and parietal areas in narcoleptics resulted in an interaction effect in which negativity over central areas was significantly smaller in narcoleptics than controls and over parietal regions was significantly larger in narcoleptics than con-

trols. This could be related to a later motor potential (related to later RTs) in narcoleptics. This more posterior spread in narcoleptics in the presence of a significantly smaller P3 over these regions gives support to the theory of independent generators of CNV and vertex evoked potentials (Donchin, et al. 1975).

The only significant amplitude difference between groups was observed for the post-CNV interval averaged over the 3300 to 5000 msec period. Narcoleptics showed greater negativity than controls. The larger negativity recorded in narcoleptics seems to differ from the post-imperative negative variations (PINV) that have been recorded in diverse groups of psychiatric patients (Timsit-Berthier et al. 1973; Abraham et al. 1974, 1976; Dubrovsky and Dongier, 1976) and in normals when a difficult distracting task has been superimposed between S1 and S2 while subjects had to attend to the imperative stimuli (S2) (Tecce & Hamilton, 1973). In the latter case the PINV seems to reflect sustained cognitive activity. While the negativity associated with PINV seems to result from a slow return to baseline (Abraham et al. 1974, 1976) the negativity of our narcoleptic group is more associated with the almost absence of positivity at the parietal location. While in both groups this measure was recorded as a negative potential at Fz, in narcoleptics the negativity spread to both Cz and Pz. In controls, a positivity potential was recorded centrally and parietally, with the maximum positivity being recorded at Pz. Controls' post-CNV frontal negativity and central and parietal positivity correspond to the topographical description reported in the past for the slow wave component (SW) reported by Squires and colleagues (1975)

in the P3 paradigm (Ruchkin et al. 1980) which was interpreted as reflecting larger effort in processing or uncertainty. Narcoleptics absence of positivity at the parietal regions could again be related to their slower motor response. The lack of normal formation of the slow wave component in narcoleptics might reflect differences in post-stimulus cognitive resolution or processing. The larger negativity recorded in narcoleptics might also reflect their larger effort related to maintaining alertness and to the cognitive-attentional requirements of the task itself. Furthermore, it can also be interpreted as reflecting a state of continuous expectancy or readiness to respond that accompanies the effort to perform and maintain alertness (Wurtz 1966).

Posner (1978) has considered the CNV to reflect the phasic alertness level of the individual with an increased alertness level being accompanied by a higher CNV amplitude and faster motor output (shorter reaction time). We observed a dissociation of the CNV and RT. The CNV of both groups were of similar amplitude, but the RTs of narcoleptics were significantly longer. In both groups we observed low correlations between the amplitude of the second half of the CNV and RTs. This agrees with the studies that showed no consistent relation (Mc Callum & Papakostopoulos, 1973) or complete dissociation (Timsit-Berthier et al. 1980) between neurophysiological activity underlying the CNV and RTs. We believe that our findings tend to support the Rebert & Tecce (1973) conclusion that the CNV and RT are measures of different psychological processes. It is also possible that as reported by Papakostopoulos & Fenelon (1975) the summation of

positive and negative intra-individual correlations, related to diffuse scatter of reaction times, associated with short reaction times tasks, had resulted in absence of correlations between CNV and RT in controls. In narcoleptics, the absence of CNV-RT correlations might have also resulted from the summation of different intra-individal correlations (REM and NREM).

Narcoleptics significantly longer RT's and greater number of anticipatory responses in the CNV paradigm contrast with the lack of significant differences in reaction times and detection levels observed in the P3 test. Differences in paradigms might explain these results. Target presentation of unpredictable stimuli in the P3 paradigm whereas this was not the case with the CNV paradigm.

In summary, our results indicate that the CNV itself is not a sensitive measure of the fluctuations of alertness which occur through the day in either narcoleptics or controls. However, the existence of such fluctuations is reflected in the N1 component in the P3 paradigm and the amplitude of the N1S2 in the CNV paradigm. While the amplitude of the CNV did not reflect the lower level of alertness of narcoleptics. The relative absence of positivity in post-CNV activity over parietal areas may provide a better index of the effects of pathological sleepiness.

Conclusion: Evidence for Differences between Normal and Pathological Sleepiness

Our results, in general, confirm previous reports with respect to differences between normal and pathological sleepiness. SSS scores confirm the greater intensity of subjectively rated sleepiness (De-

ment, 1976, Zarcone, 1973) in narcoleptics. Dement's (1979) suggestion that narcoleptics might be locked into a "sleepy state" seems to be true. Our patients claimed to be sleepier than controls regardless of the time of testing. Naps had a greater recuperative effect on narcoleptics although a comparison of absolute values showed that even after naps they were still sleepier than controls.

The greater physiological tendency to sleep that is present in patients with PS (Zorick et al. 1982, Richardson et al. 1978) was confirmed by the short sleep latency times that were observed. Although statistically significantly longer reaction times were obtained only in the CNV paradigm and not in the P3, the RTs associated with PS were always slower than those of normals, which agrees with the findings of Valley and Broughton (1981) and Guilleminault et al. (1975) Slower mobilization of responses seems to be the factor underlying slow RTs. While both types of sleepiness show a reduction in the level of arousal in the afternoon, the greater intensity of PS is reflected by slower RTs, longer times spent in deeper stages of sleep and lower detection levels. Both types of sleepiness show similar fluctuation cycles through the day, with the main difference being the larger intensity of sleepiness experienced in PS at the crest of the cycles.

The detection levels of narcoleptics in the P3 paradigm were lower, though nonsignificantly, than those of controls. Narcoleptics' performance efficiency was significantly lower in the CNV paradigm, as expressed in their greater number of premature button presses. This suggests that greater difficulties in sustaining attention can be

observed in narcoleptics when they must withhold responses until a critical time (between S1 and S2 in the CNV paradigm) than when continuous monitoring is required (during P3 paradigm).

The AEP data suggests some differences between normal and pathological sleepiness. PS appears to be characterized by: 1) a lower ability to sustain phasic alertness in the morning, as reflected by the smaller N1 amplitudes in narcoleptics; 2) an ability to compensate for this low level of alertness during the afternoon in order to remain functional, as reflected by the narcoleptics' enlarged N1 amplitude in the afternoon; 3) a deficit in the decision processes occurring before the selection of responses, as reflected by the smaller P3; and 4) a significantly larger spread of negativity over parietal areas after the imperative stimuli has been attended to, as reflected in the CNV.

The results of this study provide evidence that pathological sleepiness differs from normal sleepiness in aspects other than the intensity with which it is subjectively felt. However, before any generalization can be made, it is necessary to compare the results of this study with those obtained in populations of patients suffering from forms of pathological sleepiness other than narcolepsy.

Our findings indicate that the auditory evoked potentials recorded during a short signal detection task are useful in the quantitative evaluation of sleepiness. Indices such as the N1, N2 and P3 amplitude can be used. The N1 amplitude, though, should be considered together with RT, i.e, a large N1 amplitude recorded in the presence of a slow RT might indicate an attempt to compensate for a

low arousal level (Wilkinson & Morlock, 1967). The usefulness of AEPs in the clinical study of PS remains to be proven as there exists the possibility of misinterpretation of results. For example, while a decrease in P3 amplitude is associated with PS it may also be characteristic of the sleepiness present in sleep deprived subjects (Campbell et al. 1980). However, other indices, such as N2 amplitude might be able to differentiate between these two types of sleepiness (Campbell et al. 1980; Pressman et al. 1982). These findings are of a preliminary nature and should be researched further.

SUMMARY

Differences between normal and pathological sleepiness were investigated in a group of twelve narcoleptic-cataplectic patients and twelve healthy control subjects. Event-related potentials were recorded from the scalp five times a day on two consecutive days of testing (P3 one day, CNV the other) prior to MSLT naps at 1000, 1200, 1400, 1600 and 1800 hrs. In the P300 paradigm, the subjects received instructions to respond to target stimuli (10% probability of occurrence by pressing a button. In the CNV paradigm they were presented with a warning tone (S1) followed 3 sec later by a buzzer (S2) which they were instructed to turn off by pressing a button. Subjects filled out SSS forms approximately every 30 minutes, just prior to and following the ERP sessions, and a few minutes after each MSLT. SSS scores were significantly higher in narcoleptics than in controls throughout the day. No significant fluctuations of subjective sleepiness were observed in either group. Change of alertness scores (SSS scores before ERP and MSLT sessions minus scores after the sessions) indicated that narcoleptics felt their alertness decreased signficantly more than controls after ERP sessions and found their alertness increased more than controls after MSLT sessions. The MSLT data showed significantly shorter sleep latencies to stage 1B and 2 in narcoleptics. No differences appeared between groups in sleep times in these stages. In the early afternoon session both groups showed shorter latencies to and longer sleep times in stage 2.

In the P3 paradigm narcoleptic subjects showed significantly larger P1 amplitudes and significantly smaller P3 amplitudes. A time of day effect was observed in both groups' N1 amplitude. As a result of opposite N1 amplitude fluctuations through the day (narcoleptics increased, controls decreased) narcoleptics' N1 amplitude was significantly smaller than controls at 1000, while their N1 amplitudes in the afternoon were significantly larger than controls. N1 amplitude showed a significant decrease in controls and a significant increase in narcoleptics at 1400 as compared to the other testing sessions. Differences in N1 amplitude fluctuation through the day were interpreted as reflecting a biorhythmic variation in the level of alertness and ability to sustain attention. While both narcoleptics and controls experienced low levels of alertness in the afternoon, narcoleptics, who frequently must struggle to remain at a functional level, compensated for their low level of arousal with a high phasic alertness.

P3 was significantly attenuated in narcoleptics. This might be due to a deficit in stimulus evaluation processes, perhaps related to equivocation. P3 showed no fluctuations through the day. Although the CNV amplitude was similar between groups, a different pattern of distribution across the scalp was observed in the second half of the CNV interval. A larger spread of negativity over parietal areas was recorded in narcoleptic subjects as compared to controls. This could be related to a later motor potential, which is suggested by the longer RTs in narcoleptics. A significantly larger negativity was recorded in narcoleptics after the presentation of the second stimuli.

This larger spread of negativity in narcoleptics was interpreted as reflecting a state of continuous expectancy or readiness to respond that accompanies effort to maintain alertness. It may also reflect the attentional and cognitive requirements of the task itself. Results were discussed in the context of the potential usefulness of ERP's in the evaluation and differentiation of normal and pathological sleepiness.

TABLE I

2-Way ANOVAS comparing day 1 and day 2 sleep onset latencies in narcoleptics

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1B	Day of Testing	0.10	1,22	.757	
	Session	0.68	4,88	.604	.559
	Day x Session	0.95	4,88	.439	.419
2	Day of Testing	1.88	1,22	.185	
	Session	2.71	4,88	.035	.040 *
	Day x Session	0.99	4,88	.415	.410
REM	Day of Testing	0.82	1,22	.374	
	Session	1.09	4,88	.367	.360
	Day x Session	0.51	4,88	.731	.681

TABLE II

2-Way ANOVAS comparing day 1 and day 2 sleep time in narcoleptics

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1B	Day of Testing	3.01	1,22	.10	
	Session	2.48	4,88	.04	.05 *
	Day x session	2.21	4,88	.07	.084
2	Day of Testing	0.80	1,22	.381	
	Session	1.59	4,88	.183	.193
	Day x session	0.74	4,88	.569	.548
REM	Day of Testing	1.38	1,22	.252	
	Session	0.78	4,88	.543	.522
	Day x session	0.99	4,88	.418	.408

TABLE III

2-Way ANOVAS comparing day 1 and day 2 sleep onset latencies in controls

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1B	Day of Testing	0.26	1,22	.613	
	Session	3.65	4,88	.009	.02 *
	Day x Session	0.72	4,88	.581	.535
2	Day of Testing	0.09	1,22	.767	
	Session	6.60	4,88	.0001	.001 *
	Day x Session	0.18	4,88	.948	.888

TABLE IV

2-Way ANOVAS comparing day 1 and day 2 sleep time in controls

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1A	Day of Testing	0.01	1,22	.952	
	Session	1.14	4,88	.341	.328
	Day x Session	0.90	4,88	.468	.415
1B	Day of Testing	0.00	1,22	.951	
	Session	1.24	4,88	.299	.300
	Day x Session	1.95	4,88	.109	.117
2	Day of Testing	0.07	1,22	.796	
	Session	6.28	4,88	.0002	.0007*
	Day x session	1.06	4,88	.380	.372

TABLE V

2-Way ANOVAS comparing narcoleptics and controls sleep onset latencies

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1A	Group	0.28	1,22	.603	
	Session	1.78	4,88	.141	.150
	Session x Group	1.17	4,88	.329	.329
1B	Group	14.86	1,22	.001 *	
	Session	4.56	4,88	.002	.006 **
	Session x group	1.91	4,88	.115	.135
2	Group	5.26	1,22	.04 *	
	Session	5.09	4,88	.001	.001 *
	Session x Group	0.95	4,88	.441	.436

TABLE VI

2-Way ANOVAS comparing narcoleptics and controls sleep time

Sleep Stage	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
1A	Group	9.50	1,22	.005 *	
	Session	1.31	4,88	.325	.340
	Group x Session	1.91	4,88	.115	.135
1B	Group	0.34	1,22	.564	
	Session	0.59	4,88	.671	.603
	Group x Session	1.91	4,88	.115	.144
2	Group	0.08	4,88	.781	
	Session	6.16	4,88	.0002	.0004*
	Group x Sesssion	0.61	4,88	.654	.634

TABLE VII

Mean alertness (SSS) over different periods of time through the day. Intragroup comparisons across the day. The second row is the standard deviation.

	Morning (0900-1230)	Early Afternoon (1300-1630)	Late Afternoon (1630-1830)	F Value	P
Narcoleptics	3.4	3.3	3.1		
	1.0	1.0	1.2	.79	.70
Controls	2.2	2.1	1.8		
	.8	.7	.7	3.79	.15

TABLE VIII

2 Way ANOVAS comparing narcoleptics and controls detection levels and RT's in the P3 paradigm

	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
Detection Rate	Group	2.29	1,22	.144	
	Session	0.37	4,88	.828	.772
	Group x Session	1.04	4,88	.389	.378
False positives	Group	3.00	1,22	.097	
	Session	1.35	4,88	.256	.268
	Group x Session	1.18	4,88	.325	.321
Reaction Times	Group	1.52	1,22	.231	
	Session	0.91	4,88	.464	.422
	Group x session	0.18	4,88	.949	.863

TABLE IX

2 Way ANOVAS comparing narcoleptics and controls AEP latencies (msec) in the P3 paradigm (measured at Cz)

Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
P1	Group	1.16	1,22	.293	
	Session	1.89	4,88	.119	.136
	Group x session	1.98	4,88	.105	.121
N1	Group	0.42	1,22	.524	
	Session	1.10	4,88	.360	.351
	Group x session	0.34	4,88	.851	.780
P2	Group	3.80	1,22	.064	
	Session	0.47	4,88	.754	.727
	Group x session	0.85	4,88	.498	.485
N2	Group	0.13	1,22	.724	
	Session	0.61	4,88	.659	.584
	Group x session	0.64	4,88	.632	.562
P3	Group	0.75	1,22	.396	
	Session	0.12	4,88	.974	.909
	Group x session	0.15	4,88	.961	.885

TABLE X
3 Way-ANOVAS comparing narcoleptics and controls AEP amplitudes (uV) in the P3 Paradigm

Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability	
P1	Group	5.03	1,22	.04 *		
	Session	0.65	4,88	.625	.658	
	Electrode	8.19	2,44	.001	.003	(1)
	Group x Session	0.26	4,88	.902	.858	
	Group x Electrode	2.20	2,44	.123	.137	
	Session x Electrode	1.77	8,176	.09	.105	
	Group x Sess x Elec	1.96	8,176	.06	.120	
N1	Group	0.17	1,22	.680		
	Session	0.28	4,88	.888	.851	
	Electrode	33.77	2,44	.0001	.001	(2)
	Group x Session	6.48	4,88	.0001	.0004 *	
	Group x Electrode	0.04	2,44	.964	.947	
	Session x Electrode	1.28	8,176	.254	.280	
	Group x Sess x Elec	1.39	8,176	.205	.241	
P2	Group	0.77	1,22	.391		
	Session	0.21	4,88	.930	.866	
	Electrode	3.39	2,44	.04	.04	(3)
	Group x Session	0.70	4,88	.590	.541	
	Group x Electrode	2.45	2,44	.10	.10	
	Session x Electrode	0.60	8,176	.780	.692	
	Group x Sess x Elec	1.36	8,176	.216	.247	
N2	Group	1.15	1,22	.296		
	Session	1.51	4,88	.205	.234	
	Electrode	4.51	2,44	.02	.03	(4)
	Group x Session	2.69	4,88	.04	.09	
	Group x Electrode	2.41	2,44	.102	.121	
	Session x Electrode	1.19	8,176	.308	.301	
	Group x Sess x Elec	0.78	9.176	.623	.447	
P3	Group	4.69	1,22	.04 **		
	Session	0.16	4,88	.960	.930	
	Electrode	6.12	2,44	.005	.008	(5)
	Group x Session	0.80	4,88	.528	.505	
	Group x Electrode	1.60	2,44	.214	.219	
	Session x Electrode	0.30	8,176	.960	.876	
	Group x Sess x Elec	0.22	8,176	.988	.929	

(1) Recorded maximally at Fz and Cz
(2) Recorded maximally at Fz and Cz
(3) Recorded maximally at Cz
(4) Recorded maximally at Fz and Cz
(5) Recorded maximally at Cz and Pz

TABLE XI

2 Way ANOVAS comparing narcoleptics and controls performance measures in the CNV paradigm

	Source of Variance	F Value	df	2-Tailed Probability		Geisser-Greenhouse Probability
Reaction Time	Group	6.68	1,20	.02	*	
	Session	1.61	4,80	.180		.209
	Group x session	1.47	4,80	.217		.239
Anticipatory Responses	Group	6.11	1,20	.02	*	
	Session	0.69	4,80	.603		.555
	Group x Session	0.50	4,80	.734		.671

TABLE XII

2-Way ANOVAS comparing narcoleptics and controls EP latencies (msec) in the CNV paradigm (measured at Cz)

Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
N1S1	Group	18.69	1,20	.0003 *	
	Session	1.17	4,80	.333	.325
	Group x Session	1.31	4,80	.274	.281
P2S1	Group	0.12	1,20	.735	
	Session	5.23	4,80	.001	.002 *
	Group x Session	4.25	4,80	.004	.006 (1)
N1S2	Group	8.94	1,20	.007 *	
	Session	0.27	4,80	.900	.867
	Group x Session	0.49	4,80	.742	.706
P2S2	Group	0.01	1,20	.916	
	Session	2.01	4,80	.101	.149
	Group x Session	0.29	4,80	.882	.742

(1) - Controls P2S1 latency at 1000 significantly longer than narcoleptics P2S1 at this same time.

TABLE XIII

3-Way ANOVAS comparing narcoleptics and controls EP amplitudes (uV) in the CNV Paradigm

Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
N1S1	Group	0.02	1,20	.888	
	Session	0.61	4,80	.656	.591
	Electrode	36.57	2,40	.0001	.0001 (1)
	Group x Session	0.72	4,80	.583	.530
	Group x Electrode	0.84	2,40	.438	.430
	Session & Electrode	0.72	8,160	.677	.526
	Group x Sess x Elec	0.92	8,160	.500	.424
P2S1	Group	0.00	1,20	.978	
	Session	0.20	4,80	.936	.902
	Electrode	9.35	2,40	.0005	.0005 (2)
	Group x Session	1.24	4,80	.302	.304
	Group x Electrode	1.26	2,40	.294	.294
	Session x Electrode	0.52	8,160	.839	.727
	Group x Sess x Elec	1.61	8,160	.125	.177
N1S2	Group	0.00	1,20	.982	
	Session	0.27	4,80	.899	.854
	Electrode	35.48	2,40	.0001	.0001 (3)
	Group x Session	3.13	4,80	.02	.03 *
	Group x Electrode	2.09	2,40	.138	.150
	Session x Electrode	2.14	8,160	.036	.087
	Group x Sess x Elec	0.67	8,160	.721	.613
P2S2	Group	0.37	1,20	.548	
	Session	0.44	4,80	.779	.737
	Electrode	11.15	2,40	.0001	.0007 (4)
	Group x Session	2.05	4,80	.095	.112
	Group x Electrode	2.93	2,40	.066	.082
	Session x Electrode	2.08	8,160	.040	.093
	Group x Sess x Elec	0.74	8,160	.655	.563

(1) N1S1 amplitude recorded maximally at Cz
(2) P2S1 amplitude recorded maximally at Cz
(3) N1S2 amplitude recorded maximally at Cz
(4) P2S2 amplitude recorded maximally at Pz

TABLE XIV

3-Way ANOVAS comparing narcoleptics and controls amplitudes (uV) of different measures in the CNV paradigm

Measures	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
AMFH	Group	0.00	1,20	.966	
	Session	0.66	4,80	.621	.539
	Electrode	16.83	2,40	.0001	.0001 (1)
	Group x Session	1.65	4,80	.170	.201
	Group x Electrode	1.91	2,40	.161	.175
	Session & Electrode	0.88	8,160	.532	.464
	Group x Sess x Elec	0.71	8,160	.679	.562
AMSH	Group	0.01	1,20	.939	
	Session	0.21	4,80	.929	.880
	Electrode	9.39	2,40	.0005	.0002
	Group x Session	1.99	4,80	.105	.130
	Group x Electrode	3.85	2,40	.031	.04 (2)
	Session x Electrode	2.04	8,160	.045	.106
	Group x Sess x Elec	1.15	8,160	.337	.341
Post-CNV	Group	4.86	1,20	.04 *	
	Session	1.48	4,80	.216	.238
	Electrode	13.00	2,40	.0001	.0005 (3)
	Group x Session	1.13	4,80	.350	.338
	Group x Electrode	1.10	2,40	.345	.328
	Session x Electrode	1.17	8,160	.320	.330
	Group x Sess x Elec	1.60	8,160	.129	.190

(1) AMFH amplitude recorded maximally at Fz and Cz

(2) AMSH amplitude recorded maximally at Cz in controls and at Pz in narcoleptics

(3) Post-CNV amplitude recorded maximally at Pz

TABLE XV

Correlations of AMSH and N1S2 amplitudes in the CNV paradigm

	Test Times				
	1000	1200	1400	1600	1800
Narcoleptics					
Fz	.66	.29	.41	.71	.14
Cz	.61	.43	.13	.30	.23
Pz	.78	.77	.43	.65	.28
Controls					
Fz	.28	.10	.46	.14	.76
Cz	.30	.65	.56	.41	.87
Pz	.46	.71	.03	.25	.75

FIGURE LEGENDS

Figure 1. Mean sleep latencies for narcoleptic and control subjects. Solid lines represent sleep onset measured using the criteria of six consecutive epochs of stage 1B, broken lines represent sleep onset measured using the criteria of the first epoch of stage 1B. Narcoleptics fell asleep significantly faster than control subjects. Sleep latency in the 1800 session was significantly longer than at 1000 in both groups.

Figure 2. Mean latencies to stage 2 of narcoleptic and control subjects. Narcoleptics fell into stage 2 significantly faster than control subjects. In both groups the latency in the 1400 session was significantly shorter than at 1800.

Figure 3. Mean sleep time in stage 1B of narcoleptics and controls. Both groups spent approximately the same time in this stage at any one session.

Figure 4. Mean sleep time in stage 2 of narcoleptics and controls. Both groups spent approximately the same time in this stage with significantly more stage 2 at 1400 and 1600 than at 1800.

Figure 5. P3 paradigm. Grand average waveforms at each session and at each electrode site for narcoleptics and controls.

Figure 6. P3 paradigm. Grand mean target evoked potentials of 12 narcoleptics and controls averaged across sessions, recorded at three electrode sites. The different components measured are indicated at the Fz electrode. Significantly reduced P3 amplitudes and significantly larger P1 amplitudes were recorded in narcoleptics.

Figure 7. P3 paradigm. Mean values of the amplitude (uV) of the N1 at each session in narcoleptics and controls. Intrasessions differences were observed. In controls N1 amplitude at 1400 was significantly smaller than at 1000. Narcoleptics N1's at session 1400, 1600 and 1800 were significantly larger than those at 1000 and were significantly larger than those of controls in these same afternoon sessions. Narcoleptics N1 amplitude at 1000 was significantly smaller than the N1 of controls at this same session.

Figure 8. CNV paradigm. Grand mean of attended signals at the three electrode sites for narcoleptics and controls. A significant difference was observed in the Post-CNV negativity (after S2) between narcoleptics and controls. Narcoleptics showed larger negativity than controls.

Figure 9. CNV paradigm. Average values of the amplitude (uV) of the N1S2 component in narcoleptics and controls. Narcoleptics' N1S2 amplitude at 1000 was significantly larger than at 1800. Controls' N1S2 amplitude at 1000 was significantly smaller than at 1800.

Figure 10. P3 paradigm. Average values of the amplitude (uV) of the N200 at each session in narcoleptics and controls. At 1400 narcoleptics and controls showed opposite patterns of N2 amplitude fluctuation that paralleled that of the N1 component.

Figure 1

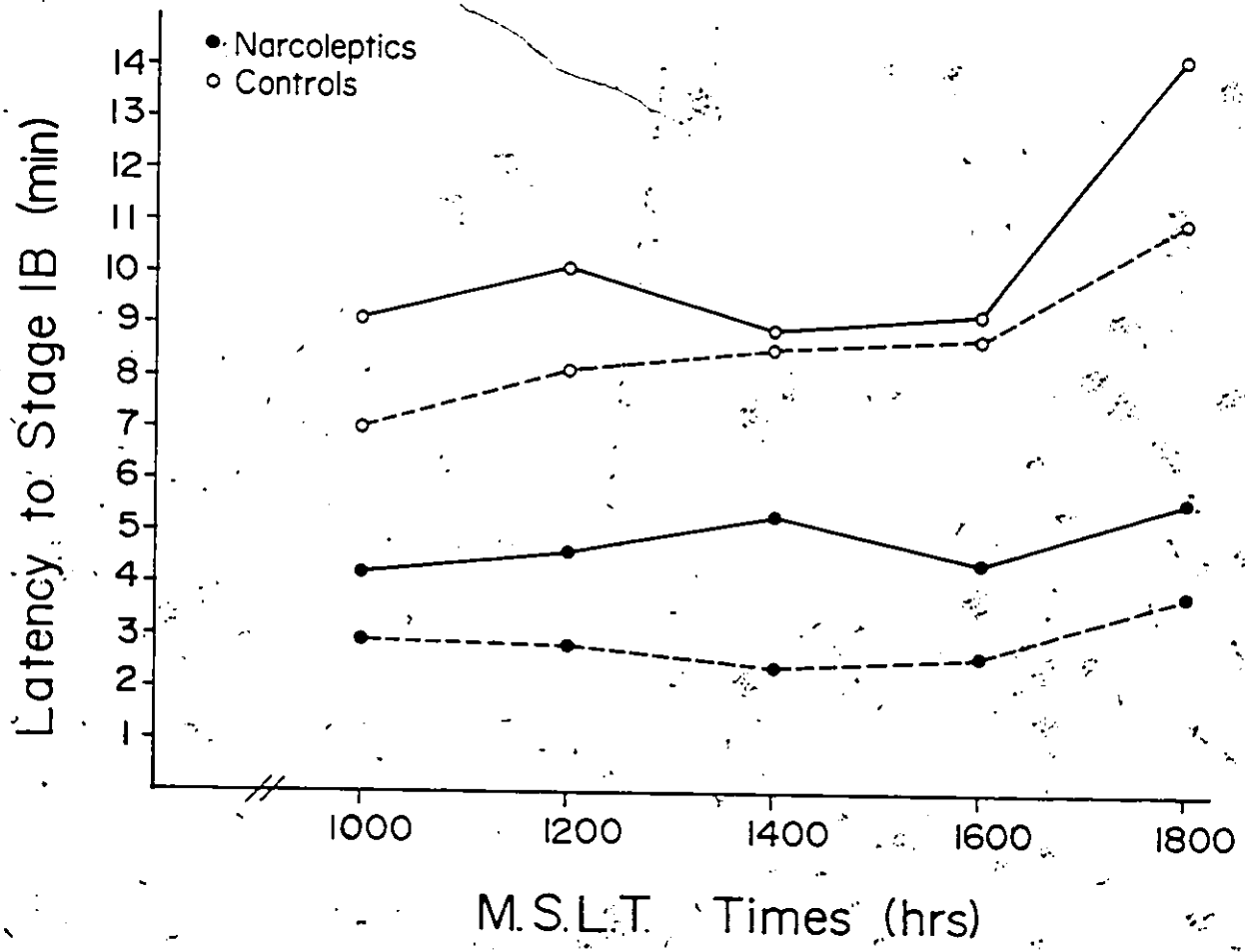

Narcoleptics
Controls
Latency to Stage IB (min)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
1000
1200
1400
1600
1800
M.S.L.T. Times (hrs)

Figure 2

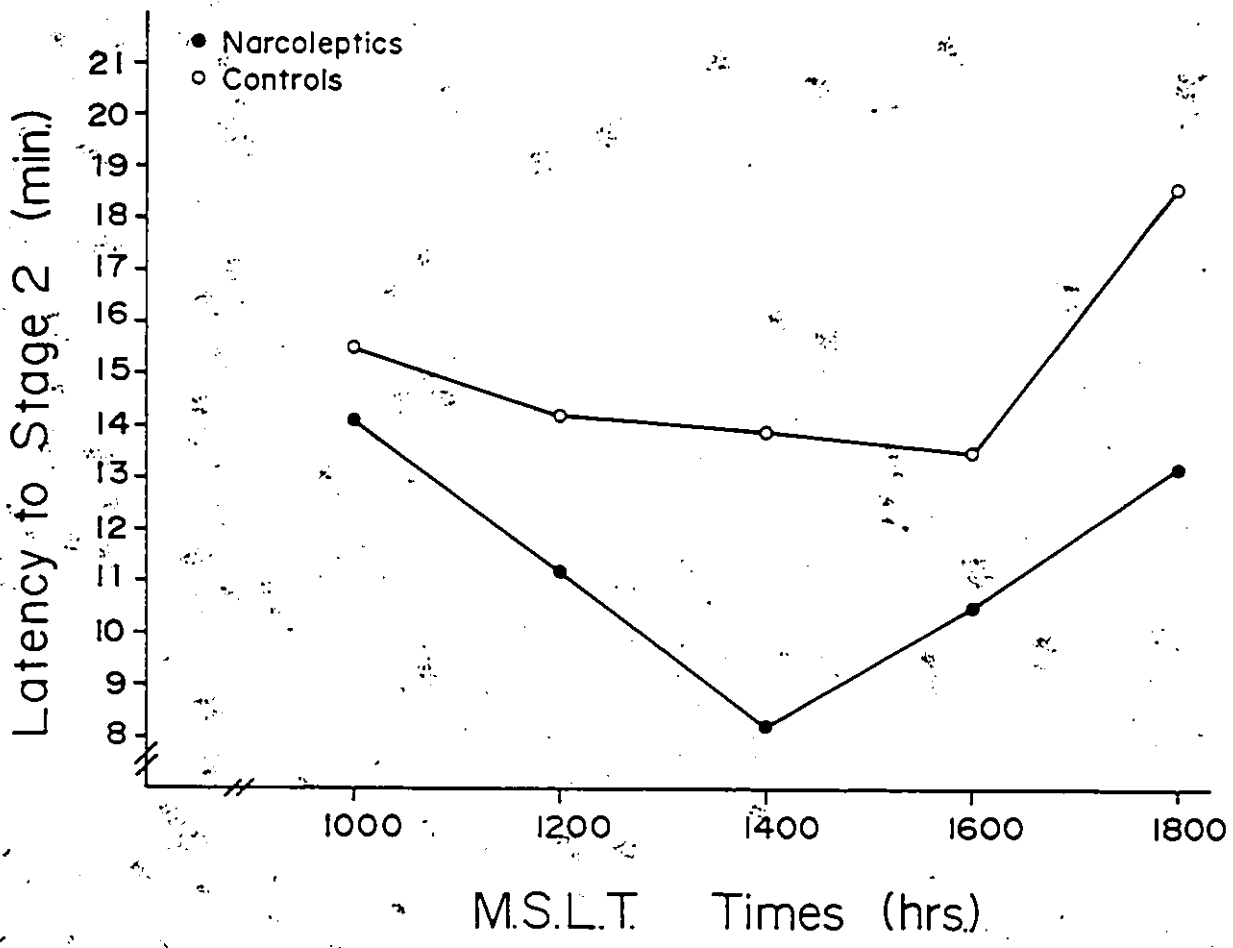

Narcoleptics
Controls
Latency to Stage 2 (min)
21
20
19
18
17
16
15
14
13
12
11
10
9
8
1000
1200
1400
1600
1800
M.S.L.T. Times (hrs.)

Figure 3

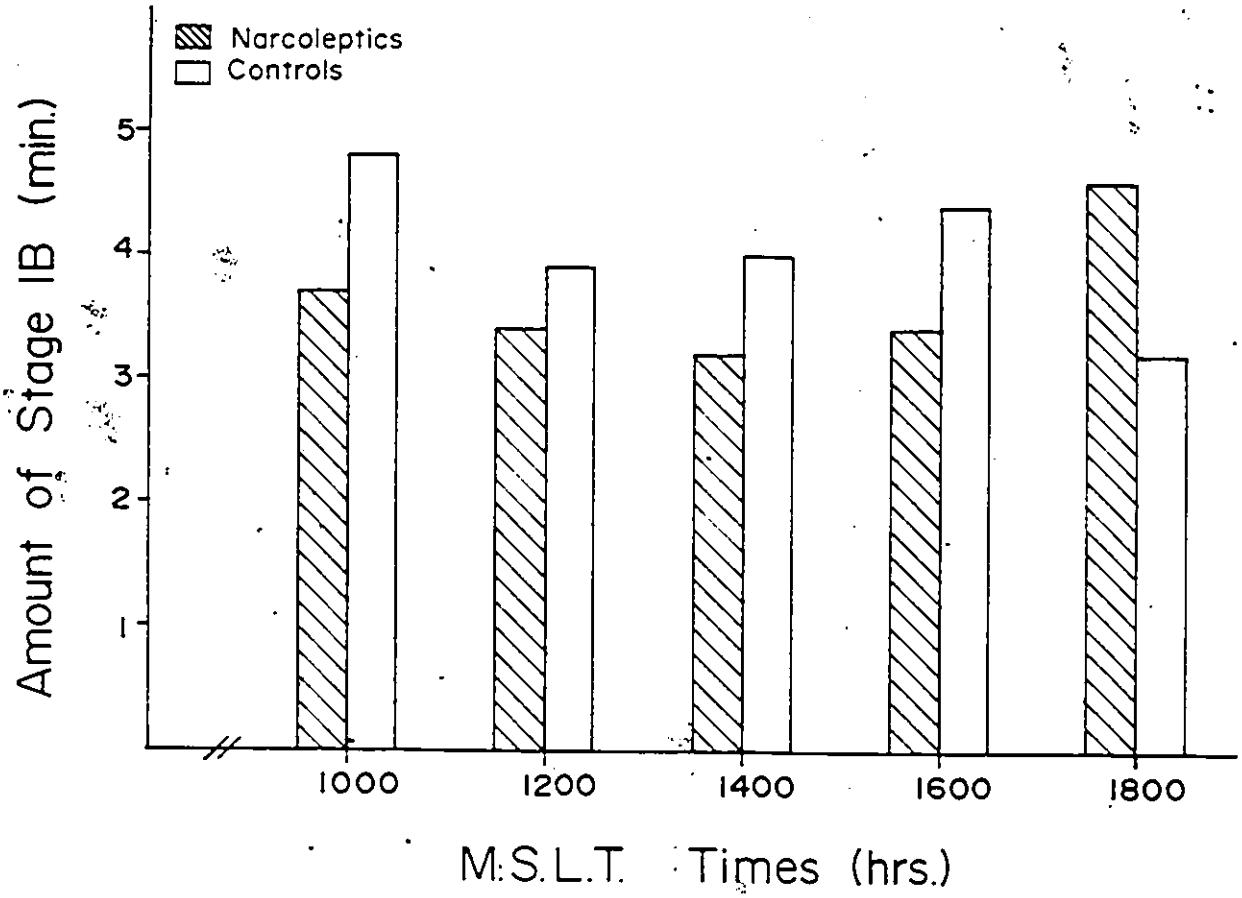

Narcoleptics
Controls
Amount of Stage IB (min.)
5
4
3
2
1
1000
1200
1400
1600
1800
M.S.L.T. Times (hrs.)

Figure 4

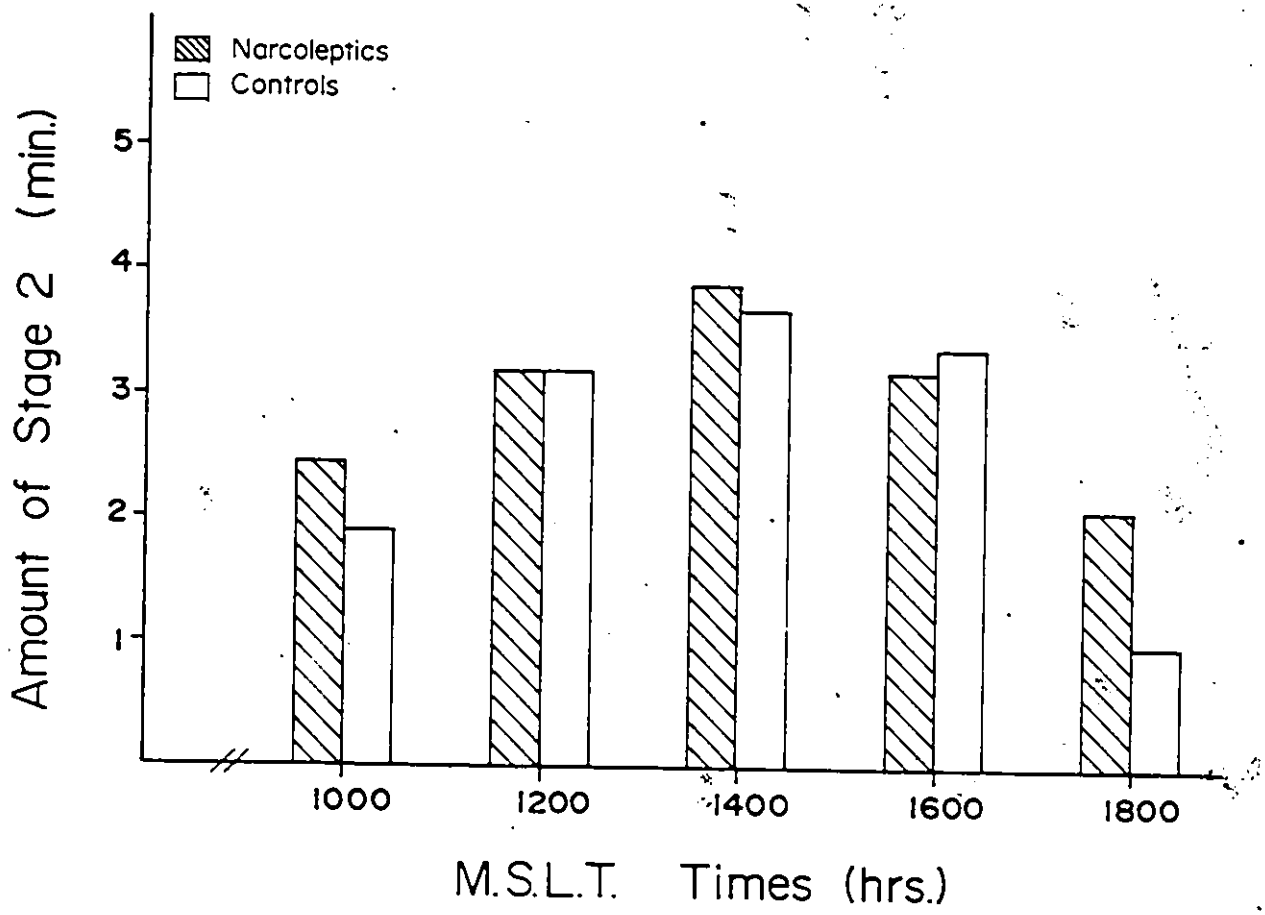

Narcoleptics
Controls
Amount of Stage 2 (min.)
5
4
3
2
1
1000
1200
1400
1600
1800
M.S.L.T. Times (hrs.)

Figure 5

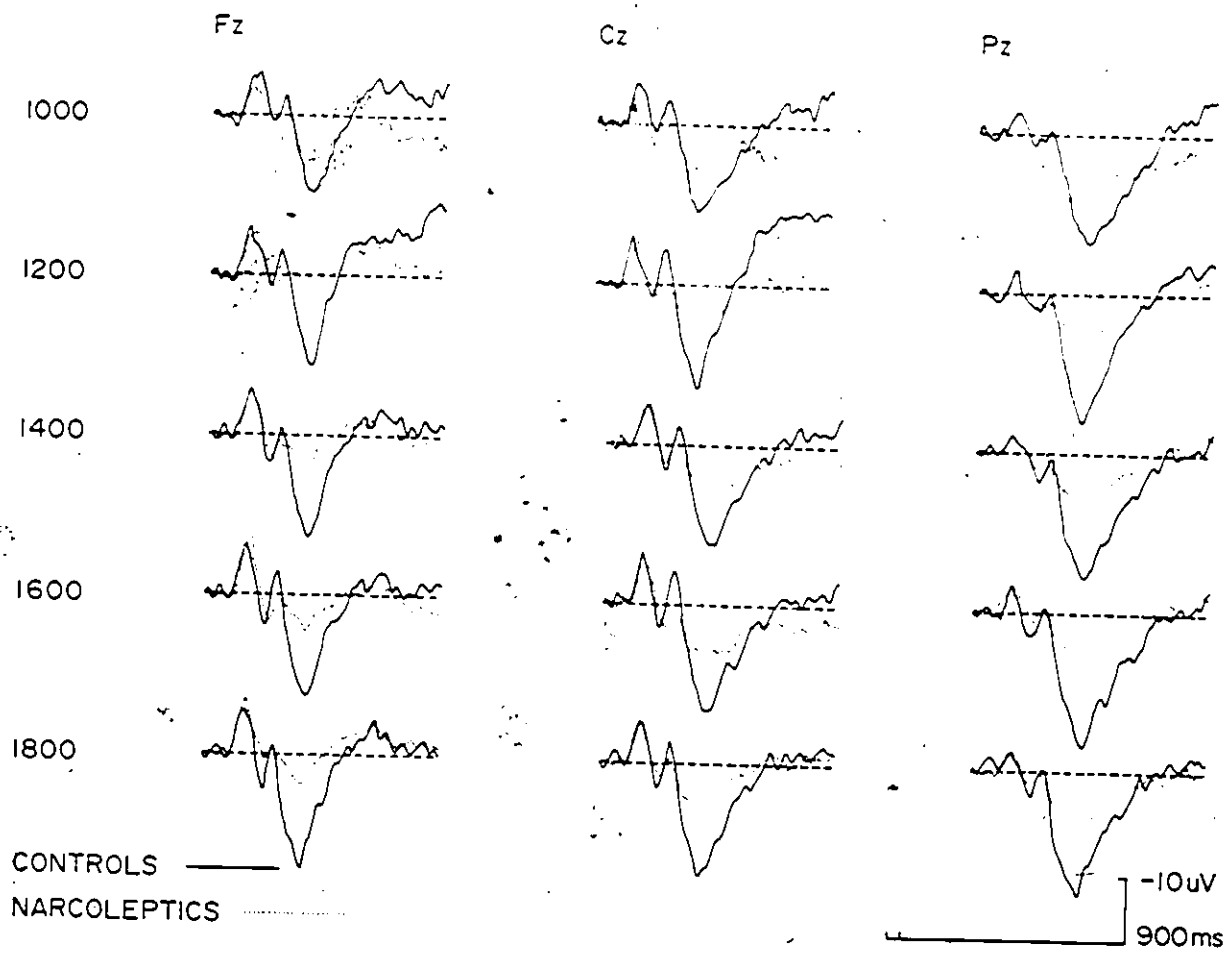

Fz
Cz
Pz
1000
1200
1400
1600
1800
CONTROLS
NARCOLEPTICS
-10uV
900ms

Figure 6

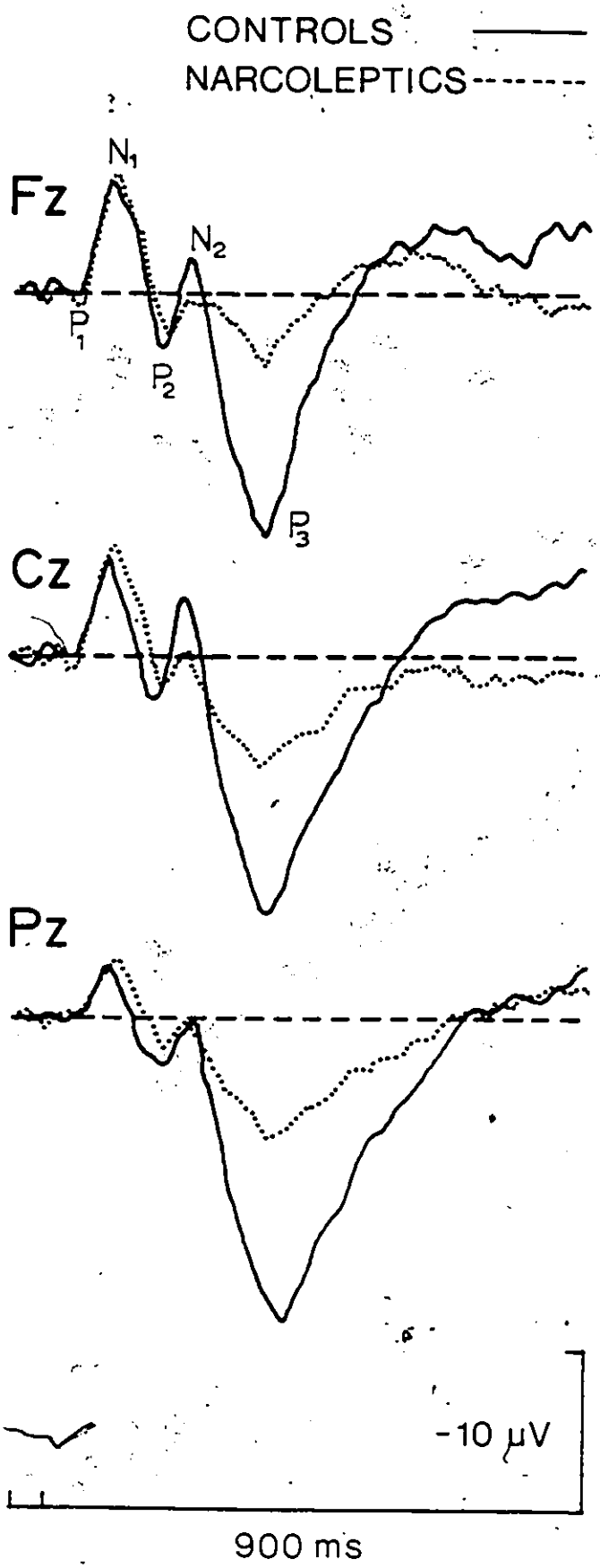


Figure 7

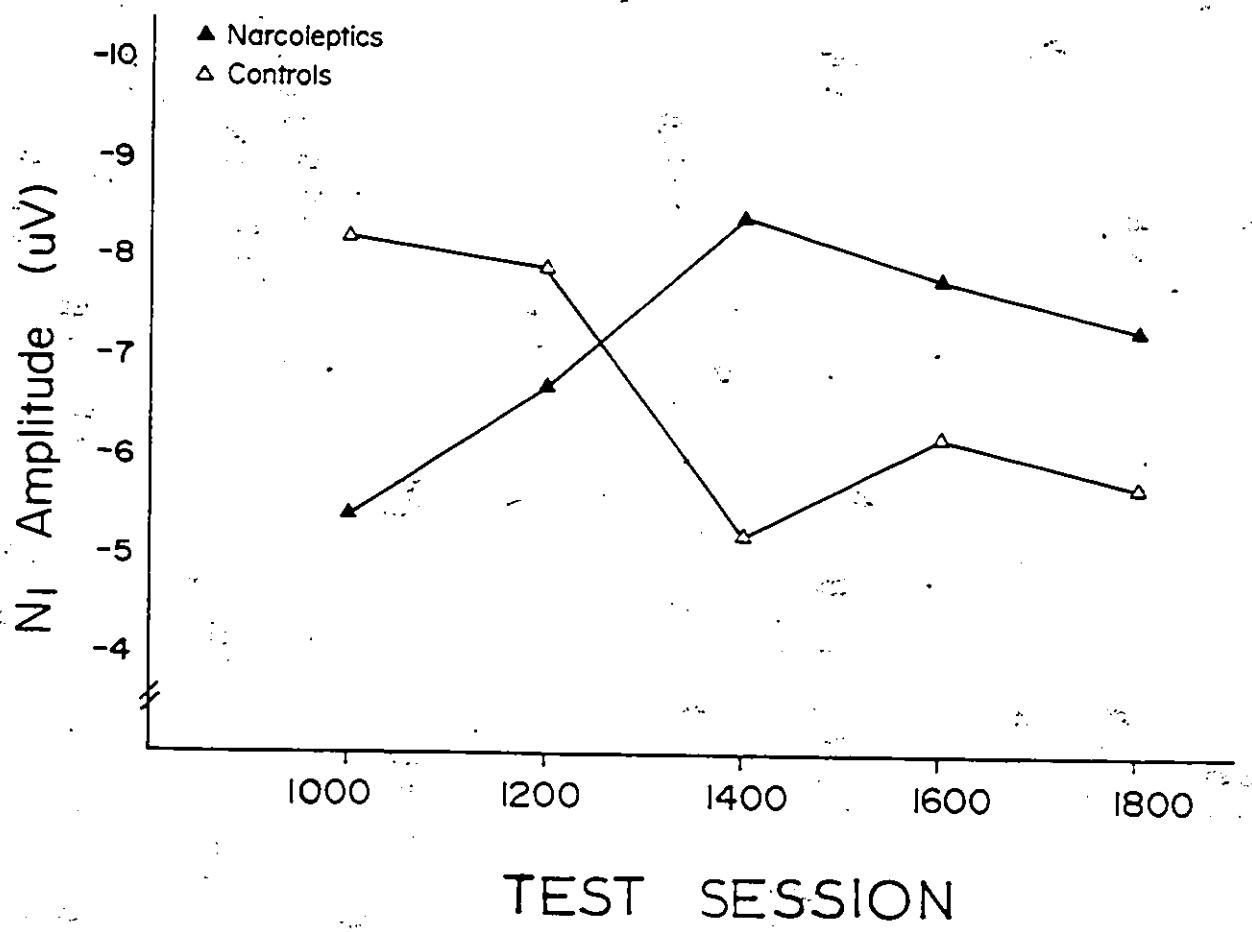

▲ Narcoleptics
△ Controls
-10
-9
-8
-7
-6
-5
-4
N1 Amplitude (uV)
1000
1200
1400
1600
1800
TEST SESSION

Figure 8

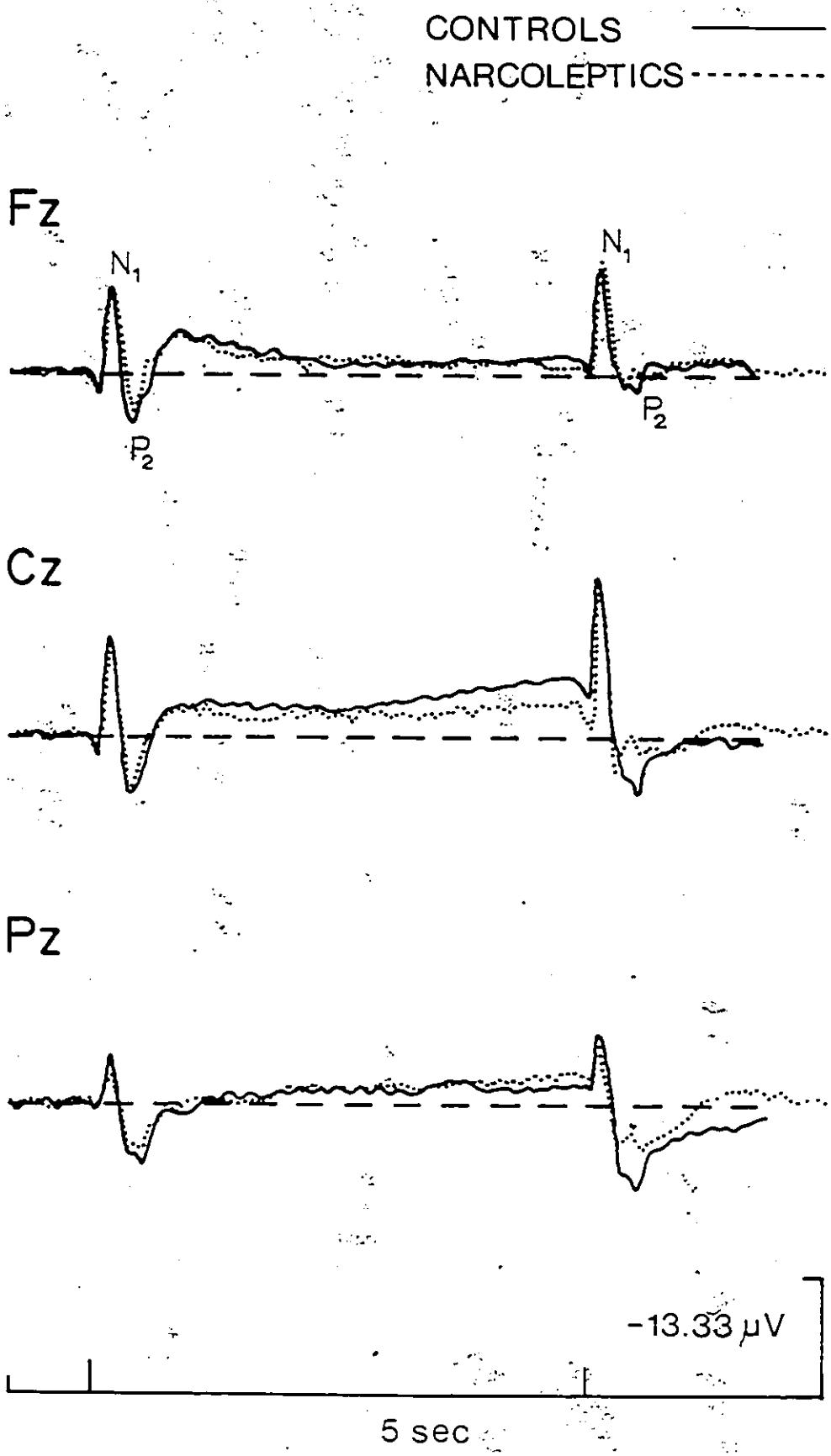


Figure 9

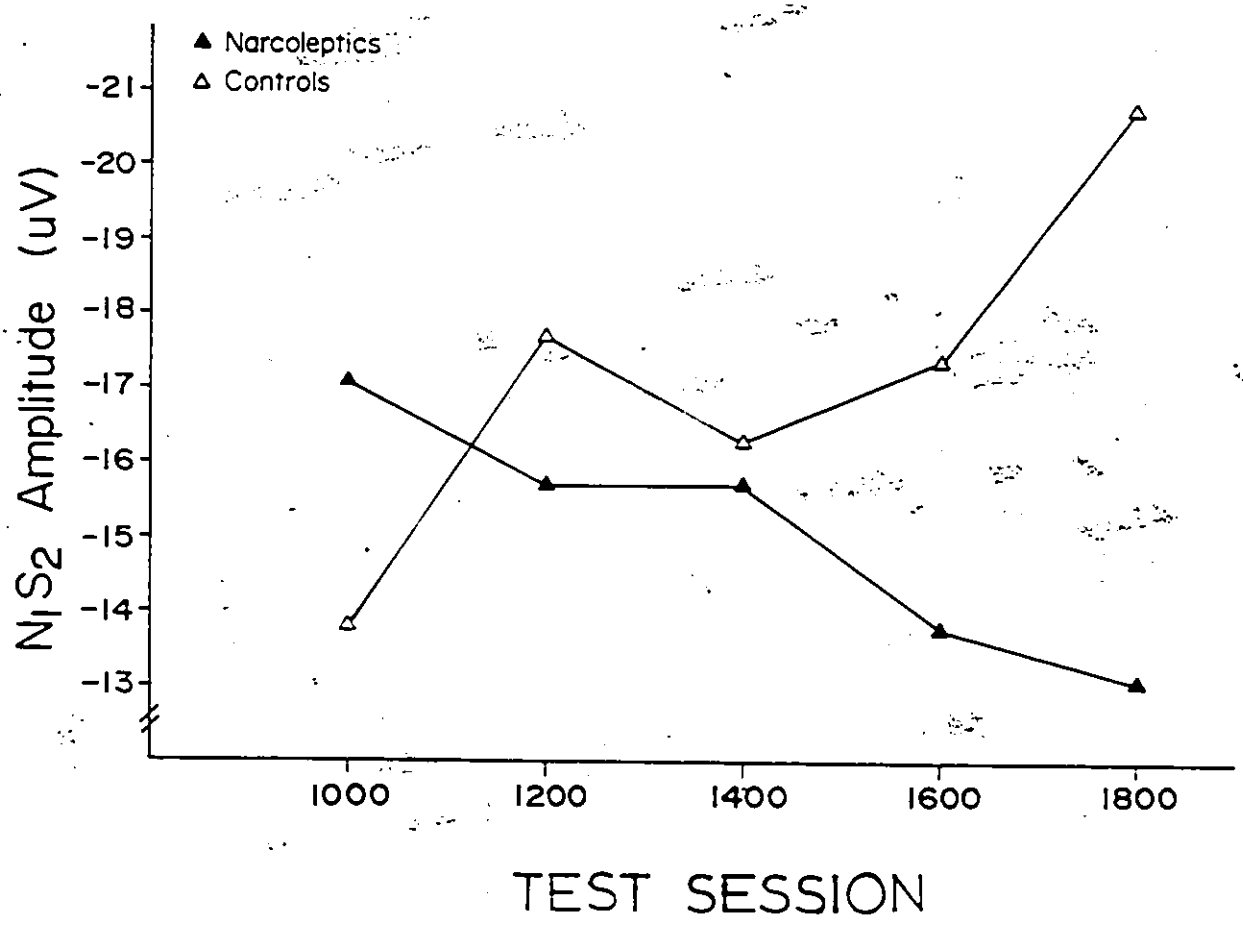
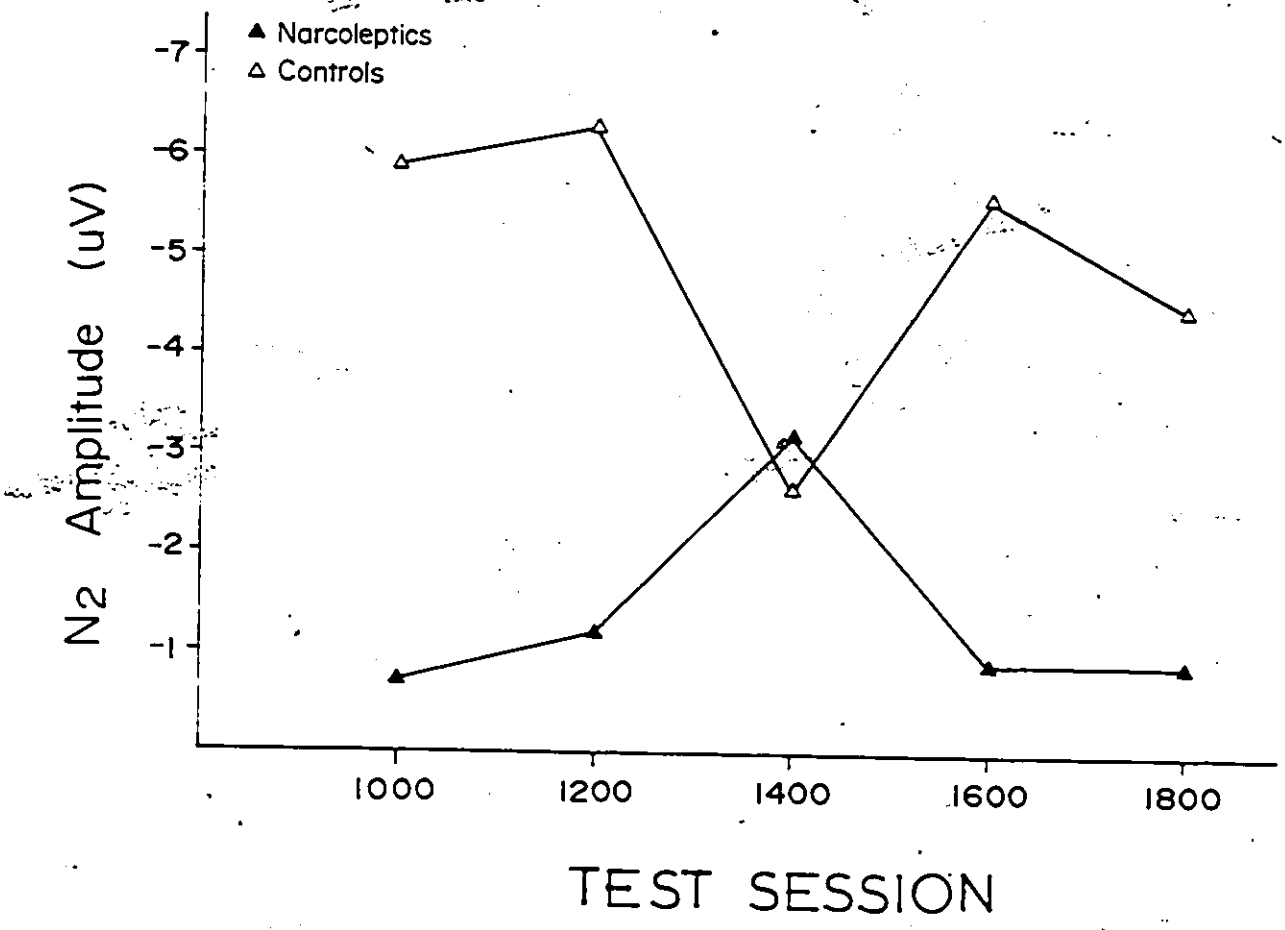

▲ Narcoleptics
△ Controls
-21
-20
-19
-18
-17
-16
-15
-14
-13
N1S2 Amplitude (uV)
1000
1200
1400
1600
1800
TEST SESSION

Figure 10


▲ Narcoleptics
△ Controls
N2 Amplitude (uV)
-7
-6
-5
-4
-3
-2
-1
1000
1200
1400
1600
1800
TEST SESSION

REM AND NREM SLEEPINESS AS DIFFERENT ELECTROPHYSIOLOGICAL STATES IN A GROUP OF NARCOLEPTIC-CATAPLECTIC PATIENTS.

INTRODUCTION

People experience transitory feelings of sleepiness in their daily life as part of normal ultradian and circadian fluctuations of vigilance (Lubin et al. 1973; Broughton 1975; Richardson et al. 1982). Sleepiness is essentially a physiological state that leads to sleep-seeking behaviour and an increased tendency to fall asleep (Dement, 1976, 1979). It can result from sleep loss (Webb, 1972, Friedman et al. 1977; Herscovitch et al. 1981), or any alteration of the normal sleep-wake cycle i.e. sleep restriction (Friedman et al. 1977) excessive night sleep (Taub & Berger, 1969) or delay or anticipation of the usual wake/sleep hours. Taub & Berger (1969, 1973), using mood description questionnaires and performance measures, have found that the sleepiness resulting from sleep deprivation is of a different nature than that produced by oversleep. The former leads to feelings of irritability and overreactivity, and the latter to feelings of thick-headedness and lethargy (Taub & Berger, 1973).

Broughton (1982) has recently suggested that sleepiness should no longer be considered a unitary phenomenon. He proposed that different types of sleepiness are associated with the neurophysiological mechanisms of wakefulness, REM sleep and NREM sleep and that each is characterized by a particular electrophysiological state. We have hypothesized that the sleepiness experienced as part of a normal circadian or ultradian fluctuation differs from that experienced by subjects with pressure for REM or NREM sleep.

Recent reports suggest that the electrophysiological states

that accompany REM and NREM sleep are not necessarily time-locked to these sleep stages (Tanguay et al. 1973), but may precede them. Pressman et al. (1982) recorded the auditory evoked potentials (AEP) of sleep deprived control subjects, non-sleep deprived controls and subjects suffering from narcolepsy. Narcolepsy is a disorder characterized by a frequent "need to sleep" (continuous excessive daytime sleepiness) and by sleep attacks causing sudden sleep onset into either NREM or REM sleep. Because of the unique pathophysiological mechanisms involved in their disorder, narcoleptics represent an ideal population to test the hypothesis that two different electrophysiological and functional sleepiness states exist, i.e. one for REM and another for NREM.

Pressman and colleagues found that the AEP's recorded in narcoleptics prior to NREM naps had amplitudes that were larger than those recorded in narcoleptics prior to REM naps and similar to those recorded in sleep deprived subjects. These researchers asked only that their subjects remain alert, rather than participate in a perceptual task. While the early AEP components they measured are sensitive to the physical characteristics of the stimuli i.e. frequency, intensity and presentation rate. (Davis, 1966; Beagley et al. 1967) these components have also been known to reflect the degree of attention paid to the stimuli by the subject (Hillyard et al. 1973; 1978). They therefore offer the opportunity to measure the degree of alertness of the subject.

Other components of the auditory evoked potential, the N2 and P3 waves, can be recorded whenever a subject is required to detect an odd or "target" signal occurring among a series of "standard" stimuli. These components occur 200 to 350 msec after the stimulus is deliver-

ed. It is not as yet certain which stage of information processing the N2-P3 complex represents. The amplitudes and latencies of these potentials have been manipulated in experiments claiming to measure selective attention (Hillyard et al. 1973), decision closure (Desmedt, 1981), contextual memory updating (Donchin et al. 1978), information value of material as reflected by the probability of occurrence of the stimulus (Tueting et al. 1971) and the level of confidence of the subject in having made the correct selection (Squires et al. 1973). The N2 and P3 have also been recorded when a stimulus is omitted among a series of standard stimuli (Simson et al. 1976).

Campbell et al. (1980) have recently reported a decreased P3 in a group of sleep deprived subjects. The sensitivity of this component to states of sleepiness prior to REM and NREM sleep has yet to be investigated.

Another event related potential (ERP) which offers the opportunity to measure brain reactivity is the contingent negative variation (CNV) (Walter et. al 1964). This slow negative potential is recorded from the scalp when a subject is waiting to respond to a second stimulus (imperative stimulus) after an initial stimulus (warning stimulus) has been presented. This ERP has been found sensitive to the effects of phasic sleepiness (Naitoh et al. 1971).

Positive (hyperpolarization) and negative (depolarization) potential shifts have been recorded during NREM and REM sleep stages respectively (Kawamura & Sawyer, 1964; Tabushi et al. 1966). If the different states of sleepiness resulting from pressure for REM or NREM sleep are similar to the states present during REM and NREM sleep, then one would expect the amplitude of the CNV, which is a slow negative DC potential shift, to reflect the different electrophysiological

states of the cortex.

This study attempts to further investigate whether the types of sleepiness experienced prior to REM and NREM sleep in narcoleptics are accompanied by different subjective (as measured by SSS), behavioural (as measured by performance levels) and electrophysiological states. The latter will be studied at macro (EEG) and micro (AEP, CNV) levels. We also attempt to determine whether or not attentional and perceptual processes are similar prior to REM and NREM sleep, as reflected by the mesogenous (N1,P2) and endogenous (N2,P3) components of the auditory evoked potentials.

METHODS

The methodology of this experiment has been described in detail in the preceding report. The population of subjects, protocol and the procedures for all tests were as reported.

The purpose of this study was to determine if differences exist between the states preceding REM and NREM sleep, as reflected by the different measures employed: MSLT, SSS and ERP's. The data recorded from each of the narcoleptics at any one of the testing sessions was considered a single observation. All narcoleptics' ERP data recorded prior to NREM sleep were collapsed and compared to the data recorded prior to REM sleep. The data of each subject was thus classified as either REM or NREM depending on type of sleep into which the subject subsequently fell. Comparisons were carried out between the 35 REM and the 25 NREM naps. Because the results to be reported in this study were done following the analysis of the results presented in the first report, it was decided to choose a more stringent alpha level of $p < .01$ rather than $p < .05$ as in the previous report.

MSLT

The MSLT naps of narcoleptics were divided into those containing some REM sleep and those containing only NREM sleep. Naps were considered REM type if REM sleep occurred during any of the 10 minutes of sleep allowed. NREM naps were those in which only this type of sleep occurred. These naps will hereafter be referred to as REM naps and NREM naps. It was assumed that the sleepiness experienced prior to these two different types of naps would represent 'REM sleepiness' and 'NREM sleepiness' respectively.

It was thought that some insight into the differences between these two sleepiness states (pre-NREM, pre-REM) could be obtained by determining the differences in the sleep parameters of the subsequent naps. The parameters include sleep onset times, number of arousals after sleep onset, time awake after sleep onset and proportions of time spent in stages 1B, 2, 3 and 4.

All pre-REM and pre-NREM sessions were considered as single observations. The SSS, behavioural measures (RT and error rates) as well as the latency of the various ERP components were compared using Student's t Test (REM vs NREM). The amplitude of the various components were submitted to a two-way ANOVA (electrode x sleepiness type). Finally time spent in each stage (stages 1, 2, and REM) within actual REM and NREM naps were tested using differences in proportions (Spiegel, 1961, p. 171).

SSS

Absolute SSS scores and alertness changes (SSS scores before minus SSS scores after both ERP and MSLT tests) observed prior to REM

naps were compared to those observed prior to NREM naps by t-tests.

P3 ERP Study

The latencies, detection levels (number of targets missed and false signal detections) and reaction times were compared by t-tests. The AEP amplitudes were analyzed by a 2-way repeated measures ANOVA (electrode x sleepiness type).

CNV ERP Study

The latency, anticipatory response and reaction time comparisons of REM vs NREM were done using t-tests. Amplitude measures were analyzed by a 2-way repeated measures ANOVA (electrode x sleepiness type).

Other Statistical Analysis

Post-hoc comparisons were done using the Tukey's Test (Kirk, 1968).

RESULTS

Raw data of each of the variables described below is found in Appendices 14 to 20.

MSLT

Narcoleptics had a total of 35 REM and 25 NREM naps on the first day and 36 REM and 24 NREM naps on the second day (Table I). A chi square test rejected the hypothesis that test time did not influence the likelihood of a REM sleep episode ($X=8.9$, $df=4$, $p < .009$). A larger number of REM naps was observed in the 1000 session.

A comparison of the differences in proportions of time spent in stages 1-4 between REM and NREM naps showed that both groups spent the same proportions in stage 1, 2 and 3 (Table II). Only two narcoleptics spent time in stages 3 and 4, mainly in NREM naps.

REM naps showed significantly shorter sleep latencies to stage 1B than NREM naps ($t=3.50$, $df=58$ $p < .001$) (Table II). No differences appeared in the number of arousals after sleep onset between REM and NREM naps ($t= .36$, $df=58$, $p < .721$). There was also no significant difference in time awake after sleep onset between NREM naps (13.5 sec) and REM naps (10.0 sec) (Table II).

Analysis of sleep onset latencies to stage 1B showed that both groups (REM and NREM) fell asleep significantly faster than their respective controls.

SSS

The comparison of absolute values prior to ERP testing sessions showed that SSS scores were higher before REM (3.3 SD=1.4) naps than before NREM (2.41 SD=1.2) naps ($t= 3.78$, $df=58$, $p < .0001$). This indicates that those subjects who subsequently fell into REM sleep were much sleepier before the ERP testing sessions than those who later fell into NREM sleep (Figure 1).

Comparison of the changes of alertness after the ERP sessions prior to REM (-.64) and NREM naps (-.73) showed a smaller reduction of alertness during the ERP testing session prior to REM naps. The greater sleepiness present prior to REM naps may have produced a floor effect that restricted the amount of change in alertness that could occur.

A comparison of change of alertness scores after REM naps vs

NREM naps showed that narcoleptics after REM sleep reported a significantly larger increase of alertness (+.87) than after NREM naps (+.39) ($t=3.48$, $d=58$, $p < .01$).

P3 ERP Study

Latencies and Amplitudes

No differences were observed in any of the latency measures (Table III). A significant difference was observed in the amplitude of the P2 component (Table IV). The amplitude recorded prior to REM was significantly larger than that recorded prior to NREM ($F=8.24$, $df=1,58$, $p < .006$) A significant electrode x sleepiness type interaction effect was observed ($F=5.55$, $df=2,116$, $p<.005$). The smallest P2 amplitude was recorded in both groups at Pz (pre-REM 3.1 uV, preNREM 2.1 uV) while significantly larger amplitudes were recorded pre-REM compared to pre-NREM at Fz ($F=5.76$, $df=2,58$ $p < .02$) and Cz ($F=17.80$, $df=2,58$, $p < .0001$). P1, N1 and N2 showed similar scalp distribution in both groups (Figure 2).

Performance

No differences appeared in the comparison of narcoleptics' performance prior to REM vs NREM naps (Table V).

CNV ERP Study

Latencies and Amplitudes

No significant differences were observed in any of the latencies (Table VI) or amplitudes of the different components (Table VII).

A significant interaction effect was observed in the AMSH ($F=4.80$, $df=2,110$, $p < .02$) (Table VIII). Although the amplitudes at Cz (pre-REM -2.4 uV, pre-NREM -4.1 uV) and Pz (pre-REM -2.5 uV, pre-NREM 3.7uV) were larger prior to NREM than pre-REM, the only significant difference was at Fz (pre-REM -0.21uV, pre-NREM -5.4uV) ($F=7.2$, $df=1,58$, $p < .01$). It is interesting to note that while statistical significance was only approached the amplitudes recorded in the first half (AMFH) ($p < .07$) and second half (AMSH) ($p < .04$) of the CNV interval were always of much larger amplitude prior to NREM (Figure 3). Another interesting finding is the larger P2 amplitude recorded prior to REM naps (Table VII). Although the amplitude differences only approached significance (P2S1 $p < .08$ and P2S2 $p < .04$) the fact that the analogous P2 amplitude in the P3 paradigm was significantly larger prior to REM suggests that this is a finding that might deserve some consideration.

Performance

No significant performance differences were observed between narcoleptics prior to REM and prior to NREM naps. There was a tendency towards a larger number of anticipatory responses prior to NREM naps (difference between groups approached significance at $p < .10$) (Table VIII). Correlations between AMSH and RT pre-NREM were as follows: $Fz=.39$ ($p < .11$), $Cz=.48$ ($p < .04$) and $Pz=.42$ $p < .08$). Prior to REM the following correlations were observed: at $Fz= -.27$ ($p < .11$), $Cz= -.12$ ($p < .49$), and $Pz= .032$ ($p < .87$).

DISCUSSION

MSLT & SSS

The degree of alertness reported by narcoleptics after REM or NREM naps was very similar to their respective SSS ratings reported prior to the ERP testing session. It seems that the naps allowed the narcoleptics to recuperate from the increase in sleepiness that they reported (SSS) following the ERP session. It appears that both REM and NREM narcoleptic naps relieve the increased pressure for sleep and enable a return to a functional level of alertness. If these naps are suppressed by the environment of the narcoleptic, the pressure for sleep may increase to the point that a sleep attack results.

A comparison of the SSS scores reported prior to ERP testing sessions showed that those narcoleptics who later fell into REM sleep were significantly sleepier than those who later fell into NREM sleep. Similar findings were reported by Carskadon & Dement (1975, 1977) who observed positive correlations between SSS scores reported prior to naps and time spent in REM sleep. Carskadon & Dement observed that their subjects, under a 60 minutes wakefulness-30 minutes sleep schedule, showed an alternation of NREM and REM naps. Because of this, they were not able to point to a causal relationship between degree of sleepiness and REM appearance. However this observation did suggest the existence of an ultradian cycle corresponding to the alternation of REM/NREM, in which the upswing of the cycle corresponded to the occurrence of NREM while the downswing corresponded to REM appearance. We did not observe alternation of REM and NREM naps. This may there-

fore suggest a relationship between increase of sleepiness and REM occurrence. It is possible that the increase in sleepiness is a predictor of the onset of REM.

Narcoleptics had more REM than NREM naps. This may reflect the fact that 10 of the 12 narcoleptics suffered from compound narcolepsy which is more commonly accompanied by REM naps (Dement et al. 1972; Guilleminault and Dement, 1974). It has been suggested that SOREMP's are also facilitated by a horizontal sleeping position (Hishikawa et al., 1968) as was used in this study.

The narcoleptics showed significantly more REM naps in the first testing session (1000). Studies in which sleep of normal subjects has been extended during the day have shown that REM also tends to occur in early sessions (Webb et al. 1966). Our finding confirms past studies which observed a typical circadian distribution of sleep stages in narcoleptics (Baldy-Moulinier et al. 1976; Broughton & Mamelak, 1979) and the tendency of narcoleptics to show a larger number of REM naps in the early morning (Passouant, 1968; Hishikawa et al. 1976).

Narcoleptics falling into REM sleep spent the same proportion of time in stages 1B and 2 as those falling into NREM sleep (both groups were allowed a maximum of min. of sleep). The decline in SSS scores following REM naps (from pre-REM) was greater than the decline from pre to post-NREM). It appears that either the time spent in REM sleep (or the combination of REM and NREM sleep) produced the larger recuperative value of REM naps. The literature suggests that no differences in performance are present when subjects are awakened from

either stage 2 or REM (Scott & Snyder, 1968; Lavie & Giora, 1973). Since our narcoleptics were most often awakened from either stage 1, 2 (in NREM and REM naps) or REM (in REM naps), the differences in alertness reported after REM and NREM naps are unlikely to be due to differences inherent in the moments of awakening from either of these types of sleep. In the past, researchers (Hartmann, 1973; Oswald, 1973, 1974) have proposed that the functional relevance of REM sleep is related to brain restoration. However, the evidence for such a theory is weak (Stern & Morgane, 1974; Brodsky, 1975). It must be considered that the larger alertness reported by narcoleptics after REM sleep may simply be related to the fact that they were initially sleepier (as indicated by their shorter sleep onset latencies and higher SSS scores).

P3

We recorded a significantly larger P2 prior to REM than to NREM. This is in disagreement with Pressman et al. (1982) who recorded significantly smaller N1-P2 and P2-N2 amplitudes prior to REM. The differences in the paradigms employed (Pressman and his group's subjects were simply asked to listen to the stimuli while in the present study the subjects were actively engaged in a signal detection task) and differences in measurements (Peak-to-peak vs baseline-to-peak) may explain the different results.

P2s recorded in subjects listening passively to a series of stimuli are much larger than those recorded in subjects asked to actively detect deviant target stimuli among a train of standard

stimuli (Simson et al. 1976, 1977). This could be due to overlapping negative waves occurring in parallel to P2. A long-lasting negative wave, termed "processing negativity" (Naatanen, 1982) beginning before N1 and lasting beyond the latency of P2, increases in amplitude in the attentive subject. In the present context, this processing negativity might have "pulled up" P2 making it less positive. Secondly, Naatanen has also described a negative-positive complex (N2a, N2b-P3a, P3b), recorded during target detection (Naatanen et al. 1980). As the latency of the negative component (N2) is in the same latency range as P2, an overlap of components may occur resulting in P2 amplitude reduction (Naatanen et al. 1980). Since N2 at Cz prior to NREM was larger than prior to REM, it is possible that its overlapping negativity "pulled up" P2 giving the appearance of reduced positivity. This explanation cannot apply to the components recorded at Fz. The N2 recorded at Fz was of equal amplitude in all narcoleptics, while the P2 pre-REM was still significantly larger than that recorded pre-NREM.

The significantly larger P2 recorded pre-REM contrasts with the failure to find differences in other objective indices, such as N1 and P3 amplitudes (Picton & Hillyard, 1974; Hink & Hillyard, 1976; Campbell et al. 1980), and RT (Wilkinson & Morlock, 1967; Campbell et al. 1980). The previous report indicated that N1 was large in the morning for controls and small for narcoleptics. Later in the day, an opposite trend was observed; a smaller N1 amplitude in controls and a larger N1 in narcoleptics. Unfortunately, due to an insufficient number of cases at the various times of day, we were unable to deter-

mine if the overall narcoleptic biorhythmic trend can be generalized to both REM and NREM naps. The absence of significant amplitude differences in the N2 and P3 does not necessarily reflect a lack of difference between attentional and perceptual processes in pre-REM and NREM states. Future research in which more complex paradigms are used, i.e. divided attention (Hink & Hillyard, 1976), passive versus active attention (Squires et al. 1975; Campbell et al. 1980) or overloading of primary memory (Israel et al. 1980), will help determine whether attentional and perceptual differences accompany these states.

CNV

A significantly smaller ($p < .01$) amplitude was recorded over the frontal areas in the second half of the CNV interval prior to REM sleep. This REM-NREM difference was also apparent in the first half of the CNV, although it failed to reach significance ($p < .07$). Two separate components which make up the CNV have been described in the literature (Loveless & Sanford, 1974a, 1974b; Gaillard, 1976, 1977). The first half of the CNV, the O wave, is largest in frontal-central areas and has been related to initial orientation and arousal. Tecce (1972) and Hillyard (Hillyard, 1969; Hillyard, 1973) have noted that the CNV is affected by manipulation of the subjects level of attention or "alertness". The second half of the CNV, the E wave, is largest in central-parietal areas and has been related to the subject's expectancy to respond. Our second-half CNV amplitude difference could therefore reflect differences in either motor preparedness or degree

of alertness (Tecce et al. 1976, 1981; Deecke, 1980). The smaller amplitudes found pre-REM would suggest less motor preparedness at this time. Although no significant RT differences were found, mean RTs indicate that subjects were in fact more prepared to respond prior to REM (317 msec.) than prior to NREM (354 msec.). That the amplitude differences do not reflect differences in motor preparedness is supported by the fact that the greatest differences were found at the frontal electrode site and not over those areas traditionally associated with motor preparedness (central and parietal) (Deecke, 1980).

Frontal areas have been associated with actions such as arousal, alertness and attention (Milner, 1963; Homskaya, 1966; Luria, 1969). The early CNV differences paralleled those in the second half suggesting at least the possibility of an effect of alertness. The SSS prior to REM indicated a lowered state of alertness. Moreover, sleep onset occurred in the MSLT more rapidly in REM naps, again suggesting a less alert or aroused state. The SSS and MSLT results provide evidence to support the belief that differences in CNV ampltudde were due to variation in the subjects; level of alertness prior to REM and NREM naps.

It could be argued that the larger CNV amplitude and slower reaction times recorded prior to NREM correspond to greater attention paid to accuracy as opposed to speed, thus reconciliating the RT-CNV paradox. However, prior to NREM a larger number of anticipatory responses were made ($p < .10$). Suggesting that subjects placed emphasis more on speed than accuracy prior to this state. There is an interpretation which can explain the presence of slow RTs in conjunc-

tion with anticipatory responses. Rabbit (1981) has noted that subjects confronted with typical RT experiments manage to improve their speed with practice. To do so, they respond faster and faster on consecutive trials until they respond too quickly and an error is made. After recognizing the error, subjects slow down considerably. In the present study, the effect of anticipatory errors prior to NREM might have been to alter subjects strategy such that following the errors, RT was slowed, assuring accuracy. The overall mean RT might therefore have been longer than in conditions in which fewer anticipatory errors were made.

The smaller pre-REM CNV amplitude recorded over the second half of the CNV interval may also have been the result of larger cortical depolarization elevating the baseline. This would allow only a relatively small CNV before a maximal level was reached (ceiling hypothesis) (Knott & Irwin, 1968). Negative DC potential shifts have been recorded during REM sleep and positive DC potentials have been recorded during NREM sleep (Kawamura & Sawyer, 1964; Tabushi et al. 1966; Kawamura & Pompeiano, 1969). The possibility that such potential shifts might have been present prior to these states could explain the different amplitudes recorded. It is also possible that the lower pre-REM CNV amplitudes were related to the hypothesized larger cortical depolarization that accompanies increased sleepiness (Broughton, 1975).

Otto & Leiffer (1973) interpreted the smaller CNV's recorded when subjects were pressing a button, as resulting from an increased depolarization associated with a larger EMG. The faster RT recorded

pre-REM agrees with the idea that greater motor preparedness was present in this state.

By contrast, the positive CNV-RT correlations we observed prior to NREM may be suggestive of a hyperpolarized cortical state. In addition, the significantly larger negativity recorded over frontal regions prior to NREM is reflective of Broughton's (1975) hypothesis of a larger degree of hyperpolarization over the frontal cortex during actual NREM sleep.

Conclusion: Evidence for the Existence of REM and NREM sleepiness

The data we have collected indicates that sleepiness experienced by narcoleptics prior to REM naps differs from that observed prior to NREM . The SSS scores show that sleepiness prior to REM sleep is subjectively experienced as more intense than that prior to NREM sleep. A number of objective measures also discriminated between the two states. Shorter sleep latencies prior to REM naps provides support for the reports of increased sleepiness. In the P3 paradigm P1 and P2 amplitudes were significantly larger prior to REM sleep. It is possible that either a slower shift from positivity to negativity occurs prior to REM or an overlap of a series of negative waves "pulls up" P2. There were no differences for RT or N2, P3 amplitudes or latencies.

Narcoleptics prior to NREM naps showed more widespread negativity throughout the CNV than prior to REM. Pre-REM showed a significantly reduced amplitude over the second half of the CNV interval at Fz. The reduced CNV amplitude prior to REM might be interpreted as

reflecting the larger degree of sleepiness subjectively experienced prior to this state. It is also possible that these differences are due to baseline shifts: negative (or depolarized) prior to REM and positive (or hyperpolarized) prior to NREM. Again, no significant differences were found in RT between pre-REM and pre-NREM naps, although there was a possibility of a speed-accuracy confounding interaction.

Since we have documented the existence of different states in a narcoleptic population, it may be that they are a phenomena unique to the narcoleptic pathology (Guilleminault & Dement, 1974) and are not present in the normal population. For more definite conclusions to be made it will be necessary to find evidence of these states in subjects with no sleep pathology. If such differences are found to exist it will be important to determine if each sleepiness state is accompanied by different functional deficits. This would require the use of more sophisticated performance measures than those used in this study (signal detection and reaction times). It might be advisable to use short memory paradigms in which encoding and recall of material with simple and complex associative value (Scrima, 1982) is tested prior to REM and NREM sleep states. There is evidence that these types of material are processed differently during REM and NREM sleep stages (Scrima, 1982).

SUMMARY

Differences between the states preceding REM and NREM sleep were studied in a group of twelve narcoleptic-cataplectic patients and were compared to the state preceding NREM sleep in 12 normal healthy subjects. Subjective (Stanford Sleepiness Scale) and objective measures of sleepiness were compared. The objective measures were sleep onset latencies and sleep times (Multiple Sleep Latency Test), latencies and amplitudes of two event-related potentials (P3 and CNV), together with reaction times and detection levels. All subjects filled out SSS forms prior to and after ERP sessions and following MSLT naps. In the P3 paradigm the subject was instructed to detect target stimuli (10% of all stimuli) by pressing a button. In the CNV paradigm the subject was asked to turn off a buzzer (S2) which was preceded 3 sec before by a warning tone (S1). All narcoleptics, both those having REM and NREM naps, showed larger sleepiness through the day than their respective controls. Pre-REM absolute SSS scores were larger than pre-NREM scores reflecting much greater sleepiness pre-REM. Those narcoleptics having REM naps experienced a larger increase in alertness after the MSLT naps than those having NREM naps. The larger sleepiness associated with the pre-REM state was objectively supported by significantly shorter stage 1B latencies in REM naps. The lack of differences between most sleep parameters in REM and NREM naps (proportion of times in stage 1B, 2, 3 and 4, number of arousals and time awake after sleep onset) suggests that either time spent in stage REM or a combination of REM and NREM sleep were the factors.

contributing to the larger recuperative value associated with REM naps. In the P3 paradigm the major ERP differences between pre-REM and pre-NREM sleepiness were significantly larger P1 and P2 amplitudes recorded prior to REM naps. An overlap between P2 and negative components or a slower shift from positivity to negativity might explain these results. A significant difference was observed between pre-REM and pre-NREM states in the CNV paradigm. A significantly smaller negativity in the second half of the CNV interval over frontal areas was recorded prior to REM sleep. No significant differences in performance measures (detection levels and reaction times) were observed between groups in either ERP paradigm. These results support the existence of two distinct states, those of REM and NREM sleepiness.

TABLE I

Number of narcoleptics' REM and NREM naps through the day.
Average of day 1 and day 2.

	Test Times				
	1000	1200	1400	1600	1800
REM	10 *	7	6	6	6
NREM	3	5	5	5	6

* $p < .04$

TABLE II

Analysis of MSLT Data according to Sleep Type

	Stage 1B		Stage 2		Stage 3		Stage 4		NUMBER OF AROUSALS	TIME AWAKE AFTER SLEEP ONSET	LATENCY TO STAGE IB
	Sec.	%	Sec.	%	Sec.	%	Sec.	%			
REM	179.7	47.0	202.4	53.0	20	4.7	20	4.7	.39	10"	106" **
NREM	289.9	42.0	392.2	57.5	60	7.0	120	13.7	.33	13"	196"
Controls	246.0	61.0	156.0	39.0					.003	51" ***	600" @

** p <.001 Significantly shorter latencies to stage 1B were present during REM naps than during NREM na

*** p <.02 Controls spent significantly longer time awake after sleep onset than either REM or NREM nap

@ p <.001 Controls showed significantly longer latencies to stage 1B than either REM or NREM naps

TABLE III

T values of REM/NREM comparisons of AEP latencies (msec) in the P3 Paradigm

Component	t Value	df	2-Tailed Probability
P1	2.39	58	.268
N1	0.17	58	.863
P2	1.05	58	.298
N2	0.07	58	.945
P3	0.22	58	.830

TABLE IV

2-Way ANOVAS of REM/NREM Comparisons of AEP amplitudes (uV) in the P3 Paradigm

Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
P1	Sleepiness	2.78	1,58	.10	
	Electrode	9.36	2,116	.0002	.0001 (1)
	Sleep. x Electrode	0.90	2,116	.411	.382
N1	Sleepiness	0.05	1,58	.803	
	Electrode	29.71	2,116	.0001	.0001 (2)
	Sleep. x Electrode	0.36	2,116	.700	.669
P2	Sleepiness	8.24	1,58	.006 *	
	Electrode	7.28	2,116	.001	.002
	Sleep. x Electrode	5.55	2,116	.005	.007 **
N2	Sleepiness	0.08	1,58	.781	
	Electrode	1.99	2,116	.141	.150
	Sleep. x Electrode	2.41	2,44	.102	.121
P3	Sleepiness	1.00	1,58	.321	
	Electrode	9.18	2,116	.0002	.0008 (3)
	Sleep. x Electrode	0.61	2,116	.544	.500

(1) Recorded maximally at Cz and minimally at Pz

(2) Recorded maximally at Fz and minimally at Pz

(3) Recorded maximally at Cz and minimally at Pz

TABLE V

T values of REM/NREM comparisons of reaction times and detection levels in the P3 paradigm

	t Value	df	2-Tailed Probability
Reaction Time	0.51	58	.611
Targets Missed	0.22	58	.824
False Positive	0.38	58	.734

TABLE VI
T values of REM/NREM comparisons of EP latencies (msec) in the CNV paradigm (Measured at Cz)

Component	t Value	df	2-Tailed Probability
N1S1	1.59	54	.119
P2S1	1.34	54	.186
N1S2	1.41	54	.165
P2S2	0.48	54	.636

TABLE VII

2-Way ANOVAS Comparing REM NREM Mean Amplitudes (uV) of EP Components in the CNV Paradigm

Amplitude of Component	Source of Variance	F Value	df	2-Tailed Probability	Geisser-Greenhouse Probability
N1S1	Sleepiness	1.62	1,54	.208	
	Electrode	71.91	2,110	.0001	.0001 (1)
	Sleep. x Electrode	0.05	2,110	.951	.910
P2S1	Sleepiness	3.28	1,54	.076	
	Electrode	21.54	2,110	.0001	.0001 (2)
	Sleep. x Electrode	1.28	2,110	.282	.280
N1S2	Sleepiness	0.00	1,54	.981	
	Electrode	37.84	2,110	.0001	.0001 (3)
	Sleep. x Electrode	0.25	2,110	.782	.763
P2S2	Sleepiness	4.43	1,54	.04	
	Electrode	4,88	2,110	.009	.02 (4)
	Sleep. x Electrode	0.06	2,110	.945	.909
AMFH	Sleepiness	3.43	1,54	.070	
	Electrode	14.71	2,110	.0001	.0001 (5)
	Sleep. x Electrode	0.72	2,110	.488	.450
AMSH	Sleepiness	4.65	1,54	.04	
	Electrode	0.23	1,110	.794	.717
	Sleep. x Electrode	4.80	2,110	.01	.02 *
POST-CNV	Sleepiness	0.01	1,54	.904	
	Electrode	1.77	2,110	.175	.185
	Sleep. x Electrode	0.36	2,110	.700	.636

(1) Recorded maximally at Fz and Cz

(2) Recorded maximally at Cz

(3) Recorded maximally at Fz and Cz

(4) Recorded maximally at Cz and Pz

(5) Recorded maximally at Fz

TABLE VIII

2-Way ANOVAS (Sleepiness Type x Electrode) comparing REM and NREM mean averaged Amplitudes (uV) of different measures in the CNV Paradigm

Component Amplitude	Source of Variance	F Value	df	2-Tailed Probability	Greenhouse Probability
AMFH	Sleepiness Type	3.43	1,54	.069	
	Electrode	14.71	2,110	.0001	.0001 (1)
	Sleep. x Electrode	0.72	2,110	.488	.450
AMSH	Sleepiness Type	4.06	1,54	.04	
	Electrode	0.21	2,110	.809	.729
	Sleep. x Electrode	4.57	2,110	.01	.02 *
Post-CNV	Sleepiness Type	0.01	1,54	.904	
	Electrode	1.77	2,110	.175	.185
	Sleep. x Electrode	0.36	2,110	.700	.636

(1) AMFH amplitude recorded maximally at Fz and Cz

TABLE IX

T Values of REM/NREM Comparisons of Detection Levels and Reaction Times in the CNV Paradigm

	t-Value	df	2-Tailed Probability
Reaction Times	0.58	54	.563
Anticipatory Responses	1.79	54	.090

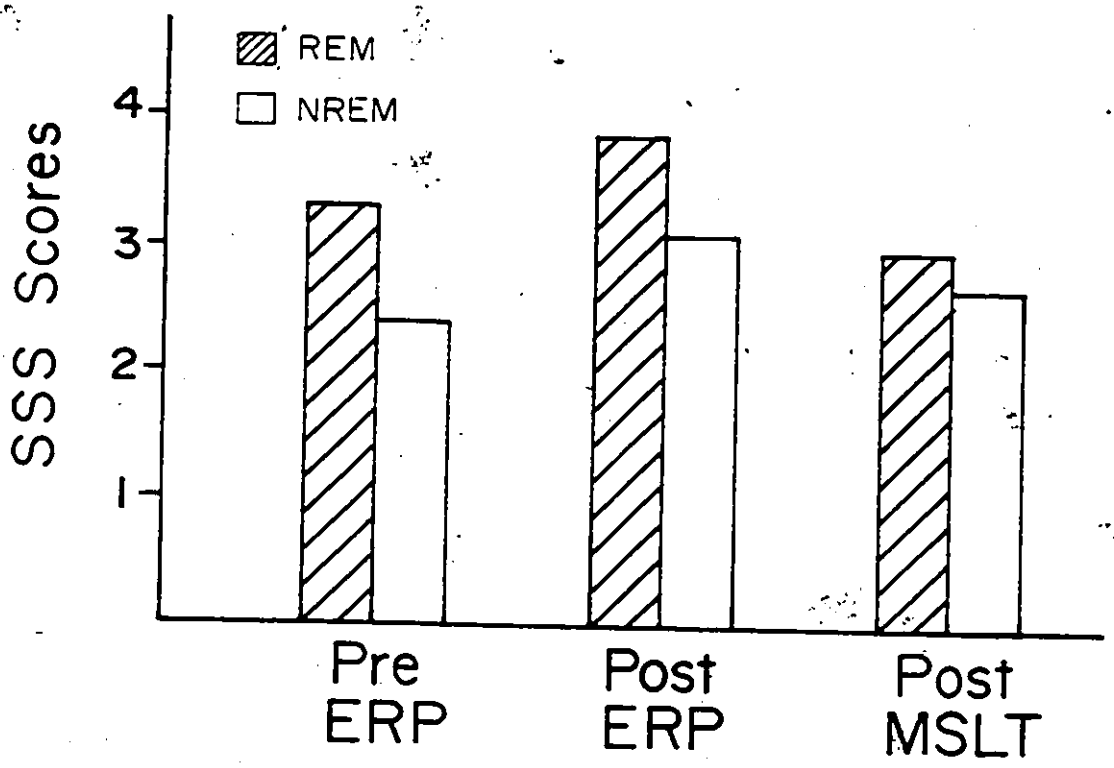
FIGURE LEGENDS

Figure 1. (Upper).- Comparison between absolute SSS scores of narcoleptics falling directly into REM or NREM sleep, before and after ERP (pre-MSLT) sessions and after MSLT naps. Narcoleptics who later fell into REM sleep were significantly sleepier prior to the ERP sessions than those who fell into NREM. (Lower).- Change of alertness (before minus after SSS scores) measured after ERP and MSLT sessions. Negative numbers indicate decrease in alertness, positive numbers indicate an increase. Narcoleptics who later fell into REM sleep were slightly less sleepy after the ERP session than those falling into NREM sleep. Narcoleptics who spent some time in REM sleep were significantly more alert after the naps than those spending time in NREM sleep only.

Figure 2. P3 Paradigm. Grand mean target evoked potentials at the three electrode sites for narcoleptics prior to REM and NREM naps. 36 REM naps and 24 NREM naps were collapsed. A significantly larger P2 was recorded prior to REM naps.

Figure 3. CNV paradigm. Grand mean waveforms at the three electrode sites for narcoleptics prior to REM and NREM naps. A significantly larger negativity was recorded prior to REM than NREM naps over frontal areas.

Figure 1


REM
NREM
SSS Scores
4
3
2
1
Pre ERP
Post ERP
Post MSLT

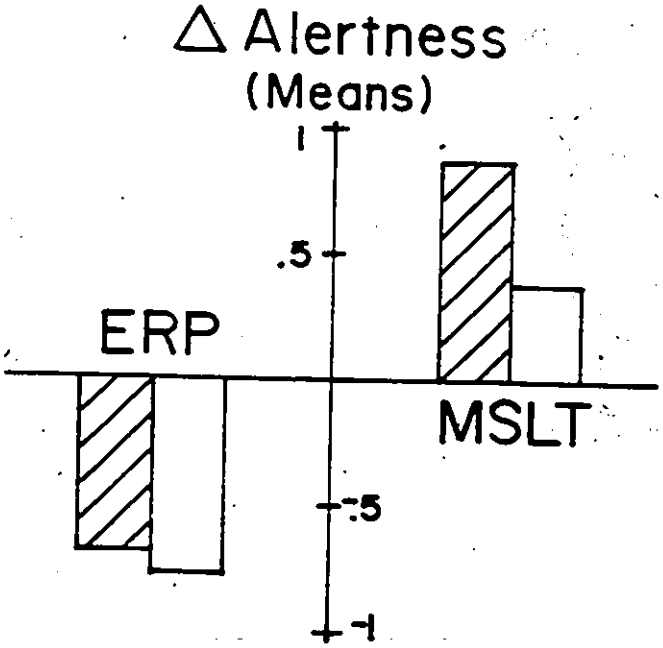

Δ Alertness
(Means)
1
.5
ERP
MSLT
-.5
-1
Pre Minus Post SSS Scores

Figure 2

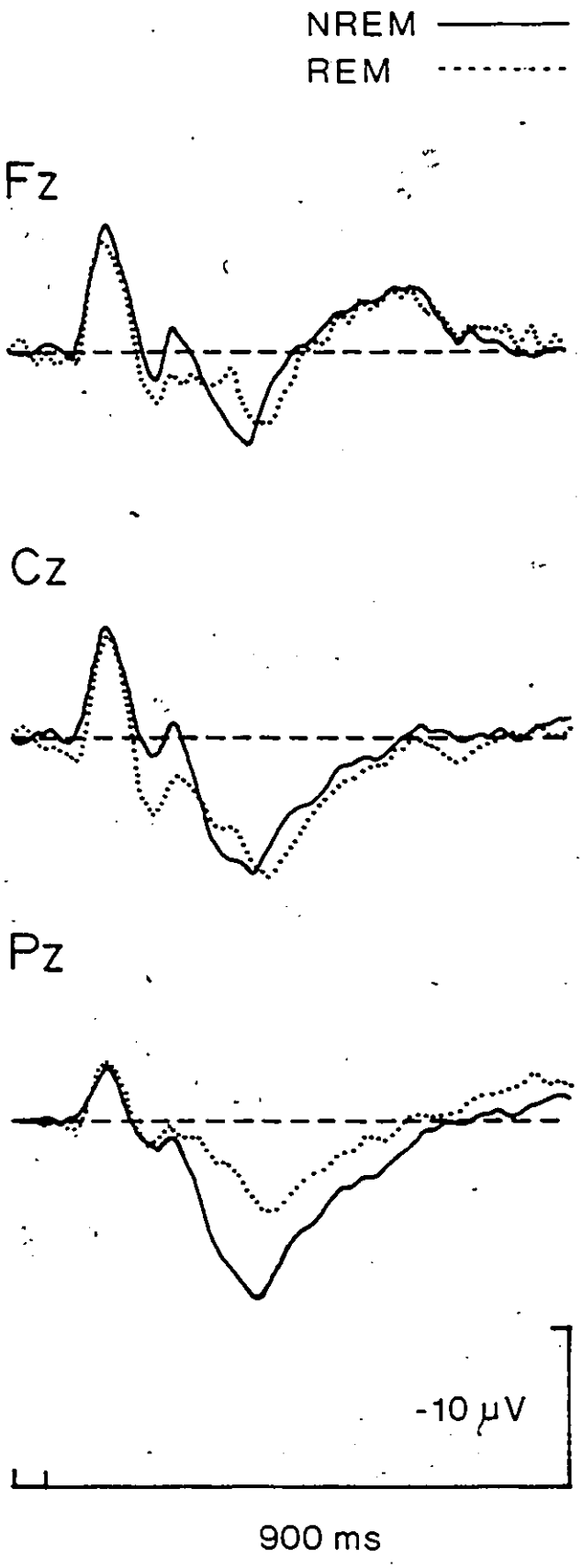
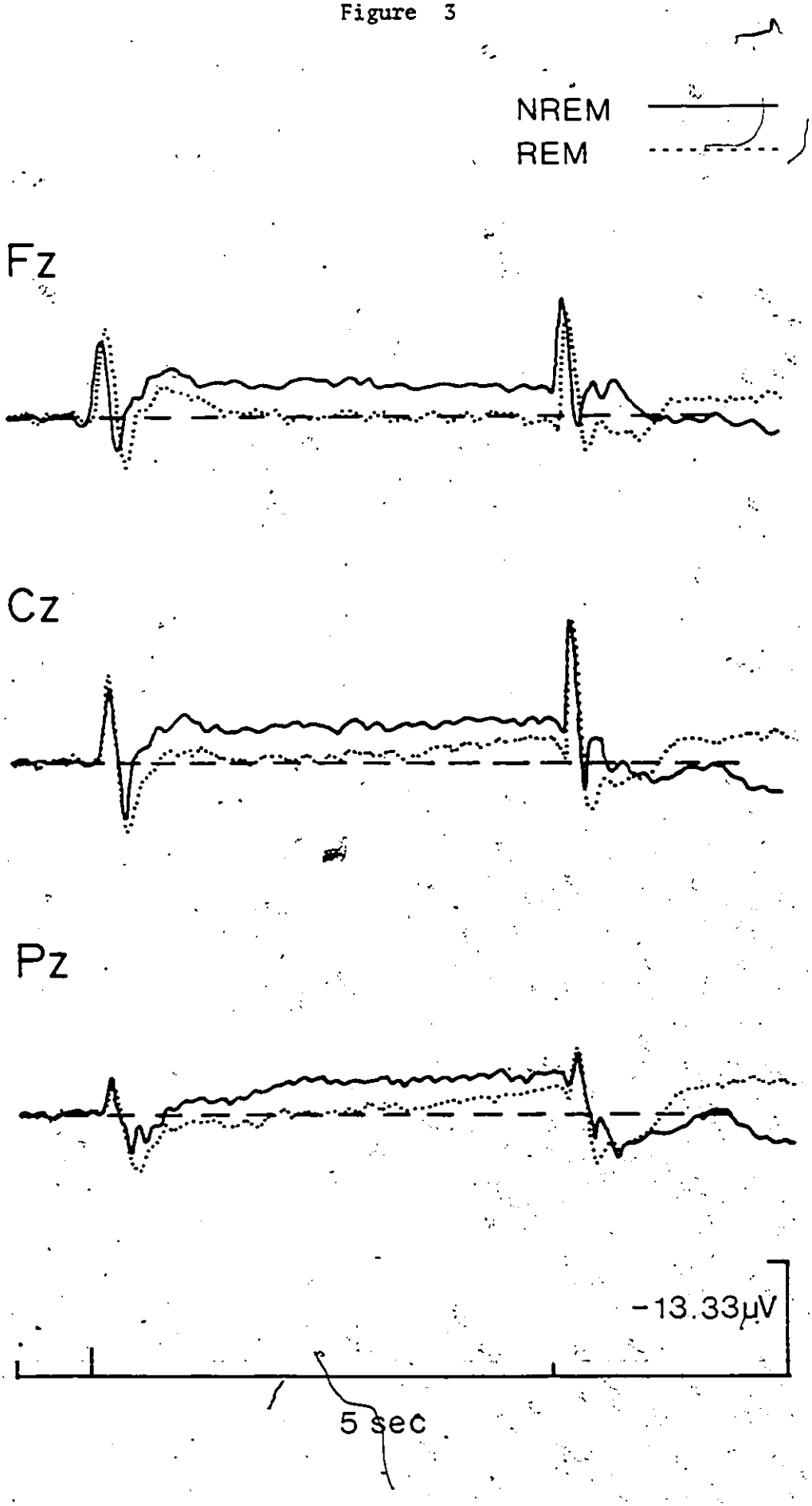


Figure 3



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APPENDICES

Appendix 1

Mean MSLT latencies (min) in narcoleptics comparing day 1 to day 2.
The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	Mean	F Value	P
Stage 1B								
Day 1	2.8	5.6	4.7	3.6	5.4	4.4		
	2.4	5.4	5.7	5.4	5.6	1.2		
							0.10	.757
Day 2	5.0	3.6	5.7	5.1	5.8	5.0		
	7.2	5.6	7.3	7.0	6.2	1.0		
Stage 2								
Day 1	16.0	14.1	8.8	12.0	12.6	12.7		
	5.3	7.3	7.1	8.6	8.2	8.2		
							1.88	.185
Day 2	11.9	8.1	7.5	9.0	13.8	10.0		
	8.6	7.5	8.1	8.4	7.4	2.7		
REM								
Day 1	12.0	13.2	13.5	11.4	14.0	12.9		
	7.4	7.5	8.0	7.7	7.5	1.0		
							.82	.374
Day 2	7.8	10.9	11.0	11.8	12.4	10.8		
	5.8	6.4	7.2	7.6	8.4	1.8		

Appendix 2

Mean MSLT latencies (min) in controls comparing day 1 to day 2.
The second row is the standard deviation.

	Test times (hrs)							
	1000	1200	1400	1600	1800	Mean	F Value	P
Stage 1B								
Day 1	10.4	11.2	7.8	9.8	13.7	10.6		
	6.2	5.8	5.5	6.6	7.1	2.1		
							0.26	.613
Day 2	7.7	8.9	9.5	8.5	14.5	9.7		
	5.8	6.4	6.5	6.6	6.9	2.5		
Stage 2								
Day 1	16.1	14.1	13.8	14.1	18.5	15.3		
	4.7	6.1	6.1	6.1	3.1	2.1		
							0.09	.767
Day 2	14.9	14.2	13.9	13.1	17.7	14.8		
	5.1	5.7	7.4	.1	4.1	1.8		

Appendix 3

Mean total time in stages 1B, 2 and REM sleep (min) during MSLT naps of narcoleptics comparing day 1 to day 2. The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	Mean	F Value	P
Stage 1B								
Day 1	4.8	4.4	4.8	4.3	4.3	4.5		
	2.9	3.4	3.4	3.0	3.7	3.3	3.01	.097
Day 2	2.7	2.1	2.1	2.3	4.6	2.7		
	1.9	1.2	1.6	1.9	3.3	1.1		
Stage 2								
Day 1	2.4	2.6	3.6	2.2	2.3	2.7		
	3.2	3.2	2.7	2.9	3.1	.6	0.80	.381
Day 2	2.5	3.8	4.2	4.3	1.9	3.3		
	3.1	3.7	3.5	3.3	2.3	1.1		
REM								
Day 1	3.3	3.1	2.3	3.1	2.3	2.8		
	3.1	3.8	3.1	3.1	3.1	.5	1.38	.252
Day 2	4.4	4.8	4.6	2.5	3.8	4.0		
	3.6	3.7	3.5	3.3	4.1	1.0		

Appendix 4

Mean total time (min) in stages 1B and 2 in controls comparing day 1 to day 2. No REM sleep was recorded in controls. The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	Mean	F Value	P
Stage 1B								
Day 1	4.4	3.0	4.9	4.2	3.3	4.0		
	2.9	2.6	3.1	3.7	3.7	.8	0.00	.951
Day 2	5.3	4.8	2.8	3.7	3.1	4.0		
	4.0	3.1	2.5	3.0	3.3	1.1		
Stage 2								
Day 1	2.2	3.9	4.0	3.2	1.0	2.9		
	2.0	3.6	3.6	3.2	2.4	1.5	0.07	.796
Day 2	1.6	2.4	3.2	3.9	1.9	2.6		
	3.1	2.7	3.7	3.1	1.6	1.2		

Appendix 5

Mean MSLT latencies (min) in narcoleptics compared to controls.
The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	Mean	F Value	P
Stage 1A								
Narcoleptics	1.3	1.9	2.0	1.5	3.6	2.1		
	.5	1.0	3.2	1.6	4.2	.8		
							0.20	.667
Controls	1.5	1.9	2.6	2.2	4.2	2.6		
	1.2	2.6	2.8	1.0	2.9	1.0		
Stage 1B								
Narcoleptics	4.2	4.6	5.3	4.4	5.6	5.1		
	4.5	3.8	4.3	3.8	6.1	1.0		
							14.86	.001
Controls	9.1	10.1	8.9	9.2	14.2	10.3		
	6.3	6.5	6.5	6.6	7.2	2.3		
Stage 2								
Narcoleptics	14.1	11.2	8.2	10.5	13.2	11.5		
	5.6	5.3	6.3	6.1	5.1	2.6		
							5.26	.032
Controls	15.5	14.2	13.9	13.5	18.6	15.5		
	4.5	5.2	6.3	5.7	3.6	2.2		

Appendix 6

Mean total times (min) in stages 1A, 1B and 2 during MSLT naps in narcoleptics versus controls. The second row is the standard deviation.

	Test time (hrs) 1000	1200	1400	1600	1800	Mean	F value	P
Stage 1A								
Narcoleptics	.6	.5	.5	.4	.8	.5		
	.7	.4	.8	.5	1.4	.2		
							9.50	.005
Controls	4.9	2.7	3.8	2.6	3.6	3.5		
	5.5	3.6	5.2	3.5	3.9	.8		
Stage 1B								
Narcoleptics	3.7	3.4	3.2	3.4	4.6	3.9		
	1.9	2.1	2.2	1.8	3.6	1.1		
							0.34	.563
Controls	4.8	3.9	4.0	4.4	3.2	4.1		
	3.3	2.6	2.3	2.9	2.8	.6		
Stage 2								
Narcoleptics	2.4	3.2	3.9	3.2	2.1	3.0		
	2.7	2.5	2.2	2.2	2.0	.7		
							0.08	.781
Controls	1.9	3.2	3.7	3.4	1.0	2.6		
	2.2	2.8	3.2	3.2	1.6	1.2		

Appendix 7

Mean error levels and reaction times during the different testing sessions of the P3 paradigm in narcoleptics compared to controls. The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	F Value	P
Targets missed - Narc.	4.08	2.92	2.67	6.33	4.92		
	6.92	6.80	5.79	8.69	8.38	2.29	.140
.. .. - Cont.	1.50	2.33	1.58	1.16	0.66		
	4.89	5.47	5.18	4.04	2.02		
False positives - Narc.	1.83	0.42	0.83	1.92	0.67		
	3.97	0.99	2.29	3.50	1.23	3.00	.100
.. .. - Cont.	0.41	0.00	0.08	0.00	0.42		
	1.65	0.00	0.28	0.00	0.90		
Reaction times - Narc.	479.42	481.75	458.75	526.33	563.75		
	182.67	188.43	197.78	240.37	266.47	1.52	.231
.. .. - Cont.	382.58	431.87	382.00	434.25	433.50		
	204.31	272.94	206.43	270.44	270.52		

Appendix 8

Mean latencies (msec) of AEP components in the P300 paradigm prior to MSLT naps in narcoleptics compared to controls. The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	F Value	P
P1 - Narc.	48.8 15.8	37.3 21.2	28.4 31.9	37.3 28.5	42.5 25.5	1.16	.293
P1 - Cont.	49.3 30.8	42.3 23.9	54.7 20.2	32.4 24.7	52.3 22.2		
N1 - Narc.	109.6 16.5	114.4 16.6	104.2 16.3	108.3 11.4	110.3 9.0	0.42	.524
N1 - Cont.	106.8 19.4	108.3 21.7	104.6 25.2	101.4 12.9	111.3 17.8		
P2 - Narc.	185.4 20.7	182.8 23.3	180.1 20.7	186.6 22.7	190.1 29.4	3.80	.064
P2 - Cont.	170.4 22.2	172.3 24.2	177.1 18.0	167.1 13.7	175.3 17.5		
N2 - Narc.	245.1 37.8	242.4 41.8	232.3 36.0	233.2 26.1	230.6 33.6	0.13	.724
N2 - Cont.	231.5 30.5	236.9 31.6	230.1 20.6	228.6 23.2	234.9 31.3		
P3 - Narc.	354.2 56.8	360.9 60.7	360.6 50.9	363.1 44.7	356.5 48.2	0.75	.397
P3 - Cont.	349.4 40.4	344.6 19.2	351.0 28.4	346.8 21.6	344.6 38.3		

Appendix 9

Mean amplitudes (uV) of AEP components in the P300 paradigm prior to MSLT naps in narcoleptics compared to controls. The second row is the standard deviation.

	1000			1200			1400			1600			1800				
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	F Value	P
P1 - Narc.	1.0	2.4	1.6	2.7	2.9	1.7	2.1	2.2	0.9	1.9	2.5	-0.2	1.1	1.9	1.1		
	2.8	1.3	2.1	3.7	2.5	2.3	2.2	2.1	3.0	2.2	2.5	0.6	2.1	1.9	3.0	5.03	.04
P1 - Cont.	1.3	0.9	0.2	1.1	1.2	0.8	-0.5	1.1	0.8	1.4	0.4	-0.2	0.6	1.0	0.9		
	2.5	2.4	2.4	3.1	1.6	1.9	1.7	1.7	2.4	1.5	1.4	3.0	2.2	2.1	2.0		
N1 - Narc.	-5.1	-5.4	-3.6	-7.5	-6.7	-3.3	-8.1	-8.4	-5.6	-8.3	-7.8	-4.8	-8.3	-7.3	-4.3		
	4.2	3.6	2.9	3.6	2.6	1.7	4.9	3.5	2.8	4.9	2.9	3.0	4.8	4.0	2.5	0.17	.683
N1 - Cont.	-8.0	-8.2	-4.6	-8.2	-7.9	-4.5	-6.4	-5.2	-2.7	-6.2	-6.3	-4.1	-7.4	-5.7	-3.7		
	3.2	2.5	2.1	2.8	3.0	2.5	2.9	2.2	2.4	3.3	2.5	2.7	3.0	3.4	2.9		
P2 - Narc.	5.7	5.7	2.8	4.3	5.0	3.2	5.6	4.0	3.0	5.4	6.7	1.9	3.4	5.2	2.6		
	6.6	4.6	7.7	6.7	6.6	3.7	3.8	5.4	4.2	5.9	5.5	5.2	4.9	4.4	3.7	0.77	.391
P2 - Cont.	1.4	2.8	2.4	3.5	3.7	3.1	2.7	5.3	4.0	2.8	3.7	2.8	2.9	3.5	3.5		
	5.9	4.5	3.4	5.1	4.9	3.5	3.4	3.7	3.6	4.4	3.2	2.5	4.3	3.9	2.9		
N2 - Narc.	-1.7	-0.7	-2.1	-1.3	-1.2	1.5	-1.7	-3.2	-0.8	-1.6	-0.9	-1.4	-1.1	-0.9	0.1		
	4.2	4.5	8.7	5.0	4.5	4.7	5.1	2.3	4.7	5.0	5.8	7.2	4.1	4.1	3.4	1.15	.296
N2 - Cont.	-5.6	-6.0	-1.7	-5.1	-6.3	-0.6	-3.1	-2.6	-0.6	-3.8	-5.6	-1.8	-3.8	-4.5	-0.4		
	6.6	7.0	5.8	7.2	6.8	6.6	6.1	6.8	4.0	5.8	5.5	4.6	5.4	5.1	4.4		
P3 - Narc.	6.2	9.4	8.0	6.6	11.0	9.9	6.8	11.9	9.6	6.4	10.4	7.6	7.4	12.1	10.4		
	5.2	5.0	11.2	6.3	5.5	6.9	6.8	5.9	10.5	6.1	9.0	11.4	4.9	6.6	7.3	4.69	.04
P3 - Cont.	10.6	13.9	15.4	11.5	12.5	16.6	10.1	13.0	14.8	11.2	13.5	15.8	9.7	12.7	14.6		
	5.2	6.8	7.6	6.9	8.8	8.8	5.9	6.6	8.3	6.9	5.9	5.5	5.9	6.3	4.2		

Appendix 10

Mean performance measures in the CNV paradigm during the different testing sessions in narcoleptics compared to controls. The second row is the standard deviation.

	Test times						
	1000	1200	1400	1600	1800	F value	P
Reaction times							
Narcoleptics	341.8	298.8	379.4	315.8	322.2		
	179.7	186.9	321.6	202.6	224.1		
						6.68	.02
Controls	176.8	170.3	167.8	166.0	162.5		
	31.1	43.5	37.7	32.0	40.0		
Anticipatory responses							
Narcoleptics	0.8	1.6	1.3	1.7	1.2		
	1.1	1.2	1.0	2.0	1.0		
						6.11	.02
Controls	0.5	0.5	1.0	0.8	0.9		
	0.6	0.6	0.8	0.5	0.9		

Appendix 11

Mean latencies (msec) of evoked potentials in CNV paradigm in narcoleptics compared to controls. The second row is the standard deviation.

	Test times (hrs) 1000	1200	1400	1600	1800	F Value	P
N1 S1 - Narc.	128.2	122.7	131.8	120.9	120.9		
	18.3	14.9	17.2	12.2	16.4		
						18.69	.0003
N1 S1 - Cont.	108.2	110.0	107.3	106.4	108.2		
	11.7	11.0	10.1	8.1	7.5		
P2 S1 - Narc.	219.1	212.7	224.6	220.0	216.4		
	24.7	19.0	21.2	24.5	26.6		
						0.12	.735
P2 S1 - Cont.	250.1	214.6	221.8	209.1	211.8		
	33.2	18.6	29.9	31.7	26.4		
N1 S2 - Narc.	117.3	117.3	119.1	119.1	119.1		
	15.6	14.2	13.0	7.0	12.2		
						8.94	.007
N1 S2 - Cont.	110.9	105.5	107.3	106.4	106.4		
	10.4	8.2	13.5	12.1	9.2		
P2 S2 - Narc.	248.2	233.6	218.2	238.2	219.1		
	60.3	68.0	26.8	56.0	48.1		
						0.01	.915
P2 S2 - Contr.	249.1	227.3	225.5	233.6	231.8		
	51.7	51.2	49.3	56.6	57.1		

Appendix 12

Mean amplitudes (uV) of evoked potentials in the CNV paradigm at the three electrode sites in narcoleptics compared to controls. The second row is the standard deviation.

	1000			1200			1400			1600			1800			F Value	P
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz		
N1 S1 - Narc.	-10.4	-12.4	- 6.5	- 7.2	-10.9	- 4.3	- 8.8	- 9.6	- 3.6	-11.1	-11.5	- 4.1	-10.7	-10.6	- 4.2		
	6.6	6.3	6.8	9.8	6.1	6.4	5.9	5.1	4.6	7.0	6.6	3.7	7.0	6.0	5.1	0.02	.888
N1 S1 - Cont.	- 8.5	-12.1	- 5.6	- 9.5	-11.8	- 6.4	- 8.8	-11.1	- 4.7	- 8.5	-10.5	- 5.3	- 8.7	-12.1	- 5.8		
	5.4	4.7	2.6	4.6	4.4	3.5	5.7	5.2	3.7	5.6	4.1	3.6	5.5	4.5	4.0		
P2 S1 - Narc.	5.8	8.6	5.2	6.4	10.4	6.5	6.5	9.5	6.8	7.6	10.4	8.4	6.7	9.4	7.7		
	6.5	7.8	7.3	7.4	7.2	6.3	5.4	5.7	5.3	5.6	6.3	4.1	5.6	6.8	4.9	0.0	.978
P2 S1 - Cont.	7.9	9.1	9.8	6.7	8.1	6.7	7.5	9.5	8.6	6.5	8.6	7.0	6.3	8.1	6.4		
	5.2	4.5	4.4	5.9	4.5	3.3	7.2	8.5	4.8	5.3	6.8	3.8	5.2	7.2	4.4		
N1 S2 - Narc.	-15.8	-17.1	-11.6	-14.4	-15.7	- 9.2	-14.2	-15.8	- 4.3	-11.7	-13.8	- 7.2	- 8.4	-13.1	- 8.7		
	8.3	8.1	6.3	6.1	9.0	7.1	8.0	6.3	4.8	11.0	11.7	9.4	10.4	10.3	10.2	0.0	.982
N1 S2 - Cont.	- 9.4	-13.8	- 6.5	-12.3	17.7	7.3	11.3	16.3	6.7	10.9	17.4	8.1	12.5	20.9	10.6		
	4.8	11.0	5.0	6.1	6.2	5.4	7.1	6.7	5.3	5.4	4.3	4.9	7.2	7.0	5.3		
P2 S2 - Narc.	2.3	7.0	4.6	1.9	6.5	6.7	3.9	5.1	8.1	5.6	8.7	6.5	6.3	7.4	6.3		
	9.7	9.1	7.6	8.2	8.4	9.3	9.7	8.4	5.4	10.6	10.8	10.2	10.7	9.4	7.7	0.37	.549
P2 S2 - Cont.	4.8	9.5	12.4	5.0	8.7	12.2	3.6	8.6	12.8	2.7	5.1	8.6	1.2	3.2	6.7		
	5.4	6.0	4.7	5.7	6.6	6.0	6.2	6.6	6.7	5.5	4.1	3.6	6.5	5.8	5.4		

Appendix 13

Amplitudes (uV) of average magnitudes over periods of time in the CNV paradigm in narcoleptics compared to controls. The second row is the standard deviation.

	1000			1200			1400			1600			1800			F Value	P
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Pz	Cz	Fz	Cz	Pz		
AMFH - Narc.	-4.1	-4.3	-3.0	-3.8	-3.1	-1.5	-2.4	-1.7	-1.6	- 2.0	-1.6	-0.1	-0.5	-0.2	0.0		
	4.5	4.6	6.4	4.2	4.0	4.7	5.1	5.2	4.2	6.3	6.2	4.8	3.5	3.2	3.5		
AMFH - Cont.	-1.9	-2.4	0.3	-2.6	-2.2	0.2	-2.1	-2.1	0.4	- 2.3	-2.8	-0.2	-3.0	-3.8	-1.4	0.01	.941
	2.5	1.8	0.9	2.0	2.5	1.5	2.2	2.6	1.7	1.7	1.7	2.0	2.5	2.9	2.5		
AMSH - Narc.	-1.7	-3.7	-4.7	-1.4	-2.4	-2.5	-1.6	-3.1	-0.7	- 1.3	-2.7	-2.9	1.2	-1.0	-3.1		
	4.2	4.2	4.6	3.1	3.5	5.2	8.0	5.7	3.2	9.7	6.5	5.3	3.6	3.5	4.7		
AMSH - Cont.	0.6	-1.8	0.0	-1.1	-2.8	-0.4	-1.9	-3.7	-1.3	- 1.6	-4.8	-2.3	-2.6	-6.0	-3.2	0.01	.939
	2.8	2.1	2.4	3.0	3.1	2.8	3.5	3.4	4.0	1.5	1.6	1.4	2.7	3.4	2.9		
POST CNV -Narc.	-5.1	-3.2	-2.5	0.9	1.4	1.4	-4.1	-3.3	0.7	- 2.7	-0.0	2.5	-2.0	-3.1	-2.1		
	9.2	5.4	6.1	9.5	5.4	4.4	8.8	6.8	4.8	11.0	8.0	8.7	8.7	7.9	8.1		
POST-CNV -Cont.	0.9	3.4	5.3	-0.5	2.4	5.2	-1.2	1.3	3.9	0.0	0.8	2.8	-1.3	-0.8	1.8	5.69	.03
	4.1	3.8	3.7	3.6	3.0	3.1	3.4	4.3	4.7	4.2	4.0	4.2	3.2	3.2	4.0		

AMFH Average magnitude first half
AMSH Average magnitude second half

Appendix 14

Mean latencies (msec) of AEP components in the P300 paradigm in REM, NREM. The second row is the standard deviation.

	P1	N1	P2	N2	P3
REM	48.6	110.6	188.2	241.1	365.5
	22.7	13.4	25.6	37.0	55.0
NREM	30.1	107.8	181.8	234.5	350.4
	26.8	16.1	21.2	38.4	50.0

Appendix 15

Mean amplitudes (uV) of AEP components in the P300 paradigm in REM, NREM.
The second row is the standard deviation.

	P1			N1			P2			N2			P3		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
REM	2.0	2.9	1.3	-7.4	-5.9	-4.5	6.1	7.4	3.1	-1.3	-1.3	-1.2	6.2	11.0	8.0
	3.0	2.2	2.7	4.9	3.6	3.0	5.7	4.7	5.9	4.7	5.5	7.1	6.5	6.9	11.0
NREM	1.4	1.6	0.6	-7.9	-7.3	-4.3	2.7	2.3	2.1	-1.3	-2.4	0.7*	7.1	11.6	10.9
	2.1	1.7	1.7	4.0	3.0	2.9	5.2	4.5	3.3	4.5	2.8	3.2	4.8	5.4	6.3

Appendix 16

Mean performance measures and reaction times of P300 Paradigm in REM, NREM. The second row is the standard deviation.

	Targets Detected	Targets Missed	False Positive	Reaction Times
REM	27.0	4.5	1.0	488.1
	1.3	5.7	2.2	58.2
NREM	24.0	3.9	1.2	501.6
	2.3	6.3	1.2	58.8

Appendix 17

Mean latencies of the evoked potentials in the CNV paradigm in REM, NREM. The second row is the standard deviation.

	N1 S1	P2 S1	N1 S2	P2 S2
REM	121.9	223.9	145.3	150.8
	14.1	21.8	170.9	484.8
NREM	129.0	208.5	69.5	240.5
	18.9	21.1	228.6	108.7

Appendix 18

Mean amplitudes (uV) of the evoked potentials in the CNV paradigm in REM, NREM. The second row is the standard deviation.

	N1 S1			P2 S1			N1 S2			P2 S2		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
REM	-11.0	-12.0	-5.4	-7.0	-10.8	-8.2	-12.8	-15.8	-8.0	5.5	8.2	7.9
	5.3	5.0	4.0	6.4	6.0	5.0	8.2	8.1	6.9	3.9	7.9	11.0
NREM	- 9.9	-10.0	-3.4	5.1	7.6	4.8	-13.5	-15.9	-7.4	2.8	4.1	3.5
	7.8	7.1	6.5	5.6	7.1	6.0	10.7	11.0	9.9	9.7	8.5	7.2

Appendix 19

Mean average amplitudes (uV) over time in the CNV Paradigm in REM, NREM. The second row is the standard deviation.

	AMFH			AMSH			POST CNV		
	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
REM	-2.0	-1.5	0.2	- 0.1	-2.2	-2.4	- 2.8	0.6	-0.5
	4.8	4.6	4.0	3.1	3.2	3.0	9.0	18.0	5.5
NREM	-4.9	-3.3	-1.7	- 2.7	-3.3	-3.6	- 3.1	- 0.6	1.2
	5.5	4.8	5.5	7.1	5.4	6.8	10.0	7.5	8.0

AMFH Average Magnitude First Half

AMSH Average Magnitude Second Half

Appendix 20

Performance measures in the CNV paradigm in REM, NREM and controls.

	Anticipatory Responses	Reaction Time
REM	2.17	317.5
	1.50	196.5
NREM	1.66	344.7
	1.32	203.4