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Pupillometric Assessment of Excessive Daytime Sleepiness in Narcolepsy-Cataplexy.

Jan Newman

School of Psychology, University of Ottawa,
Ottawa, Canada.

Running head: Pupillometric Assessment of EDS

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.

Presented in part at the Association of Professional Sleep Societies Annual Meeting, Washington, DC., USA., June, 1989.

ISBN 0-315-68058-X

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

Abstract

Ten untreated patients with narcolepsy - cataplexy and ten age and sex matched normals between the ages of 20 and 71 underwent pupillometric analyses immediately prior to each of five Multiple Sleep Latency Test (MSLT) sessions. Although narcoleptics were sleepier in terms of both their Stanford Sleepiness Scale (SSS) ratings and their latencies to sleep onset, the baseline pupil diameter, pupillary light reflex and pupillary orienting response did not differentiate between groups. Narcoleptics did, however, exhibit a significantly greater frequency of spontaneous oscillations in the dark-adapted state than did controls. These findings indicate that pupillary stability may serve as a supplementary diagnostic tool for narcolepsy-cataplexy. The results are discussed with the view that psychosensory restoration of alertness, among other extraneous variables, must be controlled for when utilizing pupillometric techniques. A review of the literature indicates a variety of methodological and statistical shortcomings that must be amended. Suggestions are made for improving the reliability and validity of the pupillometric approach.

Acknowledgements

I would like to thank the narcoleptic patients who gave of themselves for the benefit of others. Their decision to be withdrawn from medication was indeed a difficult one. For the participants, I have the deepest respect.

I equally extend my thanks to Dr. Roger Broughton for his guidance throughout the years and for instilling in me a desire to continue on in the field of sleep disorders research.

I am grateful to Wayne Dunham for his statistical expertise and for his unique ability to communicate this knowledge.

To my husband John, I thank you for your unending patience and for giving life so much meaning.

Curriculum Studorium

Janice Newman was born on September 10, 1960 in Toronto, Ontario. She received a Bachelor of Arts (honors) degree in Psychology from Brock University, St. Catherines, Ontario in 1983.

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Pupillometric Assessment of Excessive Daytime Sleepiness in Narcolepsy-Cataplexy.

For most of us, the preservation of arousal and the initiation and maintenance of sleep are processes that are regulated with ease. For some however, efforts to ward off sleepiness and to dictate the timing of one's own sleep are beyond voluntary control. Those afflicted with narcolepsy-cataplexy form an exemplary group of the latter.

Narcolepsy-cataplexy is a sleep disorder that is characterized primarily by the symptomatic tetrad of 1) daytime sleep attacks, 2) cataplexy, 3) sleep paralysis, and 4) hypnagogic hallucinations (Gelineau, 1880; Yoss & Daly, 1957; Broughton, 1990).

The most salient of these symptoms are the recurrent, irresistable sleep attacks. Such episodes may consist of Rapid Eye Movement (REM) sleep or of Non-REM (NREM) sleep, and may prove to be life-threatening (Broughton & Ghanem, 1976; Daly & Yoss, 1957; Zarcone, 1973). They are usually only a few minutes in duration and generally occur several times per day (Dement, 1976).

Cataplexy, the most prevalent of the auxilliary symptoms, refers to attacks of partial or complete loss of muscle tone in response to strong emotional

stimuli such as laughter, surprise or anticipation. The patient is fully conscious during these episodes which generally persist for five to thirty seconds and may occur anywhere from a few times per year to one hundred times per day (Guilleminault, 1976; Cohen, 1988).

The third feature of the narcoleptic syndrome is sleep paralysis which refers to a loss of muscle tone with paralysis either while falling asleep or upon awakening (Hishikawa, 1976). Again it is notable that the patient maintains full awareness during these periods which are usually one to two minutes in length and tend to occur two to three times monthly.

The final component of the tetrad is that of hypnagogic hallucinations. These complex visual and auditory experiences, which often have a bizarre, unreal quality capable of inducing fear, occur nightly upon falling asleep and are several minutes in duration (Roth, 1980).

Although this well defined tetrad of symptoms is diagnostic of the narcolepsy-cataplexy syndrome, it is becoming increasingly evident that the narcoleptic's primary complaint is typically one of excessive daytime sleepiness (EDS) (Broughton & Ghanem, 1976; Pressman, Spielman, Pollak, & Weitzman, 1982).

Valley and Broughton (1983) objectively demonstrated the effects of EDS on performance in a

group of narcoleptics who were fully awake only 44% of the time during a long, monotonous task. This chronic level of lowered vigilance is likely the source of memory deterioration, impaired job performance, and increased vehicular accidents common to the narcoleptic population (Aguirre, Broughton, & Stuss, 1985; Broughton & Ghanem, 1976; Broughton, Ghanem, et al., 1981; Rosenthal, Merlotti, Young, Zorick, Wittig, Roehrs & Roth, 1990). Unfortunately, this pressure for sleep is unrelenting and remains relatively refractory to treatment (Guilleminault & Dement, 1974). It is therefore critical that this pervasive and disabling symptom be further investigated.

The Stanford Sleepiness Scale (SSS)

One of the first systematic attempts to quantify sleepiness was through the development of the SSS (Hoddes, Dement, & Zarcone, 1972). This seven point likert scale ranging from 1) "feeling active and vital; alert; wide awake" to 7) "almost in reverie; sleep onset soon; lost struggle to remain awake" uses a subjective rating approach designed to quantify individual perceptions of sleepiness. The SSS is quite widely employed, as it has been shown to be a sensitive measure as well as an accurate predictor of performance deficits after a single night of total

sleep deprivation (Glenville & Broughton, 1979).

However, the validity of the SSS has been questioned due to the fact that behaviorally sleepy individuals often rate themselves as feeling highly alert on the SSS (Dement, 1976). Indeed, it has been demonstrated that the SSS does not correlate with performance under short-term partial sleep deprivation conditions (Herscovitch & Broughton, 1981) or in chronically sleepy narcolepsy-cataplexy patients (Valley & Broughton, 1983). Similarly, recent studies have indicated that the SSS does not correlate with the Multiple Sleep Latency Test (MSLT) (described later) in sleep apneics, in insomniacs or in non-insomniacs (Dement, Carskadon, & Richardson, 1978; Seidel et al., 1984). Such discrepancies between objective and subjective measures of sleepiness lead MacLean and his group to study the structure of the SSS (MacLean, Saskin, Fekken, & Knowles, 1989). Their results indicated that individuals who checked one level of the SSS also endorsed a wide range of items appropriate to various other levels. They concluded that the SSS would benefit from further development.

Less widely applied techniques available for the quantification of subjective sleepiness include mood-adjective check lists (Thayer, 1978) and visual analogue scales (Folstein & Luria, 1973).

The Activation-Deactivation Adjective Check List

One example of a mood-adjective check list is the Activation-Deactivation Check List (AD-ACL). The AD-ACL instructs subjects to indicate the degree to which each adjective on a hypothetical activation continuum describes his or her feelings at any given moment. The subject then chooses from a four point rating scale as follows: 1) definitely feel, 2) feel slightly, 3) cannot decide, and 4) definitely do not feel. Although this checklist was designed to identify a host of feelings ranging from extreme excitement through to overwhelming sleepiness, Clodore and colleagues found no significant relationship between the AD-ACL and the MSLT across the day (Clodore, Foret, & Benoit, 1986). Interestingly, they noted that subjective alertness and tendency to fall asleep were highest at the same time of the day.

The Visual Analogue Scale (VAS)

One form of the Visual Analogue Scale requires the individual to intersect a 10 cm line that is labeled "very sleepy" at one end and "very alert" at the other. The distance between the left end of the line and the point of intersection represents the VAS score. This subjective measure of sleepiness is more

efficient than both the SSS and the mood adjective check list in that it provides an arousal continuum rather than discrete levels of vigilance. It is also much less time consuming to complete. As is the case with the aforementioned measures of EDS, VAS scores also fail to correlate well with objective measures of sleepiness such as the MSLT (Monk, 1987).

In view of the demonstrable disparity between subjective and objective sleepiness, the majority of researchers have chosen to rely heavily upon objectively derived data for the quantification of EDS.

The Multiple Sleep Latency Test (MSLT)

The MSLT is a straight forward, objective measure of daytime sleep tendency (Carskadon & Dement, 1977). As most widely applied, it provides the individual with five 20 minute opportunities for sleep across the course of the day. These napping periods are typically made available at 2 hour intervals beginning at 1000 hrs and terminating at 1800 hrs. As the standard MSLT is administered in a setting intended to promote sleep, it is suggested that the MSLT readily accesses the underlying arousal state. In essence, it is expected that a sleepy individual will fall asleep quite readily when given the opportunity, while an

alert individual will fail to fall asleep or will experience an extended sleep latency. Accordingly, research has shown that latency to sleep decreases following sleep deprivation (Carskadon & Dement, 1977) and increases following sleep extension (Carskadon & Dement, 1979). Such face validity has lent credence to the extensive employment of the MSLT, including its application in the quantification of EDS.

It is essential, however, that the researcher be aware that certain individuals possess a facility for napping while others experience extreme difficulty in doing so, regardless of their level of arousal. In support of this notion, our lab on occasion has recorded short (< 6 min) sleep latencies, said by some to be within the pathological range, in some non-sleepy normals. Similarly, Stepanski and colleagues have observed long sleep latencies in some very sleepy chronic insomniacs and in individuals who have adapted poorly to overnight laboratory recordings (Stepanski, Glinn, Zorick, Lamphere & Roth, 1989). These exceptions to the rule suggest that the MSLT not only measures sleep pressure but also "sleep ability". Some caution must also be exercised when interpreting sleep latencies, as the imposed promotion and prohibition of sleep inherent in the administration of the MSLT may artificially mask and/or alter the true underlying biorhythmic tendencies for sleep. In

addition to these drawbacks, the MSLT is both time consuming and costly.

Maintenance of Wakefulness Tests

Variants on the MSLT, including the Maintenance of Wakefulness Test (MWT) (Mitler, Gujavarty, & Browman, 1982) and the Repeated Test of Sustained Wakefulness (RTSW) (Hartse, Roth, & Zorick, 1982) require that the individual maintain alertness at regular 2 hour intervals. Intuitively, this approach makes sense as the inability to stay awake, versus facility for sleep, is often the symptom in question. Moreover, these tests mimic a real life situation in that EDS patients experience difficulty in maintaining alertness. Results obtained from the application of the MWT are in the expected direction with narcoleptics and sleep apneics exhibiting greater difficulty in sustaining alertness than controls (Browman, Gujavarty, Sampscn, & Mitler, 1983). Unfortunately, widespread usage of the MSLT and the lack of an equivalent pool of normative data for the wake maintenance tests have impeded the careful assessment of these techniques.

Performance Testing

An alternative means frequently used to objectively quantify EDS is that of performance testing. Utilization of this approach is based upon the notion that overwhelming sleepiness will result in a decrement in performance. Although a wide variety of tests has been employed, it is generally agreed that EDS is best detected through the use of long, unstimulating tasks rather than through short, challenging tasks (Aguirre et al., 1985; Godbout & Montplaisir, 1986; Naitoh, 1976; Wilkinson, 1965, 1968).

Indeed, Valley and Broughton (1981) reported that narcoleptics performed poorer than controls on the 1 hour Wilkinson auditory vigilance test and on the 10 minute four-choice reaction time test. The former requires the detection of 40 signal tones imbedded in a series of 1800 non-signal tones, while the latter demands the continuous tracking of four alternating light sources. Both tasks are undeniably monotonous and are designed to exact sustained alertness. Conversely, the narcoleptics performed as well as the controls on the brief, stimulating tests represented by the paced auditory serial addition task and the digit span test (Valley & Broughton, 1981). Apparently, motivation to do well and/or the nature of

the test itself can enable the excessively sleepy individual to marshal his or her reserves, thereby offsetting sleepiness and sleep tendency and permitting normal levels of performance on the insensitive tasks. (Carskadon & Dement, 1987). When keeping these factors in mind, performance measures can prove useful in the quantification of EDS. However, expense and test period duration have lead researchers to explore other avenues.

Auditory Evoked Potentials (AEP's)

Auditory evoked potentials are discrete patterns of cerebral electrical activity elicited by auditory stimuli. The extraction of distinct wave components which correspond to information processing at differing levels of the Central Nervous System (CNS) has been made possible through computer averaging techniques (Picton, Hillyard, Galambos, & Schiff, 1971). One such waveform, commonly referred to as the N1-P2, is a negative-positive complex with peak latencies of approximately 100 and 200 msec, respectively. It is characteristically sensitive to the physical parameters of the stimulus (Callaway, 1973), to the level of attention allocated (Picton & Hillyard, 1974) and to the level of arousal experienced (Williams, Tepas, & Morlock, 1962). If

indeed select components fluctuate with level of alertness, it is logical to assume that AEP's will provide a sensitive means to quantify sleepiness in normal and in patient populations.

Supportive of this view are the findings that normal individuals who are drowsy, near sleep onset or sleep deprived show decreases in amplitude of the N1-P2 components (Hakkinen & Fruhstorfer, 1967; Weitzman & Kreman, 1965; Wilkinson, Edwards, & Haines, 1966; Williams et al., 1962). Broughton and co-workers similarly observed a decrease in the N1-P2 complex in a group of sleepy narcoleptics compared to alert controls (Broughton, Low, Valley, da Costa, & Liddiard 1982). Contrary to these findings, Pressman and colleagues failed to discriminate between narcoleptics and controls solely on the basis of these AEP components (Pressman et al., 1982). Such considerable discrepancies common in the AEP literature are likely the manifestations of methodological disparity, particularly that of variation in stimulus parameters and in component measurement technique (baseline-to-peak vs peak-to-peak). An awareness of these confounds and of the cognitive problems experienced by sleepy persons has prompted researchers to focus on the more robust elements of the AEP, namely event related potentials.

One AEP known to be immune to the physical

characteristics of the stimulus, including intensity and frequency, is the N2-P3 complex. This waveform, consisting of a negativity at approximately 250 msec and a positivity at approximately 300 msec, is easily evoked in either a signal or a non-signal detection paradigm (Hillyard, Hink, Schwent, & Picton, 1973). The N2 component is believed to be highly sensitive to decreases in alertness (Picton, Hillyard, Krausz, & Galambos, 1974), while the P3 component reflects attentional deficits associated with sleepiness (Campbell, Charbonneau, & Beaudoin, 1980). More specifically, studies have shown that the amplitude of the N2 component increases (Campbell et al., 1980; Pressman et al., 1982), while that of the P3 component decreases (Campbell et al., 1980), under sleep deprivation conditions.

Interestingly, these alterations in waveform are not characteristic of pathologically sleepy states. In reference to the narcoleptic population, Broughton and colleagues found a diametrically opposed decrease in N2 amplitude (Broughton, Low, Valley, da Costa, & Liddiard, 1981) with a predicted decrease in P3 amplitude (Aguirre & Broughton, 1984, 1987). Pressman and coworkers (1982) alternately were unable to discriminate between narcoleptics and controls on the basis of N2 amplitude. This paradigm, however, was not designed to elicit a P3 component. Perhaps the degree

to which subjects are required to participate i.e., active signal detection vs passive alertness, affects the N2-P3 complex in, as of yet, unexplained ways.

In addition to the N1-P2 and N2-P3 waveforms, attention has recently been directed toward the use of the Contingent Negative Variation (CNV) as an index of arousal. The CNV consists of a slow negative shift and is elicited when a warning stimulus signals an impending imperative stimulus to which a response is mandatory (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). Although the exact nature of the CNV is not clearly understood, it is generally held that it reflects a state of "preparedness to attend" which in turn may be vulnerable to ongoing fluctuations in level of alertness (Posner, 1978). Progressive reduction in CNV amplitude following sleep deprivation is supportive of this notion (Naitoh, Johnson, & Lubin, 1971). Once again, however, research involving narcoleptics has generated contradictory results. Aguirre and Broughton (1984) found no differences between narcoleptics and controls in terms of CNV amplitude.

When one considers the aforementioned indications and contraindications, it becomes readily apparent that the use of AEP's, other than P3 amplitude, in the quantification of EDS remains somewhat problematical. Nevertheless, continued research into alternate

applications of AEP technology may prove fruitful.

Quantified Electroencephalographic (EEG) Analysis

Due to the advent of high-speed digital computers and the introduction of the Fast Fourier Transform (FFT) algorithm, researchers are now able to analyze the entire spectrum of EEG frequency bands (Dumermuth & Molinari, 1987). This ability to quantify any given arousal state in terms of EEG frequency and amplitude has had much appeal and has often been used in sleep studies (Johnson, Lubin, Naitoh, Nute & Austin, 1969; Dumermuth, Walz, Scollo-Lavizzari, & Kleiner, 1972; Borbely, Baumann, Bradeis, Strauch, & Lehmann, 1980; Armitage, Hoffmann, Moffitt, & Loewy, 1989; Tobler, 1989; Armitage, Roffwarg, Purdy, & Slegel, 1990).

Similarly, quantified EEG analysis has recently been adopted as a means to study sleepiness and performance. Marked increases in delta (1-3 Hz) and theta (4-7 HZ) activity coupled with decreases in beta (14-21 Hz) activity have been shown to occur at times when performance is poor and concurrent vigilance is low (Belyavin & Wright, 1987). Alternately, Winsum and colleagues found that alpha suppression increased with an increase in reaction time, an increase in error rate, and an increase in sleepiness (Winsum, Sargeant,

& Geuze, 1984). The relationship between EEG and alertness has additionally been demonstrated by Torsvall and Akerstedt (1987) who noted increases in alpha and theta power in conjunction with subjective sleepiness and lapses in attention in night-shift train operators. The fact that some researchers have also had success in extracting ultradian rhythms in drowsiness (Manseau & Broughton, 1984) and in distinguishing drowsiness from sleep onset (Matousek & Petersen, 1983) through spectral analysis techniques, clearly suggests that this technique may be of considerable value in EDS research.

Pupillometry

A relatively unexplored means to quantify EDS, and one that is central to this paper, is that of pupillometry. Electronic pupillometry is a precise technique of infared scanning and recording of pupillary diameter at rest or in response to stimuli (Schmidt & Fortin, 1982). Its employment is based upon the observation that a large and stable pupil diameter is associated with alertness, whereas a constricted and unstable pupil is associated with sleepiness (Lowenstein & Loewenfeld, 1958; Pressman et al., 1984). These findings, in addition to the notion that pupillary diameter is largely beyond voluntary

control, have prompted some investigators to adopt pupillary change as an apparently sensitive and reliable index of arousal level. Prior to addressing this topic, a brief introduction to pupillary dynamics is in order.

The pupil of the eye is essentially the aperture of the iris. Its diameter is a function of two sets of muscles namely, the sphincter pupillae and the dilator pupillae.

Pupillary Constriction

The pupillary sphincter, which has remarkable contractile capacity, permits the normal pupil to constrict from approximately 9 mm in darkness to less than 2 mm in bright light, within seconds. This reflex contraction of the pupil involves activation of parasympathetic (cholinergic) preganglionic neurons in the Edinger-Westphal nuclei. These neurons then synapse in the ciliary ganglion which in turn projects to the ciliary muscle and sphincter pupillae (Smith, 1988).

Pupillary Dilation

Unlike the pathway subserving pupillary constriction, that which underlies dilation is

somewhat unclear. It has been suggested that sympathetic fibres projecting from the hypothalamus to the oculomotor nucleus inhibit activation of the Edinger-Westphal nuclei (Lowenstein & Loewenfeld, 1950). Alternately, it has been proferred that pupillary dilation is a function of a three part peripheral sympathetic pathway incorporating the hypothalamus, the ciliospinal centre of Budge, and the superior cervical ganglion (Loewenfeld, 1958). Sympathetic (adrenergic) postganglionic nerves from the latter release noradrenalin, which serves to contract the radial smooth muscle fibres of the dilator pupillae (Smith, 1988). Although both hypotheses seem valid, it is probable that supranuclear inhibition of the sphincter pupillae and sympathetic activation of the dilator pupillae coincide to produce pupillary dilation.

Pupillary Light Reflex (PLR)

When the eye is exposed to a light stimulus, the pupil reflexively constricts and then redilates. In the young alert individual, the pupil undergoes an initial rapid constriction phase followed by a slower rate of contraction. The primary constriction phase is due to parasympathetic activity, while the slower secondary phase is shaped by the increasing influence

of the sympathetic system. The pupil then begins to redilate in a similar fashion. In this case, the rapid primary phase is a function of parasympathetic relaxation while the secondary slower phase is a result of sympathetic excitation (Lowenstein & Loewenfeld, 1951).

Pupillary Mobility

According to Lowenstein and colleagues (1963), the pupil spontaneously exhibits two types of oscillatory movements under conditions intended to promote drowsiness. Slow, extensive waves of constriction and redilation (up to .5mm in 4-40 sec) accompany periods of sleepiness and alertness, respectively. Fast, inextensive changes in diameter (.1 mm-.3 mm in .5-1 sec), sometimes referred to as "hippus", are associated with imperfect fixation due to sleepiness (Lowenstein, Feinberg, & Loewenfeld, 1963). The former are dependent upon the interplay of sympathetic and parasympathetic systems, which in turn are activated by discharges originating from the CNS. The latter are primarily a function of parasympathetic excitation (Lowenstein & Loewenfeld, 1969).

Yoss and colleagues have since arbitrarily subdivided these two types of spontaneous movements into classifications based on amplitude and duration

(Yoss, Moyer & Hollenhorst, 1970). Accordingly, low waves are those less than .5mm in amplitude, medium waves are those between .5mm - 1mm in amplitude and high waves are those greater than 1mm in extent. Waves of short duration are less than 3 seconds in length, waves of medium duration are from 3 to 8 seconds in length, and waves of long duration are greater than 8 seconds in length. In keeping with Lowenstein and Loewenfeld (1969), Yoss and coworkers suggest that spontaneous constrictions and dilations in pupillary diameter are due to parasympathetic stimulation and inhibition, respectively.

As indicated, the basic mechanisms subserving pupillary response have been well documented. This knowledge not only provides the foundation for pupillometry as a valid research technique, it also enables a sound interpretation of deviant pupillary reactivity in terms of autonomic and CNS dysfunction (Lowenstein, 1955). It is thus not surprising that those interested in the objective quantification of EDS readily adopted pupillometry as a viable tool.

As early as 1969, Yoss and his group attempted to assess the severity of sleepiness in 50 narcoleptics through the use of pupillometry (Yoss, Moyer, & Ogle, 1969). Patients were exposed to a series of light flashes and tone bursts, followed by a 2-5 minute

stimulus-free period referred to as the darkness run. The results indicated that narcoleptics had smaller pupils and more frequent spontaneous oscillations relative to controls. Conversely, the PLR was normal. The authors concluded that unelicited changes in pupil diameter indicate the severity of decreased wakefulness. Unfortunately, replication of these results is difficult to accomplish due to the lack of information provided in the article. Details relating to the ages of the subjects and to the physical parameters of both the visual and auditory stimuli were omitted. Moreover, data for 5 of the 40 narcoleptics were merely anecdotally reported with no mention of statistical analyses whatsoever.

On the basis of these findings and on the tenets put forth by Lowenstein and colleagues (1963), Peretz Lavie (1979) adopted the view that pupillary response is a well established indicator of arousal level and further proposed that periodicity in CNS arousal would be reflected in corresponding pupillary rhythmicity. In order to determine recurrent fluctuations in pupil reactivity and in subjective sleepiness across the course of the day, data for eight normal subjects were collected every 15 minutes over a 10 hour period. During test sessions, subjects were merely required to complete the SSS and to fixate on a point for 1-2 minutes. Three, 15 W stroboscopic light flashes, 100

msec in duration, were then presented every 8-20 seconds. Dependent measures included SSS scores, pupillary diameter (mean diameter for 500 msec preceding the light stimuli), pupillary movement (absolute range of movement for each of eight 500 msec segments following the light stimuli as well as average range of movement for all 24 segments) and the PLR (mean extent of constriction across the three light reflex responses).

Contrary to expectations, ultradian rhythmicity in pupil diameter and in the PLR was not extracted through time series analyses. Moreover, there was no clear phase relationship between SSS scores and pupillary measures. Of specific interest was the presence of a 75-125 minute rhythm in pupil movement, a period of close approximation to that of Kleitman's Basic Rest-Activity Cycle (BRAC) (Kleitman, 1961). It was this similarity that led Lavie to conclude that periodicity in pupil motility reflects underlying rhythms in CNS arousal level. It is expected that such rhythmicity in spontaneous oscillations would be more robust in pathologically sleepy individuals. This premise remains unsubstantiated.

In 1982, Schmidt revived the use of pupillometry in the quantification of EDS and in the discrimination of pathological sleepy states. His subject pool consisted of 12 narcoleptics (43 $\pm$ 14 yrs), 13

idiopathic hypersomniacs (37 ± 13 yrs) and 6 patients with disorders of excessive somnolence (DOES) associated with sleep related myoclonus (SRM) (47 ± 6.7 yrs). All participants underwent 10 minutes of dark adaptation and a series of light stimuli (0.1 sec; 15 ft candles; 4.0 log neutral-density filter) immediately prior to the administration of a four-nap MSLT. Dark-adapted pupillary diameter, number of spontaneous oscillations greater than or equal to .2mm and extent of contraction to light were measured.

In concurrence with the work of Yoss and colleagues (1969), Schmidt (1982) observed that narcoleptics display a smaller resting pupil diameter but do so only prior to nap one. At this time, the latency to sleep onset is low and subsequent sleep efficiency is high. In opposition to Yoss and co-workers (1969) and to his own predictions, Schmidt found that narcoleptics produced fewer spontaneous oscillations prior to nap one and a reduced extent of contraction to light in general. Interestingly, the latter two response patterns are the inverse of those reported in sleepy normals and in tired insomniacs (Lowenstein & Loewenfeld, 1951; Schmidt & Fortin, 1982). Schmidt deemed these results as paradoxical, and suggested that the narcoleptic is excessively sleepy at the cortical level as evidenced by the instability of the pupil (incidently not seen in this

study) and is subcortically alert as indicated by the diminished response to light stimuli.

These conclusions must be interpreted with great caution for a host of reasons. Firstly, Schmidt's conclusions do not accurately reflect the observed results, despite his attempts to devise a theory to fit the data. Secondly, all results pertain to test sessions preceding naps one and three only. It is conceivable that the inclusion of data obtained from tests two and four could further support or completely negate the other findings. Moreover, it is likely that by collapsing data across all four test sessions one would obtain entirely different results. Thirdly, all conclusions are based on observed differences between narcoleptics and hypersomniacs. A control group consisting of normal sleepers was not employed. Finally, the details of statistical analysis including approach, significance levels, and summary tables were not reported, thus strictly limiting efforts to interpret and replicate this study.

During the same year, Kollarits and her team attempted to distinguish narcoleptics from controls through the use of pupillometry (Kollarits, Lechman, Kollarits, & Gillin, 1982). Seven narcoleptics and 14 age-matched controls were required to sit in the dark for 20 minutes while pupil measures were taken. Pupil area following the extinction of light, maximum

dark-adapted pupil area, latency to spontaneous miosis to the degree of 4mm2, and latency to minimum pupil area served as dependent variables.

In contrast to previous findings, this group found no quantitative pupillographic differences between narcoleptics and controls. They suggest that other researchers have observed group differences in pupil diameter due to the use of cohorts as control subjects. As these participants have a vested interest in the project, they naturally sustain alertness during the testing procedure. In short, pupillometry could not distinguish narcoleptics from bored or sleepy controls. Although this conclusion may be valid, it should be noted that testing was conducted between 0800 hrs and 0900 hrs only. Perhaps group differences would be detected at other times of the day.

In 1984, Pressman and colleagues addressed this issue by studying EDS across the course of the day in narcoleptics and controls. Pupil diameter was sampled every 2 seconds for a 150 second period every 30 minutes for 6.5 to 8 hrs. The SSS was completed immediately before and after each pupillometric session. Mean pupil diameter, pupil activity (between session diameter change) and SSS scores were analyzed.

Although visual inspection of the data suggested a 90 minute rhythm in pupil activity for two of the

narcoleptics, insufficient sampling prevented the statistical analysis of periodicity for any of the dependent variables. However, when the data were collapsed across sessions narcoleptics were found to exhibit a smaller mean pupil diameter overall, yet could not be distinguished from controls on the basis of pupil activity or SSS scores. Unfortunately this study employed only 3 subjects per group, thus reducing the generalizability of the results.

An increase in subject pool was subsequently reported by Pressman and his group who outlined the effects of naloxone on pupillary diameter and on the PLR in 10 narcoleptics and in 8 controls (Pressman, Di Phillipo, Forst-Paulus, & Fry, 1986). Of particular relevance to this review are the results pertaining to the baseline condition. Narcoleptics displayed a significantly smaller pupil diameter (5.58 ± 1.40 vs 6.57 ± 0.62 mm; $p<.05$) (note that the degree of group overlap prevents the unequivocal discrimination of those suffering from EDS), higher SSS scores, and greater VAS scores but did not differ from the norm in terms of their response to light.

The latter null result for pupillary responsiveness to light was corroborated by a recent study by Hertz and co-workers, who employed the PLR as well as several other variables to objectively assess sleepiness in sleep deprived individuals (Hertz,

Spielman, Hakerman & Pressman, 1988). Although pupil variability, defined as the standard deviation of pupil diameter over 1200 points, was greater for the sleepy group (sd = .30 vs sd = .21; $p<.05$), baseline diameter, extent of constriction and rate of constriction did not successfully distinguish sleepy from alert states.

Despite this failure to differentiate between groups on the basis of PLR findings, Pressman continued to espouse the value of the light response as a measure of arousal (Pressman & Fry, 1989). He suggested that the obtained negative correlations between the MSLT and constriction velocity and between SSS scores and redilation velocity support the use of PLR measures in the study of EDS. However, recent work by Fredrickson and colleagues does not confirm this view (Fredrickson, Kaplan, Renaux, Lin, Richardson, & Harris, 1990). Although the latter found a decrease in redilation velocity with increasing sleepiness in nine sleep apnea patients as measured by the MSLT, this trend did not reach statistical significance. Moreover, there was no indication that contraction velocity increases with greater sleepiness. Although these null results cast doubt on the use of PLR measures in the detection of sleepiness, it should be noted that this study failed to incorporate a control group. In short, the usefulness of this variable has

yet to be determined.

Indeed, the utility of the pupillometric approach as it is currently applied, remains questionable. As indicated above, baseline diameter, pupillary stability, and pupillary response to light do not appear to systematically vary with changes in arousal. Inadequacies in research design and in statistical applications are likely accountable to a certain degree and must be amended.

The main objective of this study is to execute a sound experimental protocol and thereby clarify the efficacy or lack of efficacy of pupillometric measures in the detection and study of EDS. Secondary to this aim is the qualitative differentiation of subtypes of sleepiness or de-arousal through pupillometric techniques. According to Broughton, there are at least two different forms of EDS which are manifested as pressure for REM and NREM sleep (Broughton, 1982). Support for this hypothesis has been found in the AEP literature wherein auditory evoked potentials have been noted to undergo different modifications in pre-REM and pre-NREM states (Aguirre & Broughton, 1984; Pressman et al., 1982). It is possible that pupillometry may serve as a means to assess these qualitatively different types of sleepiness. The evaluation of the pupillary orienting response as an alternate index of arousal will also be evaluated.

Before outlining the basic predictions to be substantiated, a brief introduction to the OR literature is also requisite.

The Orienting Response (OR)

The OR is an investigatory or "What is it ?" reflex which increases the sensitivity of the mechanisms essential for the transmission and perception of current and future information (Pavlov, 1927; Siddle & Spinks, 1979). It may be elicited by stimulus change or novel information and is diminished or habituated upon repeated presentation of the initial eliciting factor (Sokolov, 1963).

Although it is agreed that the OR is characterized by various autonomic responses including increased pupil dilation (Sokolov, 1963), the specific processes that are reflected in pupillary change remain in question.

For Ohman (1979), the OR represents a "call" for processing in a central limited-capacity channel. According to this model, there are two features of stimulus input that are recognized by the pre-attentive mechanisms and lead to a call for this type of information processing. The first criterion is a mismatch between the stimulus and the contents of the short-term memory store. When this is the case, a

search through the long-term memory store for matching elements is initiated. The second criterion is a match between the stimulus and the memory representation that is contextually primed as significant. This condition allows the stimulus to be admitted to the central channel for further processing. If there is a match and the representation is not significant, further processing of the input is blocked, the OR does not ensue and the stimulus is not attended to. In short, OR evocation is linked with a call for central processing rather than with processing itself.

Conversely, Kahneman (1973) proposed that the OR reflects a transient effort to process and analyze the eliciting stimulus. If the stimulus is deteced as novel or significant, the organism's allocation policy will alter such that the stimulus may be more intensely processed.

Pribram and McGuinness (1975) equated the OR with the arousal system of involuntary attention. According to this view, the OR not only reflects the registration of the stimulus in awareness, its magnitude represents the degree to which the item has undergone consolidation in the CNS.

Regardless of the particular theory adopted, it is generally held that the OR is part of an activational mechanism and is a relatively uncontaminated index of arousal level (Sokolov, 1963;

Thompson, Berry, Rinaldi, & Berger, 1979; Spinks & Siddle, 1983). If this is indeed the case, the pupillary OR should serve to discriminate sleepy from alert individuals and possibly REM from NREM sleepiness.

Hypotheses

The following predictions are based on our current knowledge of the mechanisms of pupillary response and on the fact that under conditions of fatigue, sympathetic influence deteriorates prior to parasympathetic influence (Lowenstein & Loewenfeld, 1951).

A sleepy narcoleptic relative to an alert control will be characterized by:

1) a smaller baseline pupil diameter (Lowenstein et al., 1963; Yoss et al., 1969; Schmidt, 1982; Pressman et al., 1984; Pressman et al., 1986).

2) a greater frequency of spontaneous oscillations (Lowenstein & Loewenfeld, 1951, 1952; Lowenstein et al., 1963; Yoss et al., 1969; Hertz et al., 1988; Lin, McLaren, Harris, Holubar, Richardson, Erie & Fredrickson, 1990).
3) a PLR with:
   a) a shorter latency to constriction (Lowenstein & Lowenfeld, 1951).
   b) a greater extent of constriction (Lowenstein & Loewenfeld, 1952; Schmidt, 1982).
   c) a faster rate of constriction/constriction velocity (Lowenstein & Loewenfeld, 1952; Pressman & Fry, 1989).
   d) a smaller redilated diameter (Lowenstein & Loewenfeld, 1951; Lowenstein et al., 1963).
   e) a slower rate of redilation/redilation velocity (Pressman & Fry, 1989; Fredrickson et al., 1990).
4) a smaller pupillary OR (Lowenstein & Loewenfeld, 1969).

As REM sleepiness has been shown to be a more intense type of sleepiness than NREM sleepiness (Broughton & Aguirre, 1987), it will therefore be reflected in pupillary changes similar to those just stated.

Method

Subjects

Six male and 4 female patients diagnosed as having had narcolepsy-cataplexy for at least 5 years (ASDC criteria) (Roffwarg, 1979) and 10 age and sex matched non-napping individuals with normal nocturnal sleep duration (6.5-8.0 hrs of sleep/night) were studied. Narcoleptic patients ranged in age from 21-70 years ($\underline{M}$ = 48.60 $\pm$ 13.57) while controls ranged in age from 20-71 years ($\underline{M}$ = 49.00 $\pm$ 13.80). A screening polysomnogram (PSG), when possible, was used to exclude from the study subjects who had 1) a sleep apnea index exceeding five per hour or 2) more than 25% of their nocturnal sleep period characterized by periodic movements in sleep (PMS). All subjects were further assessed for suitability through the use of sleep histories, personal sleep logs, and audiometric testing (Amplivox Audiometer Model 2). In narcoleptics, tricyclics were withdrawn for a 3 week period preceding the study while CNS stimulants (methylphenidate - no subjects were receiving amphetamines) were withdrawn for 1 week. Although patient referrals to the sleep clinic are large in number, most of the narcoleptics are working and are

hesitant to be withdrawn from medication. As a result, it took 2 years to solicit 10 patients willing to participate. A more detailed description of the patient population can be found in Appendix A (see Appendix A). Control subjects were remunerated for their participation. The protocol was accepted by the local human experimental procedures committee and consent forms were signed.

Apparatus

The pupillometer is an instrument designed to record and transmit changes in pupil diameter. The polymetric pupillometer (Model V-1165-1R) used in this study consisted of a metal frame to which a chin rest, an RCA video camera, and a Bausch and Lomb infared light apparatus were mounted. Monocular video signals from the system were monitored on a television screen and charted on a 10-channel Grass Model 6 EEG machine. The hard copy records were then manually scored with reference to calibration signals. The system had a sensitivity of 0.1 mm for pupillary diameter.

Light stimuli were administered to both eyes through a multiple stimulus display box manufactured by the Lafayette Instrument Company. The magnitude of the stimulus and the area of illumination varied as a function of the desired response.

Auditory stimuli were delivered to both ears through headphones. Once initiated, a 90 db tone characterized by a 50 msec rise-time persisted for a 2 second period. The positioning of a toggle switch determined the frequency of the tone to be administered (1000 or 2000 Hz).

On day one, 24-hour ambulatory monitoring of sleep-wake variables was accomplished through the use of a four-channel Medilog recorder (Oxford Medical Systems). Standard polysomnographic variables, which were monitored continuously during the following 10 hour test day, were recorded on the EEG machine described previously, along with pupillometric measures and synch pulse during the test sessions.

Procedure

Day 1: Ambulatory Monitoring of Prior Sleep

At 0800 hrs, subjects reported to the lab for audiometric testing and electrode application. Electroencephalographic (EEG), electro-oculographic (EOG) and electromyographic (EMG) data were obtained from scalp (C3-A2), outer canthi, and submental sites using the portable Medilog unit. Participants wore the recording device for a 24-hour period beginning at 0830 hrs. This permitted documentation of prior sleep

which may have influenced subsequent pupillometric measures. During this time, they were to adhere closely to their daily routines and to complete the SSS (Hoddes et al., 1972) every 30 mins during wakefulness.

Day 2: Pupillometry and MSLT Testing

Upon returning to the lab at approximately 0830 hrs, the Medilog system was removed and electrodes for the MSLT were applied. These included C3-A2, C4-A1, O2-A1, right and left EOG, and submental EMG. Subjects were then briefed on the protocol and familiarized with the equipment. Pupillary and polygraphic calibrations were made.

The MSLT was administered at 1000, 1200, 1400, 1600 and 1800 hrs. Each scheduled nap was terminated following either 20 minutes of wakefulness or 10 minutes of sleep (with sleep onset defined as two consecutive 40 sec epochs of stage 1 or REM). Sleep stage criteria were those of Rechtschaffen and Kales (Rechtschaffen and Kales, 1968).

Just prior to each MSLT, the accompanying 18 minute protocol was followed.

The subject was fitted with welding glasses for a 7 minute dark-adaptation period. Not only did this approach serve to increase pupil diameter to

accepted dark-adapted levels (Birren, Casperson & Botwinick, 1950), it also permitted subjects to move freely about the laboratory and to thereby maintain alertness. The individual was then instructed to sit in a darkened room at the pupillometer with his/her chin on the chin-rest and to fixate on a dimly illuminated (.02 lux) square display (1.2 x 1.2 cm) approximately 80 cm anterior to the subject at eye level. This target restricted movement of the eyes away from the camera and permitted relatively artifact-free recording of the dark-adapted pupil for a 1 minute period.

Immediately thereafter, 11 tone bursts at 10-30 second intervals were presented. The frequency of the tones alternated between 1000 Hz and 2000 Hz across pre-nap periods. Half of the subjects heard 1000 Hz tones prior to their first, third, and fifth naps and 2000 Hz tones prior to their second and fourth naps. The remaining subjects heard the inverse pattern beginning with the 2000 Hz series. To dishabituate within each session, the 11th tone of each series differed from the first 10 presentations. More specifically, the 10th tone of each 1000 Hz series was followed by a 2000 Hz tone and the 10th tone of each 2000 Hz series was followed by a 1000 Hz tone.

Subsequent to the final auditory stimulus subjects were given a 1 minute break, during which

fixation was still required but no stimuli were presented. An additional 1 minute period of spontaneous pupillary fluctuations was then recorded.

During the final phase of the test session, the PLR was elicited through the administration of ten 0.1 second low intensity (30 lux) light flashes (3.6 x 4.9 cm display) at 10-20 second intervals.

Half of the participants received the auditory stimuli first while the other half received the visual sequence first. All stimuli were presented manually to prevent the coincidence of stimuli and artifacts. If at any time lid closure occurred, the subject was verbally alerted through the use of an intercom system. Stimulus presentation resumed upon pupil restabilization to baseline diameter. (The use of an eyelid crutch was found to be both awkward and disruptive). The SSS was completed every 30 minutes as well as promptly following each MSLT session.

Pupillary Variables

1) Dark-Adapted Pupil Diameter: The mean pupil diameter derived from 30 samples taken from the first recorded minute of each test session (mm) (Plouffe & Stelmack, 1979).

2) Latency to Maximum Constriction: The latency from stimulus onset to the point of minumum pupil diameter (sec) (Plouffe & Stelmack, 1979).
3) Extent of Constriction: The difference between pupil diameter at the onset of the stimulus and that at the point of maximum constriction (mm) (Plouffe & Stelmack, 1979).
4) Rate of Constriction: The ratio of extent of constriction to the latency to maximum constriction (mm/sec) (Plouffe & Stelmack, 1979).
5) Constriction Velocity: The slope of the primary constriction phase (Pressman & Fry, 1989).
6) Maximum Redilated Diameter: The largest pupil diameter achieved during the 10 second period following stimulus offset (mm) (Plouffe & Stelmack, 1979).
7) Rate of Redilation: The ratio of pupil diameter to the latency to maximum redilation (taken at 1mm intervals and then averaged) (mm/sec) (Plouffe & Stelmack, 1979).
8) Redilation Velocity: The slope of the secondary redilation phase (Pressman & Fry, 1989).

9) Pupillary OR: The difference between pre-stimulus pupil diameter (mean of five samples taken at 1 second intervals immediately preceding the tone) and pupil diameter achieved following the stimulus (mean of three samples taken from the 1 second period following the tone) (mm) (Stelmack & Siddle, 1982).
10) Spontaneous Oscillations: Total number of pupillary fluctuations greater than or equal to .2mm (Schmidt, 1982).

Pictoral descriptions of the PLR measures are given in Figures 1 and 2 (see Figures 1 and 2).

Data Analysis

Subjective sleepiness measures for narcoleptics and controls were analyzed across test sessions, as well as immediately preceding versus promptly following each MSLT session using a 2 x 2 x 5 related samples analysis of rank means (Meddis, 1982). Comparisons of SSS scores every half hour across days 1 and 2 for both groups were made using a 2 x 2 x 21 related samples analysis of rank means (Meddis, 1982). Post hoc simple effects were extracted using a modified nonparametric Tukey Honestly Significant Difference (HSD) statistic suggested by Marascuilo and

Figure 1. PLR to .01 sec light stimulus. a) latency to maximum constriction; b) extent of constriction; c) rate of constriction; d) maximum redilated diameter; e) rate of redilation. [Adapted from Plouffe and Stelmack, 1979. See text for explanation of variables].

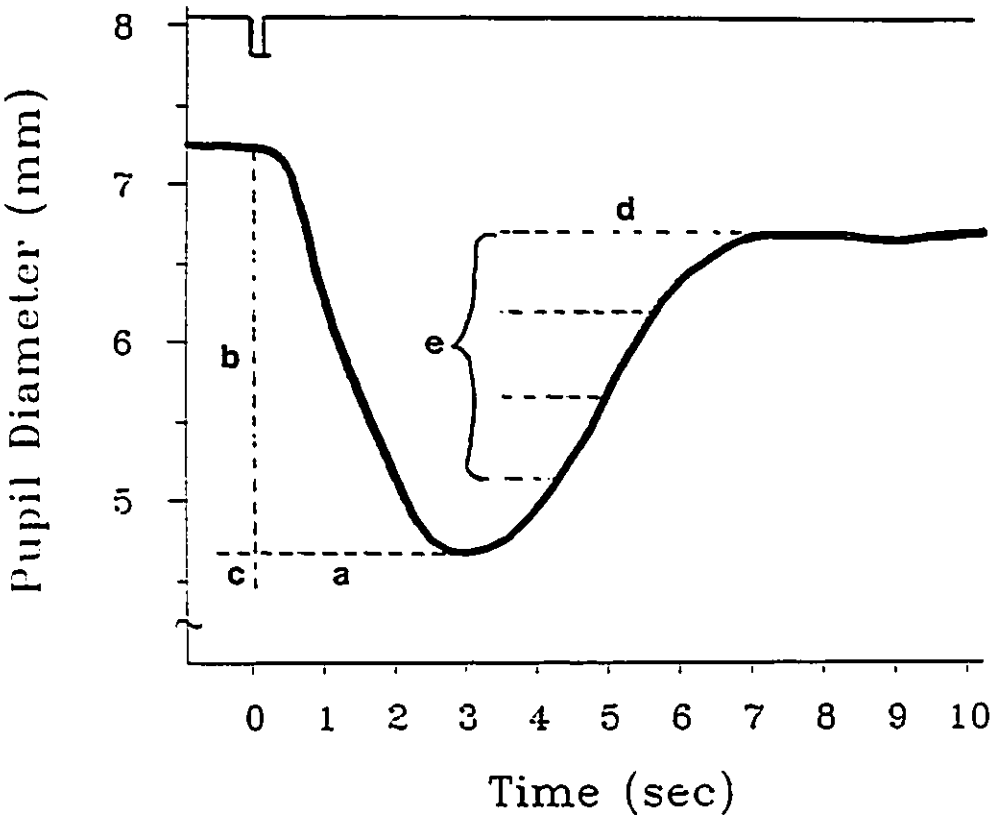
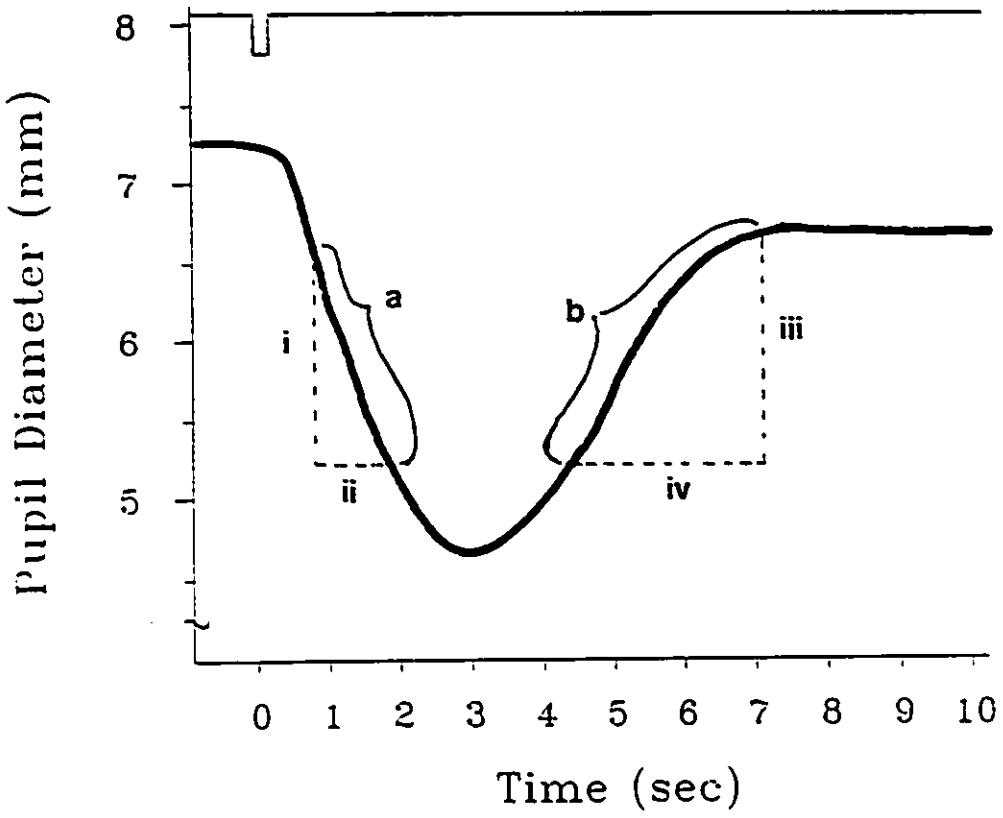

Pupil Diameter (mm)
8
7
6
5
b
c
a
d
e
0
1
2
3
4
5
6
7
8
9
10
Time (sec)

Figure 2. PLR to .01 sec light stimulus.
a) constriction velocity = i/ii;
b) redilation velocity = iii/iv.
[Adapted from Pressman and Fry, 1989].


Pupil Diameter (mm)
8
7
6
5
i
ii
a
b
iii
iv
0
1
2
3
4
5
6
7
8
9
10
Time (sec)

McSweeney (1977).

MSLT variables, including the latencies to stages 1, 2, 3, 4 and REM were analyzed between groups and across sessions with 2 x 5 analyses of variance (ANOVA).

All statistical comparisons of pupillary variables were made between groups across the five test sessions and for each individual stimulus where applicable. Intergroup variations in dark-adapted pupil diameter and in the frequency of spontaneous oscillations were investigated using a 2 x 5 ANOVA and a 2 x 5 related samples analysis of rank means (Meddis, 1982), respectively.

The majority of PLR indices including latency to maximum constriction, extent of constriction, rate of constriction, maximum redilated diameter and rate of redilation were compared using 2 x 5 x 10 ANOVA's. Constriction velocity and redilation velocity following the first stimuli only were analysed between groups and across test sessions using 2 x 5 ANOVA's. Due to the additional test stimulus presented in the auditory series, the pupillary orienting responses were tested using 2 x 5 x 11 ANOVA's. Significant stimulus effects were further scrutinized using the Newman-Keuls test (Kirk, 1982).

Prior sleep effects (total nocturnal sleep time recorded via 24-hr ambulant monitoring) were removed

from the pupillary data by repeated measures analyses of covariance (ANCOVA) (Kirk, 1982). Significance achieved in ANOVA and ANCOVA interactions was determined using the conservative Geisser-Greenhouse (GG) approach (Kirk, 1982).

Within group latency to sleep onset and spontaneous oscillation data were collapsed across sessions and correlated using the Pearson Product-Moment Correlation (Glass & Stanley, 1982). These data were then correlated with pre-nap SSS scores using the Spearman Rank Correlation (Hays, 1981). These analyses were done in order to discern the relationships between observed pupillary changes and established measures of objective and subjective measures of sleepiness.

All pupillary variables were further analyzed as a function of pre-REM and pre-NREM sleepy state using Student t-tests for dependent samples (Kirk, 1982). The data were extracted from the pupillometry sessions which immediately preceded 14 REM naps and 14 NREM naps (matched for time of day within the narcoleptic group only).

Results

SSS Findings

When SSS scores for both groups were analyzed across days one and two at 30 minute intervals, the data indicated that narcoleptics felt subjectively sleepier ($\underline{M}$ = 2.95) than controls ($\underline{M}$ = 1.74) overall, $\underline{H}(1) = 106.32$, $p < .001$ (see Figure 3 and Table 1). In addition to this main group effect, day main effects (ambulatory day versus testing day) and time of day main effects (based on 21 time points corresponding to 0830 through 1830 hrs) were also extracted. More specifically, narcoleptics and controls rated themselves as feeling sleepier on day one ($\underline{M}$ = 2.71) than on day two ($\underline{M}$ = 1.97), $\underline{H}(1) = 29.50$, $p < .001$ (see Figure 4 and Table 2). No doubt this was due to the unstructured nature of the time spent at home which provided greater opportunities for periods of drowsiness. Both groups also displayed pronounced sleepiness at particular times of the day, $\underline{H}(20) = 35.15$, $p < .02$. SSS scores reported at 1000 hrs, from 1300-1400 hrs, from 1500-1600 hrs, and at 1800 were significantly greater than those reported for the other 13 time points sampled (see Figure 5 and Table 3). These peaks in sleepiness naturally reflect

Figure 3. SSS ratings for narcoleptics and controls recorded at 30 minute intervals. Data are collapsed across days 1 and 2.

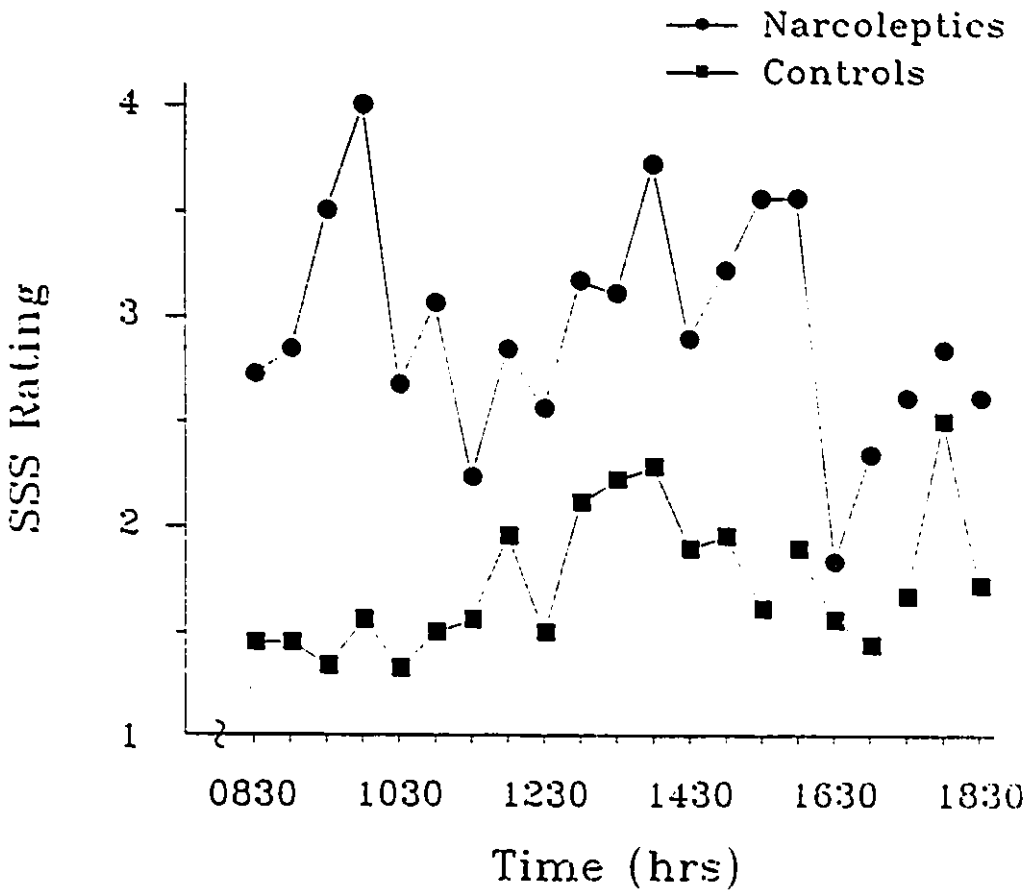

Narcoleptics
Controls
SSS Rating
4
3
2
1
0830
1030
1230
1430
1630
1830
Time (hrs)

Table 1

SSS Ratings : Main Group Effect and Group x Time Interaction

Group Means and Standard Errors

Time (hrs)	Narcoleptics	Controls
0830	2.72 ± .34	1.45 ± .22
0900	2.84 ± .48	1.45 ± .31
0930	3.50 ± .68	1.34 ± .23
1000	4.00 ± .66	1.56 ± .27
1030	2.67 ± .54	1.33 ± .20
1100	3.06 ± .67	1.50 ± .34
1130	2.23 ± .46	1.56 ± .29
1200	2.84 ± .51	1.95 ± .41
1230	2.56 ± .45	1.50 ± .29
1300	3.17 ± .67	2.11 ± .40
1330	3.11 ± .58	2.22 ± .35
1400	3.72 ± .72	2.28 ± .44
1430	2.89 ± .68	1.89 ± .44
1500	3.22 ± .80	1.95 ± .42
1530	3.56 ± .66	1.61 ± .33
1600	3.56 ± .64	1.89 ± .33
1630	1.83 ± .25	1.56 ± .29
1700	2.34 ± .45	1.44 ± .24
1730	2.61 ± .53	1.67 ± .30
1800	2.84 ± .46	2.50 ± .57
1830	2.61 ± .48	1.72 ± .47
Overall Group M	2.95 ± .56	1.74 ± .32 **

** $p < .001$

Figure 4. SSS ratings on days 1 and 2 recorded at 30 minute intervals. Data are collapsed across groups.

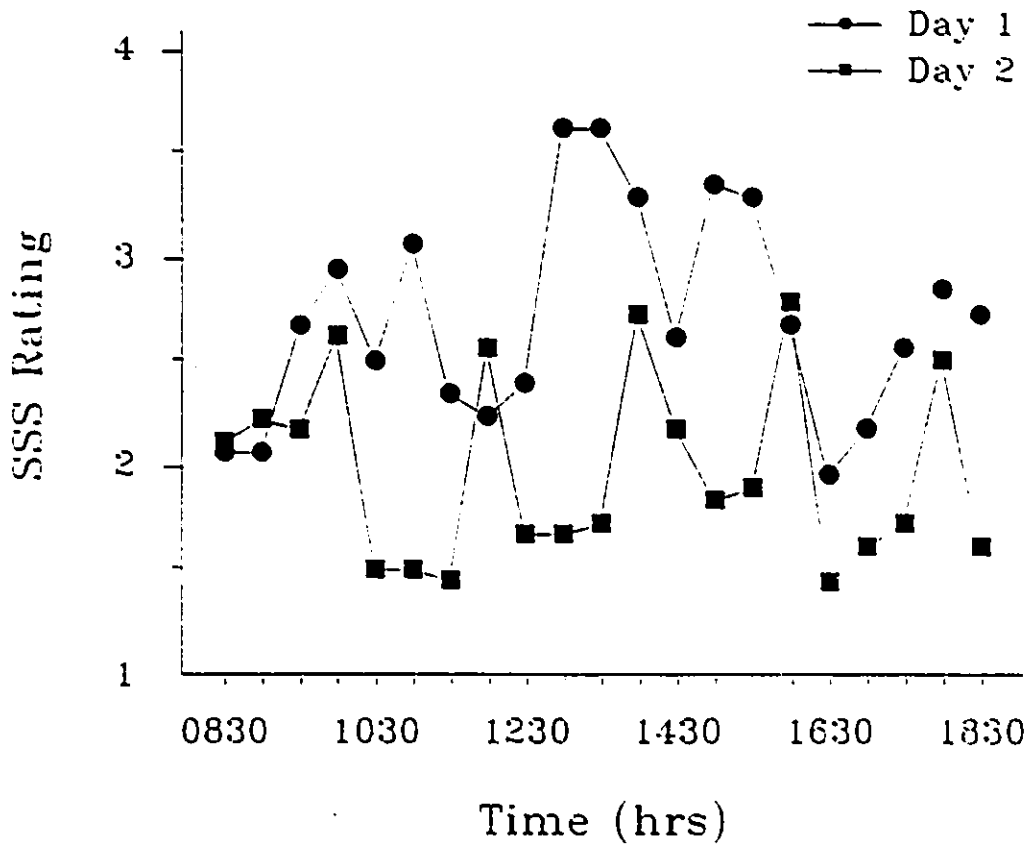

Day 1
Day 2
SSS Rating
4
3
2
1
0830
1030
1230
1430
1630
1830
Time (hrs)

Table 2

SSS Ratings : Main Day Effect and
Day x Time Interaction
Group Means and Standard Errors

Time (hrs)	Day 1	Day 2	
0830	2.06 ± .33	2.11 ± .23	
0900	2.06 ± .38	2.22 ± .41	
0930	2.67 ± .52	2.17 ± .39	
1000	2.94 ± .50	2.62 ± .43	
1030	2.50 ± .52	1.50 ± .22	
1100	3.06 ± .74	1.50 ± .27	*
1130	2.34 ± .52	1.45 ± .23	
1200	2.23 ± .53	2.56 ± .39	
1230	2.39 ± .45	1.67 ± .21	
1300	3.61 ± .73	1.67 ± .34	*
1330	3.61 ± .70	1.72 ± .22	*
1400	3.28 ± .57	2.72 ± .58	
1430	2.61 ± .51	2.17 ± .61	
1500	3.34 ± .80	1.83 ± .42	*
1530	3.28 ± .71	1.89 ± .28	
1600	2.67 ± .56	2.78 ± .40	
1630	1.95 ± .31	1.44 ± .24	
1700	2.17 ± .43	1.61 ± .26	
1730	2.56 ± .56	1.72 ± .27	
1800	2.84 ± .65	2.50 ± .38	
1830	2.72 ± .65	1.61 ± .30	
Overall Group M	2.71 ± .56	1.97 ± .34	**

* $p < .05$
** $p < .001$

Figure 5. SSS ratings recorded at 30 minute intervals. Data are collapsed across groups and across days.

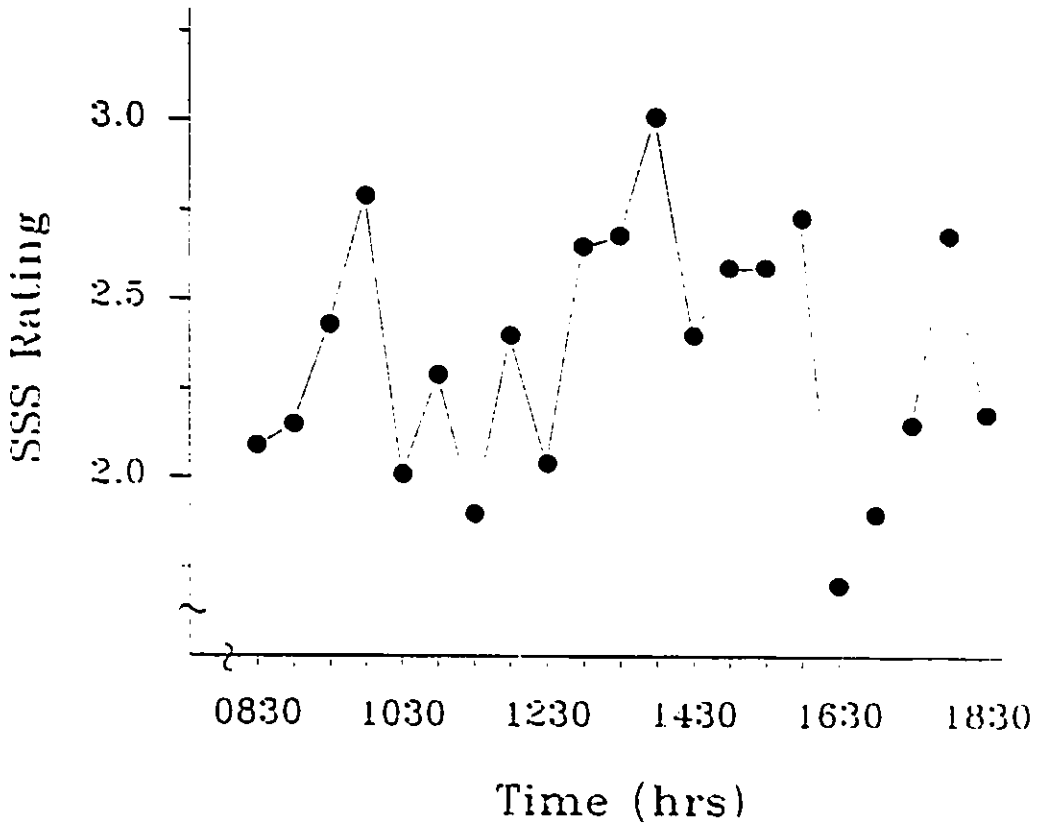

SSS Rating
3.0
2.5
2.0
0830
1030
1230
1430
1630
1830
Time (hrs)

Table 3

SSS Rating : Main Time Effect
Group Means and Standard Errors

Time (hrs)	SSS Rating
0830	2.08 ± .28
0900	2.14 ± .39
0930	2.42 ± .45
1000	2.78 ± .46 *
1030	2.00 ± .37
1100	2.28 ± .50
1130	1.89 ± .37
1200	2.39 ± .46
1230	2.03 ± .33
1300	2.64 ± .54 *
1330	2.67 ± .46 *
1400	3.00 ± .58 *
1430	2.39 ± .56
1500	2.58 ± .61 *
1530	2.58 ± .49 *
1600	2.72 ± .48 *
1630	1.69 ± .27
1700	1.89 ± .34
1730	2.14 ± .41
1800	2.67 ± .51 *
1830	2.17 ± .47

* $p < .05$

contamination of the MSLT sessions.

Examination of the day x time interaction indicated that sleepy periods on day one did not necessarily mirror those on day two, $\underline{H}(20) = 33.04$, $p < .05$ (see Figure 4 and Table 2). In fact, SSS scores at 1100, 1300, 1330 and 1500 hrs were significantly greater in the home relative to the lab. Not surprisingly, the timing of the sleepy periods at home coincided with the enforcement of alertness between MSLT naps on the laboratory day (Carskadon et al., 1986).

Further analysis of SSS scores for the MSLT day alone revealed that narcoleptics reported themselves as feeling sleepier ($\underline{M} = 2.62$) than controls ($\underline{M} = 2.12$), $\underline{H}(1) = 5.35$, $p < .025$ (see Figure 6 and Table 4). In addition, a main time effect indicated that both groups were sleepier in the pre-nap condition ($\underline{M} = 2.53$) relative to the post-nap condition ($\underline{M} = 2.21$), $\underline{H}(1) = 4.27$, $p < .05$ (see Figure 7 and Table 5), confirming the subjective recuperative effect of naps in general (Aguirre & Broughton, 1984; Stampi, Broughton, Mullington, & Rivers; 1989).

Analysis of ranks summary tables are detailed in the appendices (see Appendices B and C).

Figure 6. MSLT day SSS ratings for narcoleptics and controls. Data are collapsed across pre-MSLT and post-MSLT conditions.

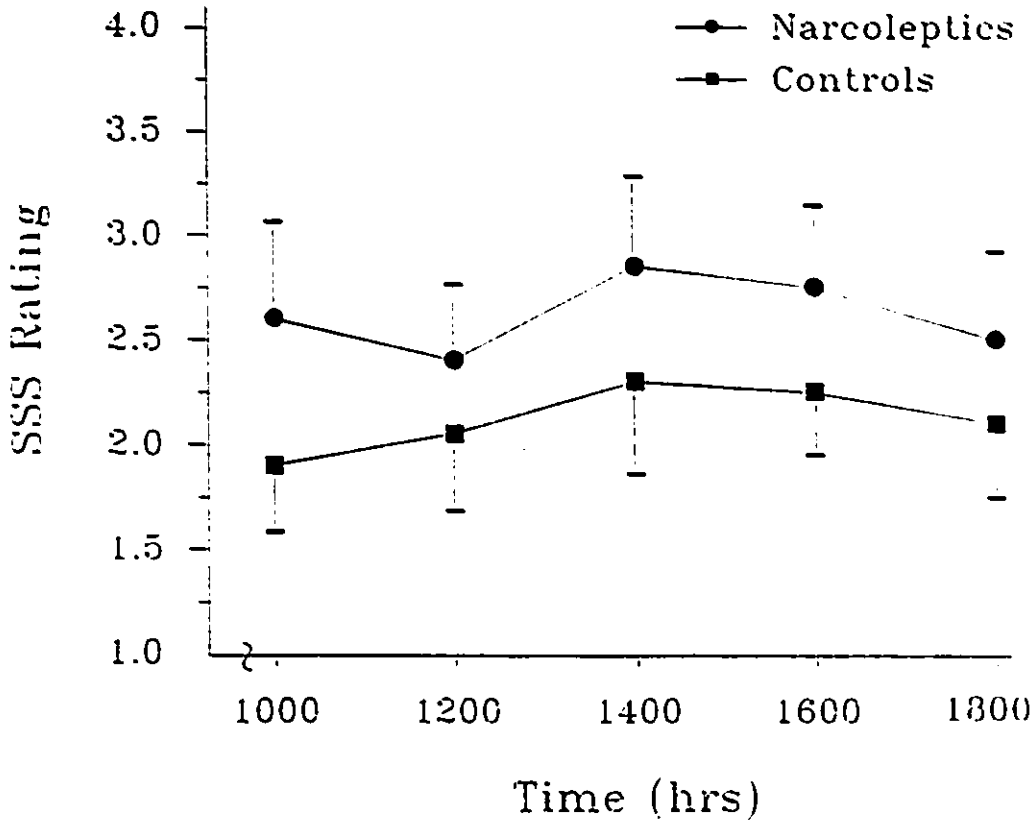

Narcoleptics
Controls
SSS Rating
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1000
1200
1400
1600
1800
Time (hrs)

Table 4

MSLT Day SSS Ratings Main Group Effect and Group x Session Interaction Means and Standard Errors

Time (hrs)	Narcoleptics	Controls
1000	2.60 ± .46	1.90 ± .32
1200	2.40 ± .36	2.05 ± .37
1400	2.85 ± .43	2.30 ± .44
1600	2.75 ± .39	2.25 ± .30
1800	2.50 ± .42	2.10 ± .35
Overall Group M	2.62 ± .41	2.12 ± .35 *

* $p < .05$

Figure 7. Pre-MSLT SSS ratings versus post-MSLT SSS ratings. Data are collapsed across groups.

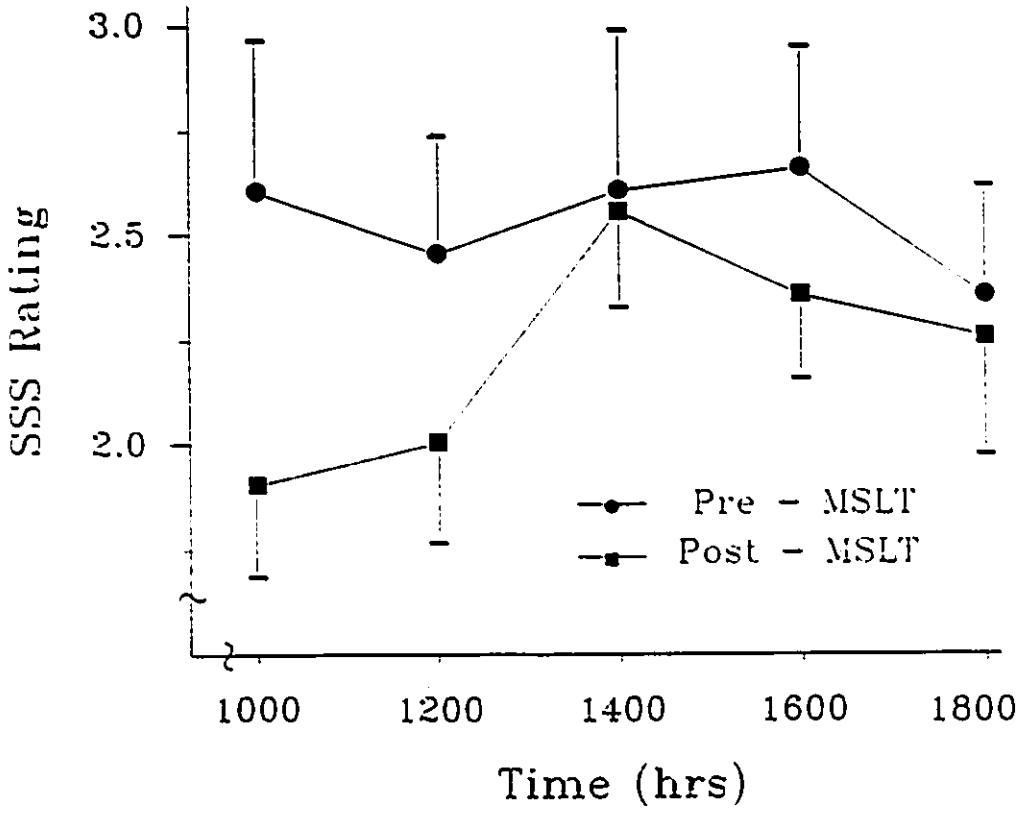

3.0
2.5
2.0
SSS Rating
Pre - MSLT
Post - MSLT
1000
1200
1400
1600
1800
Time (hrs)

Table 5

Pre–MSLT vs Post–MSLT SSS Ratings Main Time Effect and Time x Session Interaction Means and Standard Errors

Time (hrs)	Pre–MSLT	Post–MSLT
1000	2.60 ± .36	1.90 ± .22
1200	2.45 ± .28	2.00 ± .24
1400	2.60 ± .38	2.55 ± .23
1600	2.65 ± .29	2.35 ± .20
1800	2.35 ± .26	2.25 ± .28
Overall Group M	2.53 ± .31	2.21 ± .23 *

* $p < .05$

MSLT Findings

Statistical analysis of the MSLT data revealed that narcoleptics experienced shorter latencies to stage 1 (M = 3.35) compared to controls (M = 10.05), $F(1, 18) = 13.10$, $p < .002$ (see Figure 8 and Table 6). As also expected, the data indicated that narcoleptics entered REM sleep earlier (M = 9.67) than their counterpart controls (M = 20.00), $F(1, 18) = 29.57$, $p < .001$ who showed no REM patterns (see Figure 9 and Table 7). In contrast, latencies to stages 2 and 3 did not serve to differentiate between groups (see Tables 8 and 9). ANOVA summary tables are detailed in the appendices (see Appendices D through G). Stage 4 was not achieved by either group. Inter-rater reliability for sleep staging (from 24-hr recordings) was .90.

Pupillary Findings

There were no significant group differences whatsoever in baseline pupil diameter, in any component of the PLR, or in the pupillary OR (see Figures 10 to 18 and Tables 10 to 24). Narcoleptics (M = 25.76) were however distinguished from controls (M = 11.36) by their greater frequency of spontaneous oscillations, $H(1) = 21.27$, $p < .001$ (see Figure 19

Figure 8. Latency to stage 1 as a function of group and MSLT session.

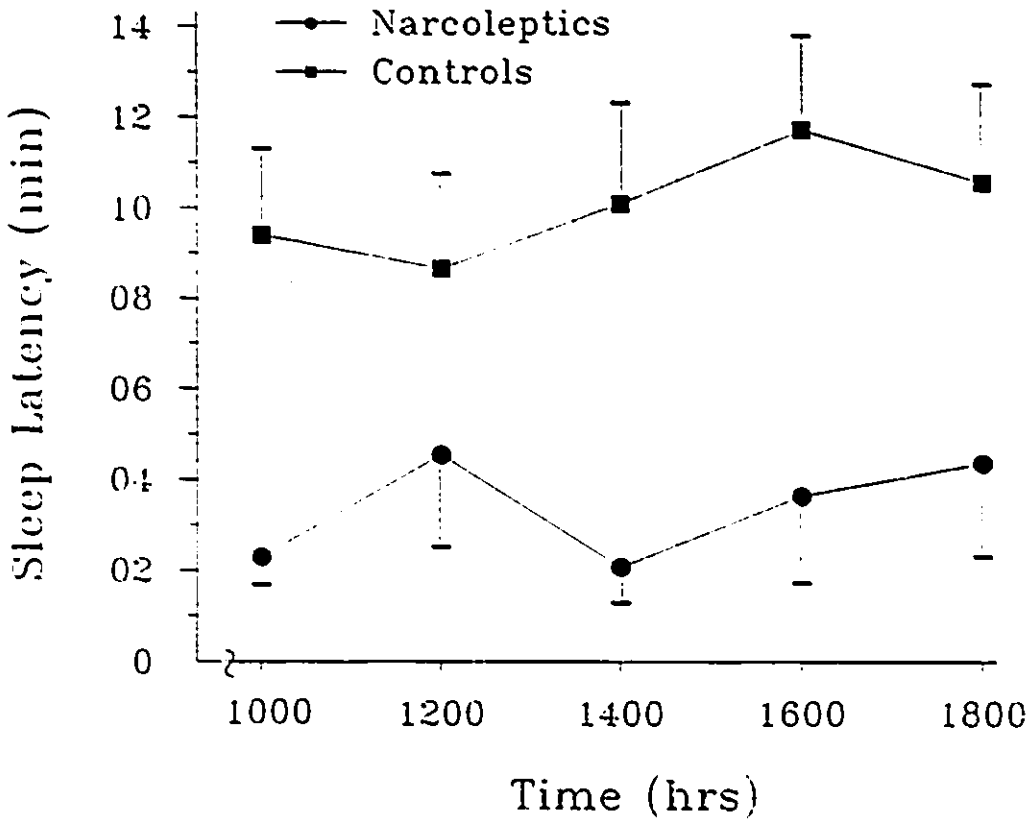

Narcoleptics
Controls
Sleep Latency (min)
14
12
10
08
06
04
02
0
1000
1200
1400
1600
1800
Time (hrs)

Table 6

MSLT : Latency to Stage 1
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (min)

Time (hrs)	Narcoleptics	Controls
1000	2.27 ± .60	9.38 ± 1.91
1200	4.52 ± 2.03	8.62 ± 2.11
1400	2.04 ± .78	10.05 ± 2.24
1600	3.61 ± 1.92	11.68 ± 2.08
1800	4.33 ± 2.05	10.50 ± 2.18
Overall Group M	3.35 ± 1.48	10.05 ± 2.10 *

* $p < .05$

Figure 9. Latency to REM sleep as a function of group and MSLT session.

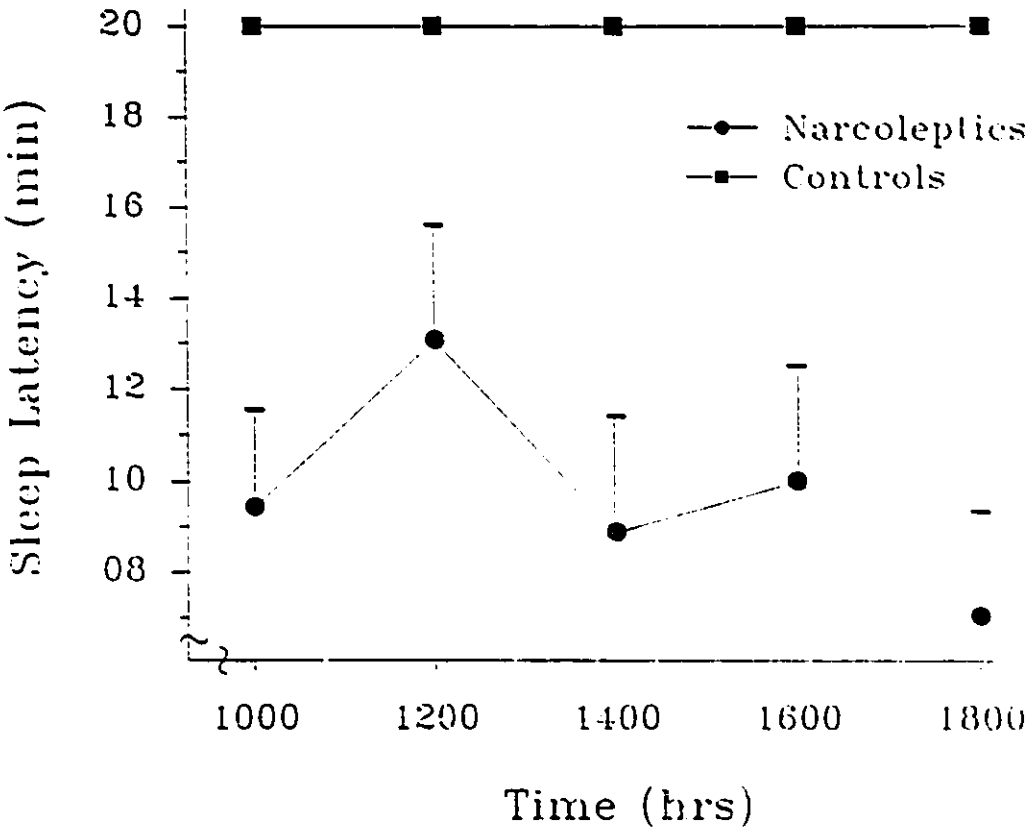

20
18
16
14
12
10
08
Sleep Latency (min)
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 7

MSLT : Latency to Stage REM
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (min)

Time (hrs)	Narcoleptics	Controls
1000	9.41 ± 2.12	20.00 ± .00
1200	13.06 ± 2.53	20.00 ± .00
1400	8.87 ± 2.53	20.00 ± .00
1600	9.99 ± 2.51	20.00 ± .00
1800	7.04 ± 2.30	20.00 ± .00
Overall Group M	9.67 ± 2.40	20.00 ± .00 **

** $p < .001$

Table 8

MSLT : Latency to Stage 2
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (min)

Time (hrs)	Narcoleptics	Controls
1000	12.77 ± 2.44	12.73 ± 1.72
1200	11.55 ± 2.59	12.07 ± 1.90
1400	9.73 ± 2.07	11.83 ± 2.09
1600	10.72 ± 2.81	13.15 ± 1.80
1800	16.02 ± 2.07	14.15 ± 2.14
Overall Group M	12.16 ± 2.40	12.79 ± 1.93

Table 9

MSLT : Latency to Stage 3
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (min)

Time (hrs)	Narcoleptics	Controls
1000	20.00 ± .00	20.00 ± .00
1200	20.48 ± .48	20.00 ± .00
1400	20.00 ± .00	20.00 ± .00
1600	20.00 ± .00	20.00 ± .00
1800	20.00 ± .00	20.63 ± .63
Overall Group M	20.10 ± .10	20.13 ± .13

Figure 10. Mean pupil diameter during dark-adaptation as a function of group and testing session.

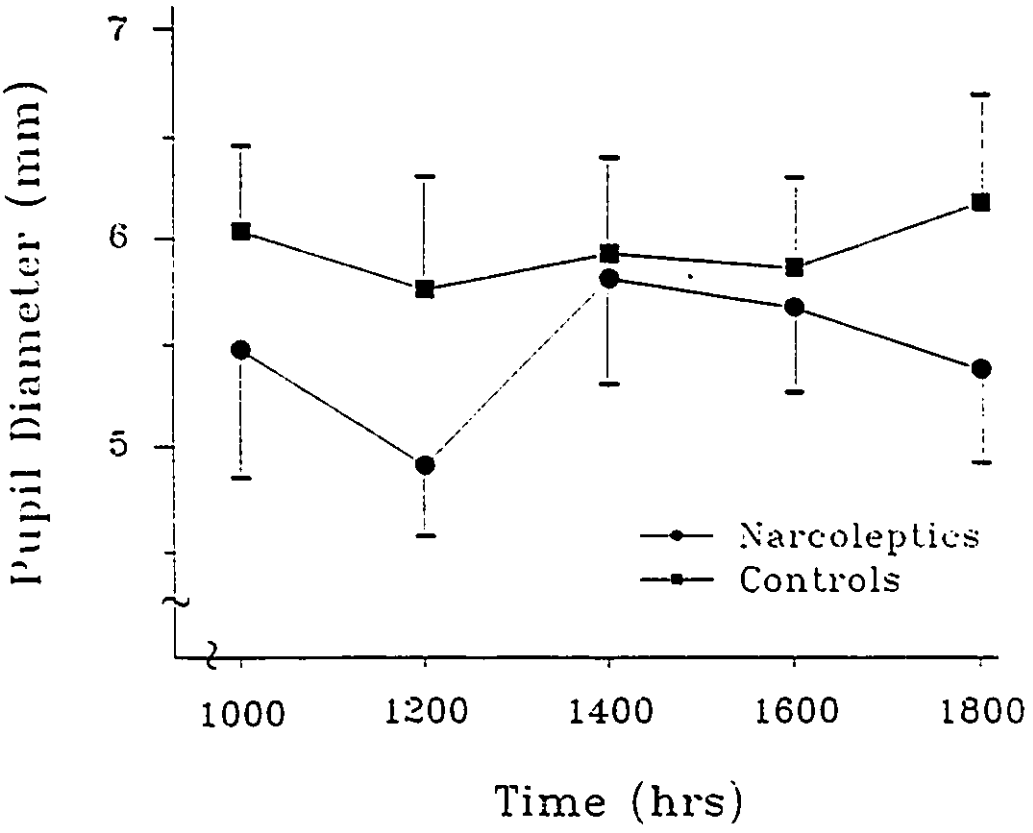

Pupil Diameter (mm)
7
6
5
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 10

Dark-Adapted Pupil Diameter Main Group Effect and Group x Session Interaction Means and Standard Errors (mm)

Time (hrs)	Narcoleptics	Controls
1000	5.47 ± .62	6.04 ± .41
1200	4.91 ± .34	5.76 ± .54
1400	5.81 ± .51	5.93 ± .46
1600	5.67 ± .41	5.86 ± .43
1800	5.37 ± .45	6.17 ± .52
Overall Group M	5.45 ± .47	5.95 ± .47

Figure 11. Latency to pupillary constriction as a function of group and testing session.

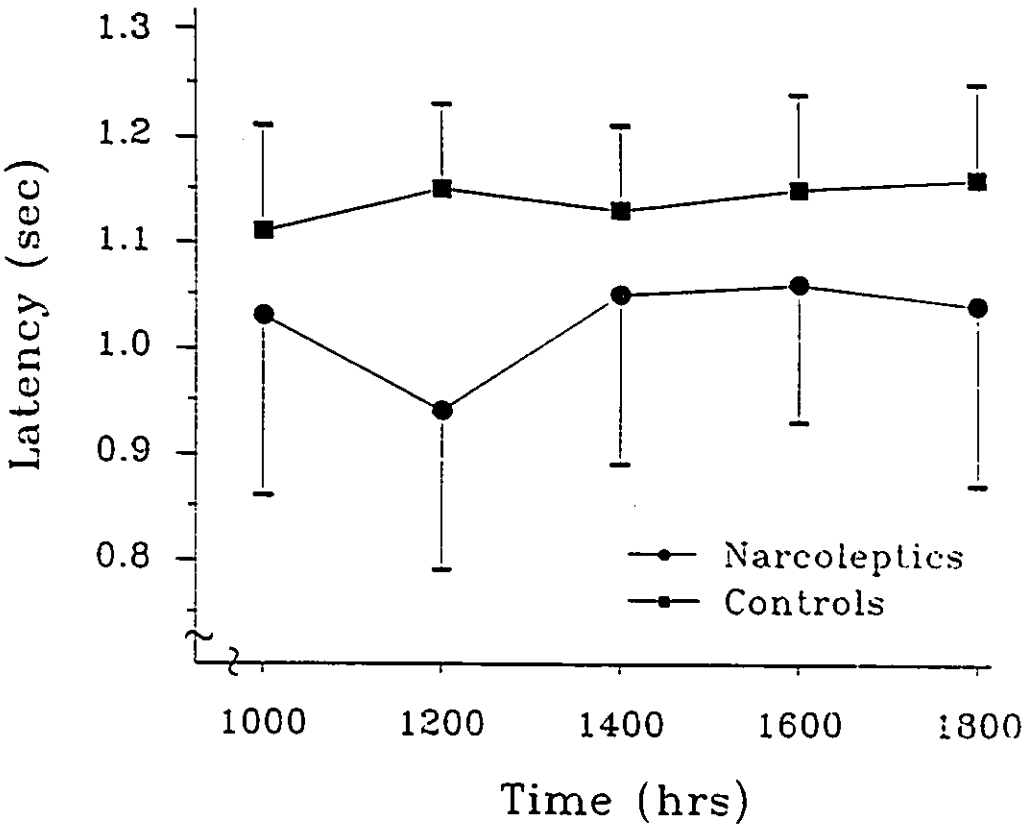

1.3
1.2
1.1
1.0
0.9
0.8
Latency (sec)
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 11

PLR : Latency to Constriction
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (sec)

Time (hrs)	Narcoleptics	Controls
1000	1.03 ± .17	1.11 ± .10
1200	.94 ± .15	1.15 ± .08
1400	1.05 ± .16	1.13 ± .08
1600	1.06 ± .13	1.15 ± .09
1800	1.04 ± .17	1.16 ± .09
Overall Group M	1.02 ± .16	1.14 ± .09

Table 12

PLR : Latency to Constriction
Group x Stimulus Interaction
Means and Standard Errors (sec)

Stimulus	Narcoleptics	Controls
1	1.06 ± .07	1.16 ± .05
2	1.04 ± .07	1.17 ± .05
3	.94 ± .04	1.15 ± .04
4	.97 ± .04	1.14 ± .04
5	1.08 ± .08	1.09 ± .02
6	.99 ± .07	1.11 ± .03
7	.98 ± .05	1.20 ± .03
8	1.06 ± .08	1.12 ± .03
9	1.11 ± .10	1.11 ± .03
10	1.02 ± .08	1.15 ± .04

Figure 12. Extent of pupillary constriction as a function of group and testing session.

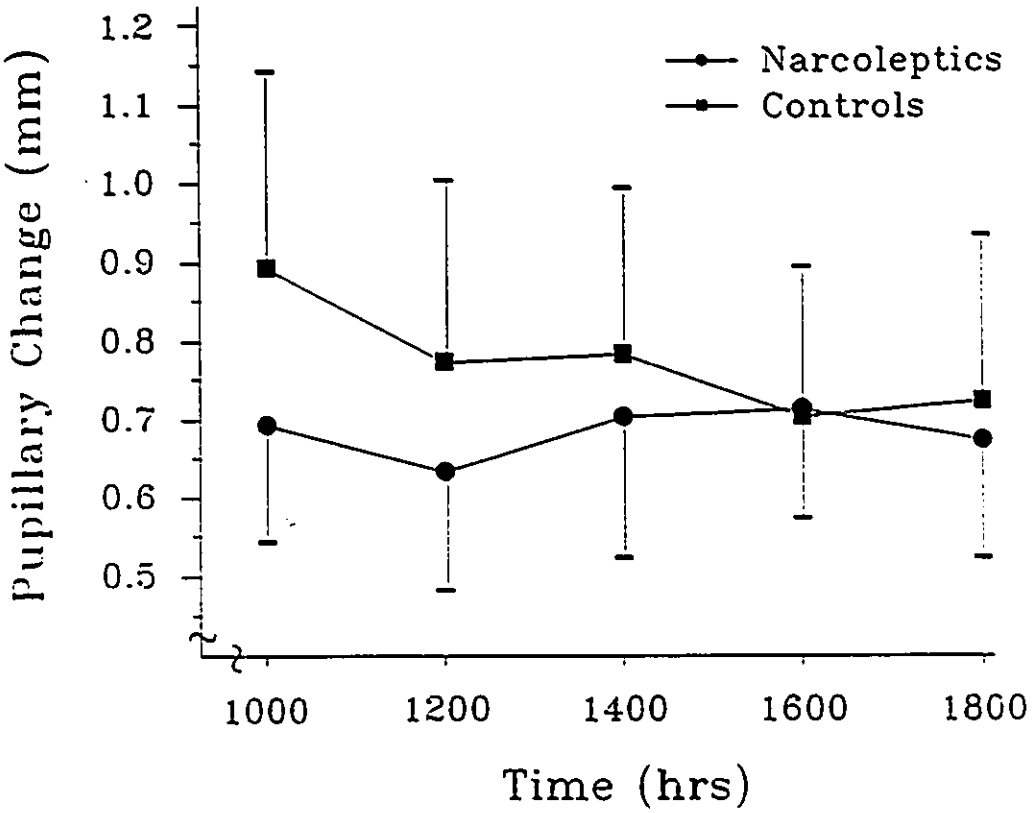

Pupillary Change (mm)
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 13

PLR : Extent of Constriction
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (mm)

Time (hrs)	Narcoleptics	Controls
1000	.69 ± .15	.89 ± .25
1200	.63 ± .15	.77 ± .23
1400	.70 ± .18	.78 ± .21
1600	.71 ± .14	.70 ± .19
1800	.67 ± .15	.72 ± .21
Overall Group M	.68 ± .15	.77 ± .22

Table 14

PLR : Extent of Constriction
Group x Stimulus Interaction
Means and Standard Errors (mm)

Stimulus	Narcoleptics	Controls
1	.73 ± .07	.72 ± .09
2	.69 ± .06	.76 ± .10
3	.60 ± .07	.79 ± .09
4	.66 ± .07	.78 ± .10
5	.82 ± .07	.74 ± .10
6	.67 ± .07	.77 ± .09
7	.63 ± .06	.78 ± .11
8	.69 ± .05	.81 ± .10
9	.70 ± .09	.81 ± .10
10	.61 ± .06	.76 ± .10

Figure 13. Rate of pupillary constriction as a function of group and testing session.

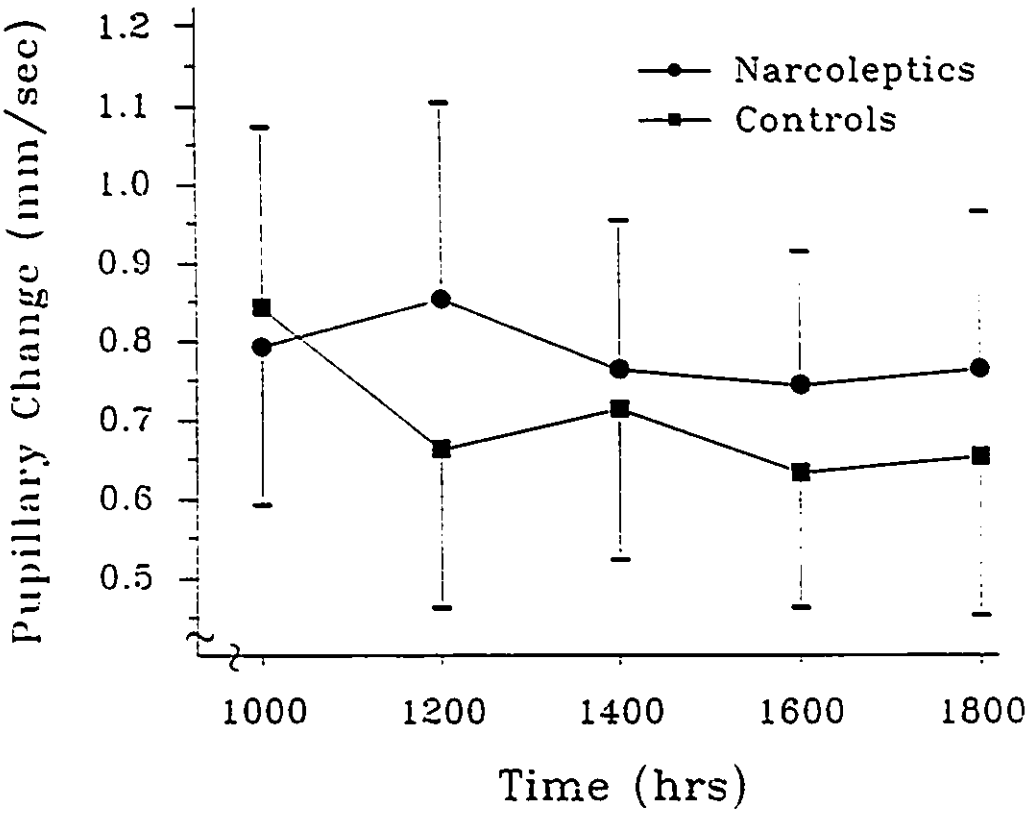

Pupillary Change (mm/sec)
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 15

PLR : Rate of Constriction
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (mm/sec)

Time (hrs)	Narcoleptics	Controls
1000	.79 ± .20	.84 ± .23
1200	.85 ± .25	.66 ± .20
1400	.76 ± .19	.71 ± .19
1600	.74 ± .17	.63 ± .17
1800	.76 ± .20	.65 ± .20
Overall Group M	.78 ± .20	.70 ± .20

Table 16

PLR : Rate of Constriction
Group x Stimulus Interaction
Means and Standard Errors (mm/sec)

Stimulus	Narcoleptics	Controls
1	.78 ± .08	.65 ± .08
2	.79 ± .09	.68 ± .09
3	.74 ± .09	.70 ± .09
4	.76 ± .08	.71 ± .09
5	.96 ± .13	.68 ± .09
6	.72 ± .08	.72 ± .09
7	.72 ± .08	.66 ± .09
8	.82 ± .08	.73 ± .09
9	.80 ± .12	.75 ± .09
10	.72 ± .08	.69 ± .09

Figure 14. Constriction velocity as a function of group and testing session.

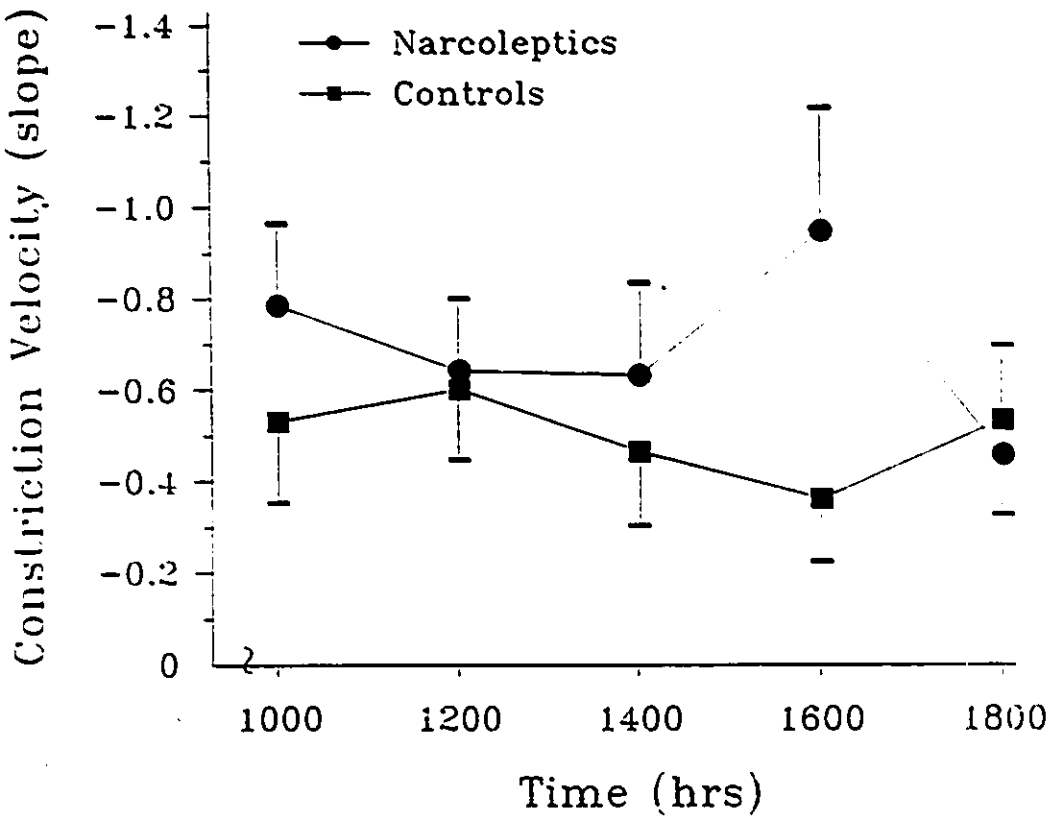

Constriction Velocity (slope)
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 17

PLR: Constriction Velocity
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (slope)

Time (hrs)	Narcoleptics	Controls
1000	−.79 ± .18	−.57 ± .21
1200	−.65 ± .16	−.61 ± .15
1400	−.64 ± .20	−.47 ± .16
1600	−.95 ± .27	−.37 ± .14
1800	−.46 ± .13	−.54 ± .16
Overall Group M	−.70 ± .19	−.51 ± .17

Figure 15. Maximum redilated pupil diameter as a function of group and testing session.

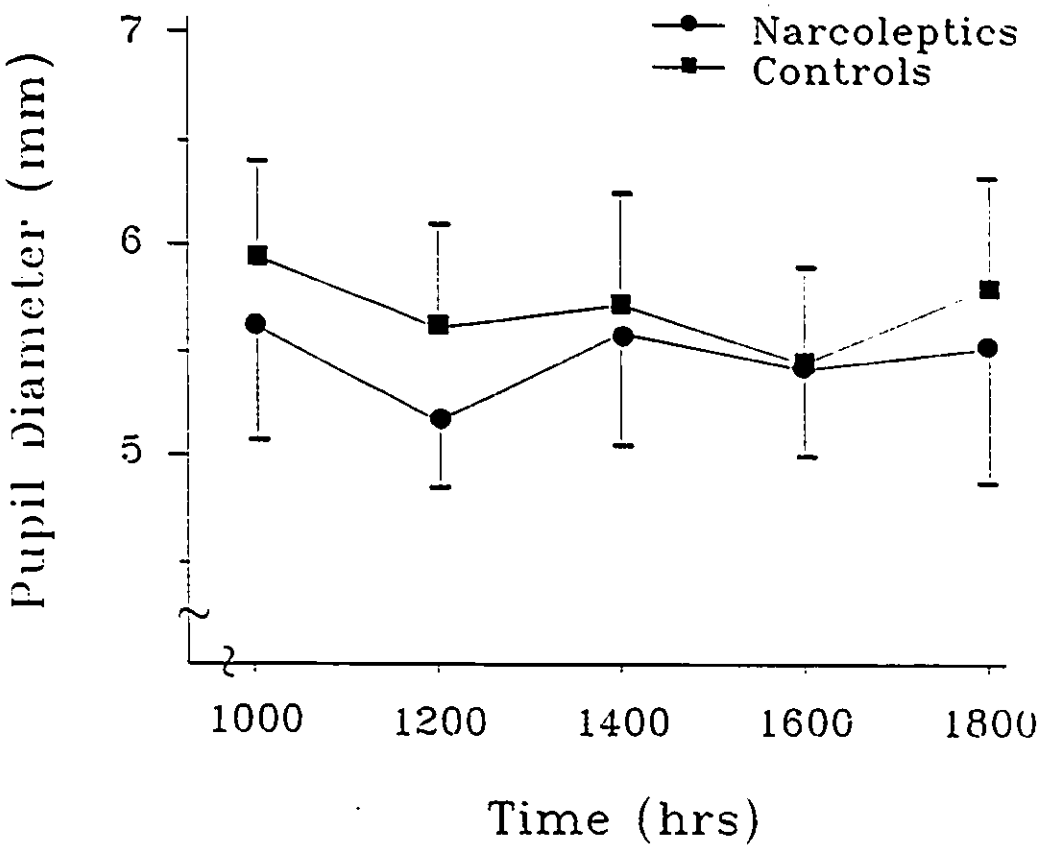

Narcoleptics
Controls
Pupil Diameter (mm)
7
6
5
1000
1200
1400
1600
1800
Time (hrs)

Table 18

PLR : Maximum Redilated Diameter Main Group Effect and Group x Session Interaction Means and Standard Errors (mm)

Time (hrs)	Narcoleptics	Controls
1000	5.61 ± .56	5.94 ± .45
1200	5.15 ± .33	5.60 ± .49
1400	5.57 ± .54	5.71 ± .53
1600	5.40 ± .42	5.43 ± .46
1800	5.50 ± .56	5.79 ± .52
Overall Group M	5.45 ± .48	5.69 ± .49

Table 19

PLR : Maximum Redilated Diameter
Group x Stimulus Interaction
Means and Standard Errors (mm)

Stimulus	Narcoleptics	Controls
1	5.67 ± .22	5.94 ± .22
2	5.54 ± .23	5.80 ± .22
3	5.46 ± .22	5.56 ± .24
4	5.36 ± .21	5.65 ± .23
5	5.41 ± .21	5.62 ± .21
6	5.45 ± .23	5.66 ± .22
7	5.50 ± .24	5.71 ± .22
8	5.39 ± .22	5.70 ± .22
9	5.38 ± .22	5.65 ± .22
10	5.29 ± .22	5.66 ± .22

Figure 16. Rate of pupillary redilation as a function of group and testing session.

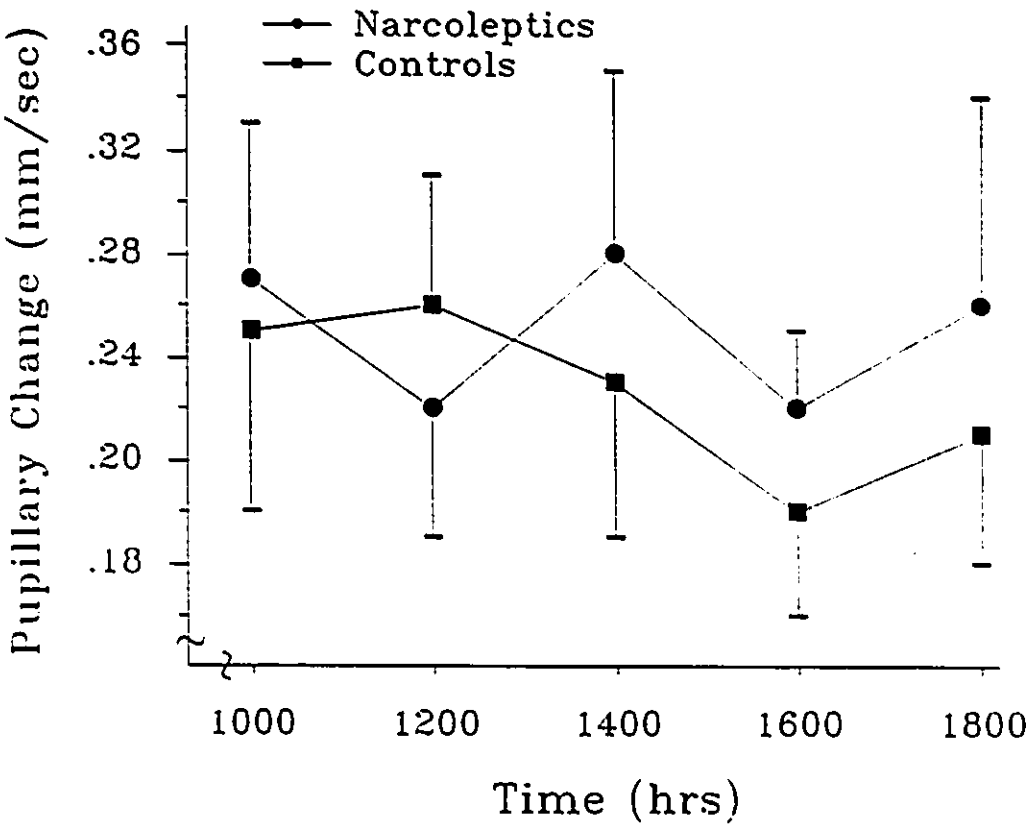

Narcoleptics
Controls
Pupillary Change (mm/sec)
.36
.32
.28
.24
.20
.18
1000
1200
1400
1600
1800
Time (hrs)

Table 20

PLR : Rate of Redilation
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (mm/sec)

Time (hrs)	Narcoleptics	Controls
1000	.27 ± .06	.25 ± .07
1200	.22 ± .05	.26 ± .05
1400	.28 ± .07	.23 ± .06
1600	.22 ± .03	.18 ± .04
1800	.26 ± .08	.21 ± .05
Overall Group M	.25 ± .06	.23 ± .05

Table 21

PLR : Rate of Redilation
Group x Stimulus Interaction
Means and Standard Errors (mm/sec)

Stimulus	Narcoleptics	Controls
1	.23 ± .02	.22 ± .02
2	.23 ± .03	.19 ± .02
3	.24 ± .02	.22 ± .03
4	.24 ± .02	.22 ± .03
5	.27 ± .03	.19 ± 02
6	.25 ± .03	.22 ± .03
7	.26 ± .03	.22 ± .03
8	.26 ± .02	.24 ± .03
9	.27 ± .04	.22 ± .02
10	.24 ± .02	.23 ± .03

Figure 17. Redilation velocity as a function of group and testing session.

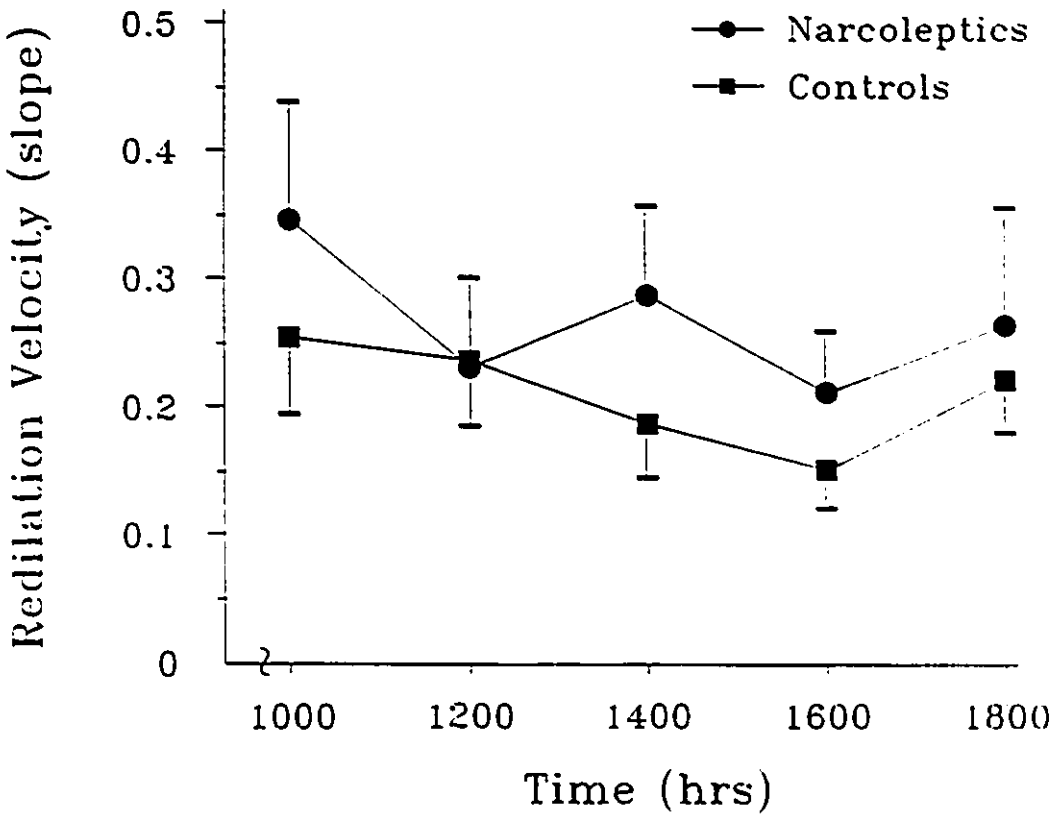

Redilation Velocity (slope)
0.5
0.4
0.3
0.2
0.1
0
Narcoleptics
Controls
1000
1200
1400
1600
1800
Time (hrs)

Table 22

PLR: Redilation Velocity
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (slope)

Time (hrs)	Narcoleptics	Controls
1000	.35 ± .09	.26 ± .06
1200	.23 ± .05	.24 ± .06
1400	.29 ± .07	.19 ± .04
1600	.21 ± .05	.15 ± .03
1800	.26 ± .09	.22 ± .04
Overall Group M	.27 ± .07	.21 ± .05

Figure 18. Pupillary orienting response to tones as a function of group and testing session.

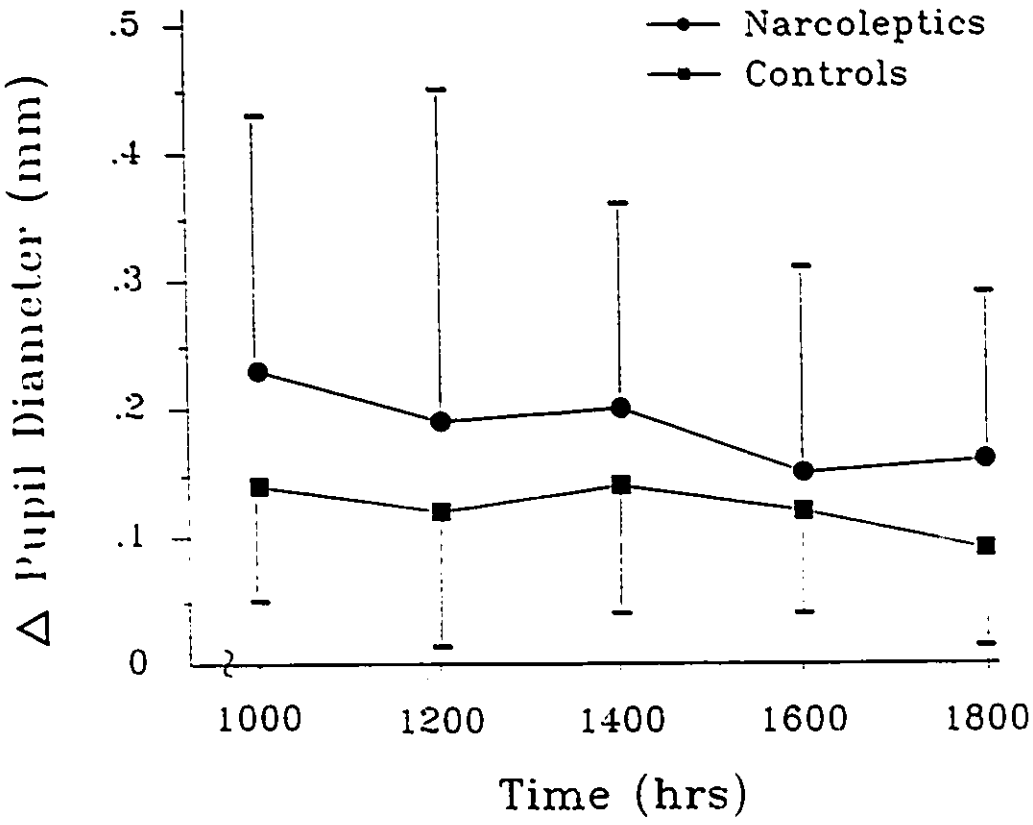

Narcoleptics
Controls
Δ Pupil Diameter (mm)
.5
.4
.3
.2
.1
0
1000
1200
1400
1600
1800
Time (hrs)

Table 23

Pupillary Orienting Response to Tones Main Group Effect and Group x Session Interaction Means and Standard Errors (mm)

Time (hrs)	Narcoleptics	Controls
1000	.23 ± .20	.14 ± .09
1200	.19 ± .26	.12 ± .12
1400	.20 ± .16	.14 ± .10
1600	.15 ± .16	.12 ± .08
1800	.16 ± .13	.09 ± .09
Overall Group M	.19 ± .18	.12 ± .10

Table 24

Pupillary Orienting Response to Tones
Group x Stimulus Interaction
Means and Standard Errors (mm)

Stimulus	Narcoleptics	Controls
1	.37 ± .07	.28 ± .06
2	.10 ± .10	.13 ± .04
3	.23 ± .07	.12 ± 03
4	.21 ± .06	.17 ± .03
5	.06 ± .04	.11 ± .03
6	.17 ± .11	.07 ± .03
7	.15 ± .08	.09 ± .04
8	.10 ± .09	.00 ± .03
9	−.02 ± .08	.12 ± .04
10	.30 ± .09	.09 ± .06
11	.36 ± .09	.21 ± .06

Figure 19. Frequency of spontaneous oscillations as a function of group and testing session.

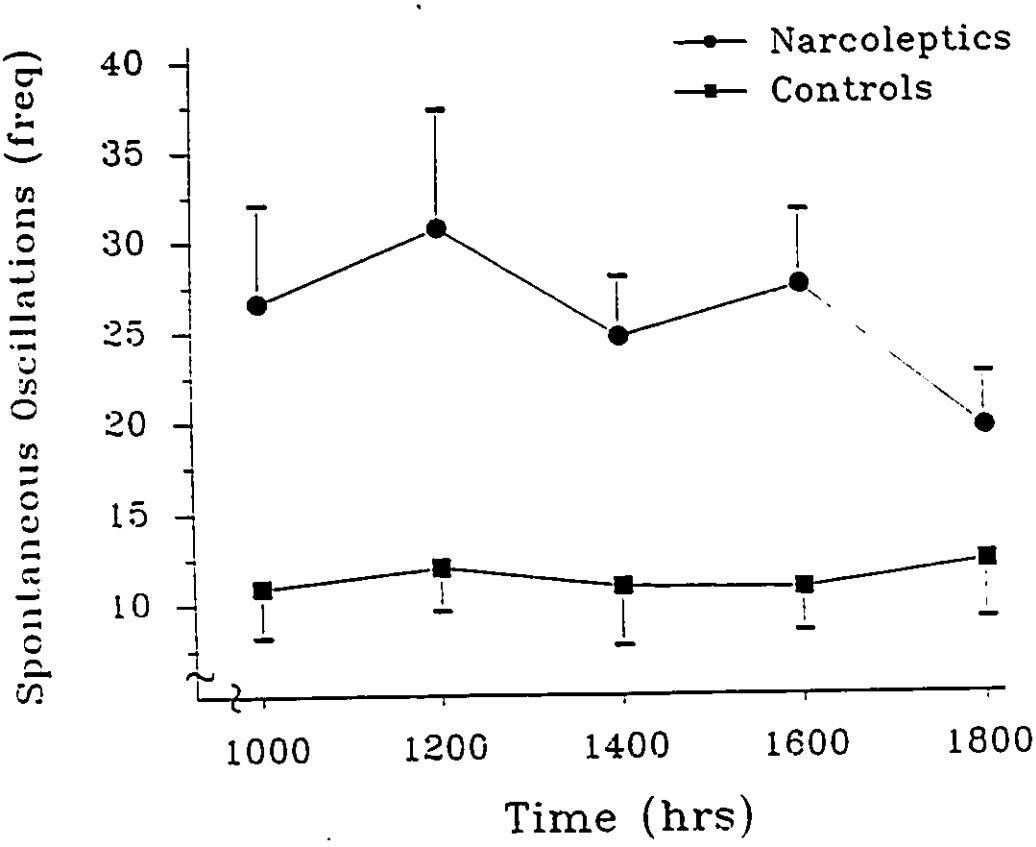

Narcoleptics
Controls
Spontaneous Oscillations (freq)
40
35
30
25
20
15
10
1000
1200
1400
1600
1800
Time (hrs)

Table 25

Spontaneous Oscillations
Main Group Effect and
Group x Session Interaction
Means and Standard Errors (freq)

Time (hrs)	Narcoleptics	Controls
1000	26.60 ± 5.47	10.90 ± 2.73
1200	30.70 ± 6.58	12.00 ± 2.40
1400	24.60 ± 3.31	10.90 ± 3.24
1600	27.40 ± 4.15	10.80 ± 2.38
1800	19.50 ± 3.01	12.20 ± 3.17
Overall Group M	25.76 ± 4.50	11.36 ± 2.78 **

** $p < .001$

and Table 25). Summary tables for all pupillary variables are detailed in the appendices (see Appendices H through Q).

Other significant findings include a reduction in the magnitude of the redilated diameter across the 10 light stimuli, $F(9, 162) = 3.16$, $p < .002$ (see Figure 20) and an increase in the magnitude of the pupillary OR following the 11th tone, $F(10, 180) = 3.99$, $p < .001$ (see Figure 21). The former may reflect habituation of one component of the PLR (Lowenstein, 1955) while the latter indicates the successful employment of the test stimulus in the tone series.

No additional significance was achieved by any pupillary variable upon the statistical removal of prior amount of sleep.

The frequency of spontaneous oscillations significantly correlated with MSLT latencies in the controls ($r = -.52$, $p < .001$) but not in the narcoleptics ($r = -.16$, $p > .01$). No significant correlations were found between spontaneous oscillations and SSS scores in either group.

Pupillary variables did not differentiate pre-REM sleepiness from pre-NREM sleepiness (see Table 26 and Appendix R) (constriction velocity and redilation velocity were not used in these analyses).

Figure 20. Maximum redilated pupil diameter as a function of stimulus presentation.

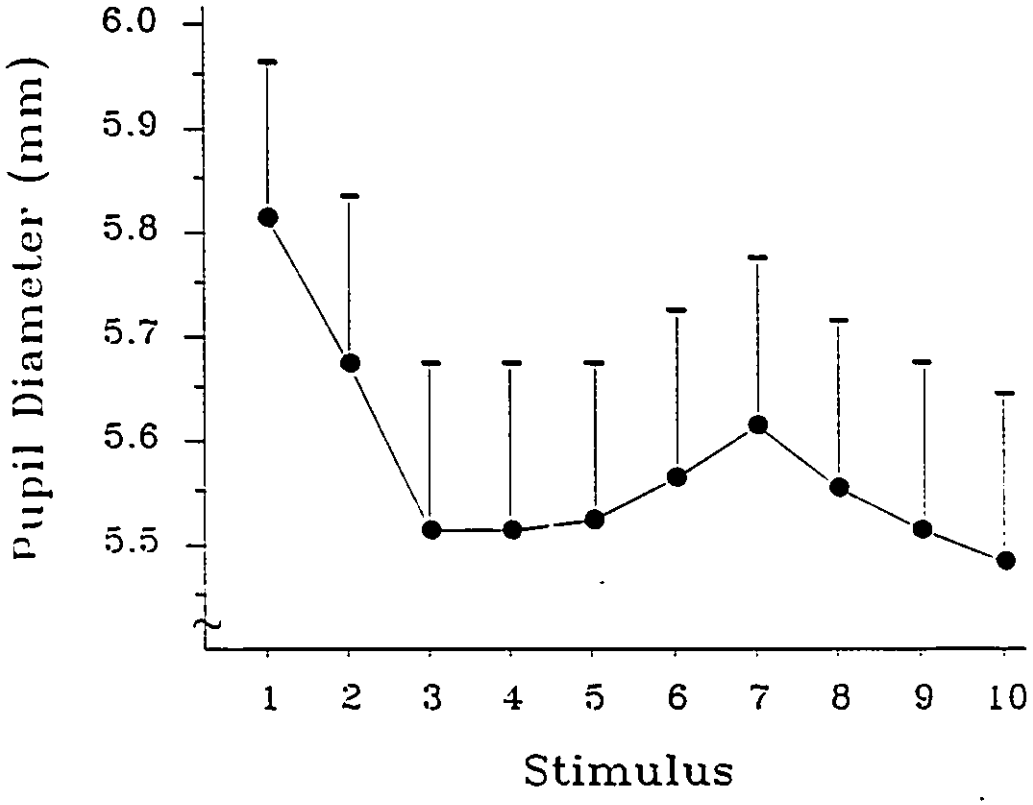

Pupil Diameter (mm)
6.0
5.9
5.8
5.7
5.6
5.5
1
2
3
4
5
6
7
8
9
10
Stimulus

Figure 21. Pupillary orienting response to tones as a function of stimulus presentation.

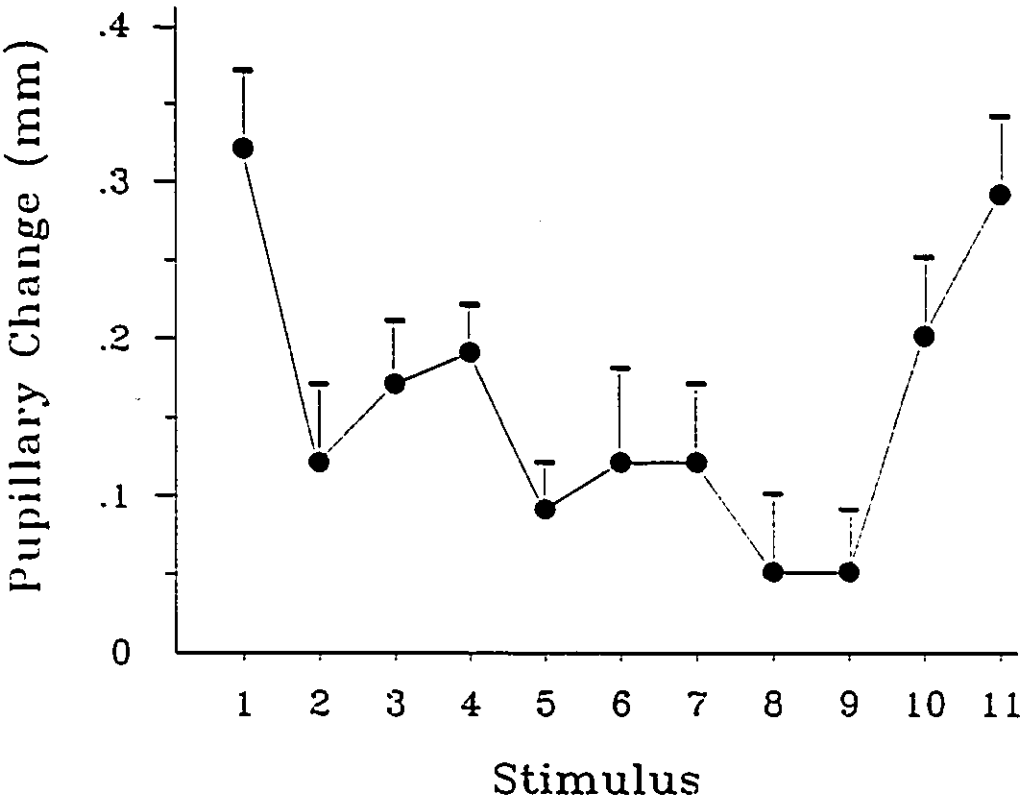

Pupillary Change (mm)
.4
.3
.2
.1
0
1
2
3
4
5
6
7
8
9
10
11
Stimulus

Table 26

REM Sleepiness vs NREM Sleepiness
Main Group Effects
Means and Standard Errors

Pupillary Variables	REM Sleepiness	NREM Sleepiness
Base Diam	5.74 ± .22	5.47 ± .52
Lat Const	1.10 ± .09	1.08 ± .05
Ext Const	.65 ± .06	.66 ± .11
Rate Const	.73 ± .13	.70 ± .09
Max Redil	5.54 ± .26	5.27 ± .39
Rate Redil	.27 ± .04	.22 ± .03
Pupil OR	.26 ± .07	.25 ± .06
Spont Osc	27.43 ± 2.7	28.90 ± 5.4

Discussion

Although narcoleptics were sleepier than controls both subjectively and objectively as evidenced by SSS scores and MSLT latencies, the majority of pupillary measures did not serve to differentiate between groups.

This apparent inadequacy of the pupil as an index of sleepiness may however be misleading as pupillary size and response, which are believed to indicate the level of alertness (Lowenstein et al., 1963), may be additionally influenced by a variety of psychophysiological functions (Lowenstein, 1920). These include mental effort (Schaefer, Ferguson, Klein & Rawson, 1968), attention (Goldwater, 1972), anxiety (Simpson & Molloy, 1971), fear (Nunnally, Knott, Duchnowski & Parker, 1967), motivation (Hess, 1972), thought (Johnson, 1971), counting (Bumke, 1911), and muscle tension (Simpson & Paivio, 1966). Bumke (1911) aptly summarized the situation when he stated that, "in general every active intellectual process, every psychical effort, every exertion of attention, every active mental image, regardless of content, particularly every affect just as truly produces pupil enlargement as does every sensory stimulus (p. 60)." In physiological terms, psychosensory and physical stimuli alter the existing sympathetic-parasympathetic

balance and thus modify the course of arousal (Lowenstein & Loewenfeld, 1952). These often uncontrolled factors may explain why both inter-subject and intra-subject pupillary variability are quite high (Loewenfeld, 1966; Woodmansee, 1966) and why the probability of group discrimination on the basis of pupil response remains low.

In order to control for the many extraneous sources of error, and thereby tease out the effects of level of alertness alone, it has been suggested that cognitive relaxation be emphasized in pupillary studies (Geacintov & Peavler, 1974). This condition was met in the current study only during the 2 minute periods of quiescence that separated the auditory from the visual sequences. As subjects were then permitted to temporarily blink freely and were well informed of the existence and length of the break, it is conceivable that this segment of the experiment was experienced as less demanding or stressful and thus more likely to promote sleepiness. It is notable that the only pupillary variable that differentiated between groups was the greater number of spontaneous oscillations experienced by the narcoleptics during this 2 minute interval. The failure to detect similar group differences in pupillary fluctuations during the baseline recording periods may have been due to feelings of anticipation or anxiety at the onset of

each test. Narcoleptics are, in fact, capable of producing normal pupillographic tracings during periods of heightened arousal (Norman & Dyer, 1987).

These findings, in conjunction with the observed negative correlation between spontaneous oscillations and MSLT latencies in the controls, suggest that spontaneous oscillations may be a truly robust measure of level of alertness, which in turn may be more clearly isolated when the individual is at ease. Under the latter condition, boredom is promoted and the effort needed to remain awake, particularly for the chronically sleepy narcoleptic group, is maximal. It is this very struggle to maintain alertness that is believed to result in autonomic imbalance and consequent pupillary fluctuations (Lowenstein & Loewenfeld, 1951). More specifically, as the individual becomes sleepy, sympathetic influence begins to deteriorate and supranuclear inhibition gradually decreases, resulting in pupillary constriction (Lowenstein et al., 1963). As sensations of sleepiness become even greater, the individual makes conscious efforts to remain awake which result in temporary inhibition of the oculomotor nucleus, an increase in sympathetic tone, and pupillary dilation (Lowenstein & Loewenfeld, 1951). As the individual has periodic success at alerting himself or herself, the pupil rhythmically constricts and redilates.

On the basis of this knowledge, it makes sense to utilize a protocol that promotes sleepiness yet requires alertness when measuring spontaneous oscillations as a function of arousal. As narcoleptics appear to be particularly vulnerable to such conditions (Valley & Broughton, 1983) it seems likely that, given the same circumstances, other EDS patients would also display increased pupillary activity.

Perhaps the conflicting reports in the literature regarding the relationship between spontaneous pupil activity and arousal level (Lowenstein & Loewenfeld, 1951; Lowenstein et al., 1963; Lin et al., 1990 vs Schmidt, 1982; Kollarits et al., 1982; Pressman, 1984) are largely due to the differing conditions under which these oscillations have been measured. It is expected that standardization of procedure will aid in clearly demonstrating that pupil variability during conditions of cognitive relaxation is the most reliable pupillometric measure of EDS. A follow-up study to this end would be most illuminating.

In contrast to pupil stability, the PLR and the OR to tones did not discriminate between groups. The relative ineffectiveness of these measures may have been due to the alerting effects of the stimuli themselves (Woodmansee, 1966) and/or to the probable intrusion of various psychosensory factors including counting (Bumke, 1911). As sleepiness is discouraged

under such conditions, it is not surprising that pupil changes as a function of EDS were undetected. Perhaps the methodology can be altered in future such that the alerting effects of the stimuli are curtailed (ie., lower intensity) and the struggle to remain awake is enhanced (ie., longer intervals between stimuli).

Although there has been some suggestion in previous work that the PLR may be used to distinguish sleepy from alert individuals (Lowenstein, 1955; Schmidt, 1982; Pressman & Fry, 1989), the majority of recent findings indicate otherwise (Pressman et al., 1986; Hertz et al., 1988; Fredrickson et al., 1990). Perhaps such inconsistencies in the literature are due to poor or varying design, a lack of standardization of experimental conditions, interfering sensory or emotional stimuli (Lowenstein, 1955), and/or interpersonal differences. Indeed, the PLR may well vary a great deal among individuals, as well as quite erratically within the same individual from moment to moment (Lowenstein et al., 1964).

In addition to the alerting effects of the stimuli, such variability (Raskin, 1973) likely also accounts for the inadequacy of the pupillary OR as a measure of EDS. Moreover, one must question the validity of this measure as the observed minute changes in diameter following the tones may have been due to spontaneous activity rather than to the

orienting reflexes themselves (Maher & Furedy, 1979).

Perhaps the use of the task-evoked pupillary response (TEPR) would have proven a more valid measure of arousal. The TEPR is a brief dilation of the pupil following the onset of a meaningful stimulus. It has a latency of .1 - .2 seconds and continues until cognitive processing is complete (Beatty, 1989). In essence the TEPR, which is a function of sympathetic activation and parasympathetic inhibition, is a physiological index of the degree of cognitive processing imposed by a meaningful stimulus (Beatty, 1986). It is expected that a vigilance decrement would result in decreased attentiveness and a reduction in amplitude of the TEPR (Beatty, 1982). In view of the need to create sufficient monotony yet preserve wakefulness, it seems likely that adoption of the TEPR as a dependent measure for the Wilkinson auditory vigilance test (Valley & Broughton, 1981) would prove ideal for assessing EDS. To my knowledge, the TEPR has not been previously used as a means to discriminate alert individuals from EDS patients.

In keeping with the PLR and OR data, similar null results were also achieved for the baseline diameter variable. These findings may be explained in terms of the alerting effects of motivational factors and/or of feelings of anxiety experienced upon the initiation of each test. Yet, such factors cannot

account for the negative results obtained during the supposedly relaxing 2 min breaks.

Why is it that pupil diameter does not serve to differentiate groups at a time when the narcoleptics, unlike the controls, are clearly struggling to remain awake ? If one expects the spontaneous oscillations to cancel one another out, the under-riding baseline diameter should remain uncontaminated and thereby reflect these differing levels of alertness. Perhaps in the final analysis, resting pupil diameter may not prove to be a sensitive measure of arousal level in the usual laboratory setting, as some have proposed (Lowenstein & Loewenfeld, 1958; Yoss et al., 1969; Schmidt, 1982; Pressman et al., 1984 & 1986). As these authors have reported decreases in pupil diameter with increases in sleepiness, it is difficult to understand why the untreated narcoleptic patients, with short MSLT sleep latencies, did not show this change. Perhaps the methodological shortcomings outlined in the literature review are accountable to some degree.

As most pupillary measures were unable to clearly differentiate sleepy from alert individuals, it is not surprising that each of the pupillary variables failed to further discriminate REM from NREM sleepiness. Despite our knowledge that pupillary physiology in REM sleep is quite different from that in NREM sleep (Berlucci, Moruzzi, Falir, & Strata, 1964) and that

subjective sleepiness (Broughton & Aguirre, 1987), sleep latency (Broughton & Aguirre, 1987) and event-related potential (Broughton & Aguirre, 1987; Pressman et al., 1982) measures differentiate between REM and NREM sleepiness, pupillometry appears insensitive to these states.

In order to fully clarify the potential usefulness of pupillometry for the detection and assessment of EDS in general, corrective action in a variety of areas must be taken.

Firstly, there must be standardization of dependent measures. In this study, any unelicited fluctuation in pupil diameter of .2 mm or more was considered to be a spontaneous oscillation. This amplitude criterion, however, has not been universally adopted. The quantification of pupillary instability has varied from strictly statistical measures such as the standard deviation (Hertz et al., 1988) or range (Lavie, 1979) of movement to classification on the basis of amplitude and duration (Yoss et al., 1970). If any degree of reliability across studies is to be achieved, it is critical that uniform measures be derived and agreed upon. As a corollary, it is essential that the conditions under which each variable is measured be carefully controlled and be clearly detailed. A workshop on the standardization of methodology in the pupillometric assessment of

arousal would certainly help lead to this end.

Secondly, the experimental design itself must not only control for the alerting effects of psychosensory phenomena in general, it must also minimize the many other sources of unwanted error variance.

One well known confound is that of age. Indeed, it is an undisputed fact that decreases in pupil diameter (Birren, Casperson & Botwinick, 1950), increases in pupil variability (Kumnick, 1954, 1956), and an inability to retain focus (Woodmansee, 1966) accompany aging and must therefore be controlled. As participants were matched for age and sex and the point of fixation remained constant in this study, it is unlikely that any significant age effects were present in the data (Goldwater, 1972). It should be kept in mind, however, that an age restriction of less than 30 years and placement of the stimuli at a distance of approximately 3-4 meters will decrease the liklihood of the near vision reflex which is manifested in a 10%-30% pupillary constriction response (Woodmansee, 1966).

In addition to age, consideration of time-of-day effects is also essential (Pressman & Fry, 1989). As periodic fluctuations in pupil diameter and variability are partly due to both ultradian (Lavie, 1979) and circadian (Doring & Schaefers, 1950)

influences, it is necessary to test all subjects at consistent times across the course of the day.

Another possible confounding variable is that of amount and quality of prior sleep. Although there were no effects of prior nocturnal sleep in this particular study, Pressman and Fry (1989) found the quality of prior sleep in apnea patients to be reflected in various components of the PLR. It is thus advisable to tease out potential prior sleep effects from the data, whether it be through design manipulation or by statistical means.

Although age, time of day, and prior sleep do not nearly encompass the many sources of error in pupillometry research, they do represent three important influential factors that must be regulated.

The final, and foremost recommendation, is that the validity of pupillary response as a measure of sleepiness be further assessed. As the number of spontaneous oscillations did not significantly correlate with SSS scores in either group or with MSLT latencies in the narcoleptics, nor were there any comparable autonomic indices of arousal recorded in this study, it is difficult to state with any certainty what precisely is being measured (Goldwater, 1972). It in fact remains unclear whether pupillometry primarily reflects variations in the alertness - sleepiness dimension, variations in autonomic arousal,

or something altogether different.

In order to begin to resolve this issue, it is imperative that we first attempt to clearly define the phenomenon or phenomena which we are trying to measure. Moreover, by distinguishing between differing types of "activation", we may come to understand why the various indices of sleepiness do not necessarily correlate with one another. Indeed, traditional measures of sleepiness may be each measuring different entities which may or may not be reflected in the various purported autonomic indices of arousal including core body temperature, pupillary change, electrodermal response (EDR), and heart rate (HR).

Evidence to support a multidimensional concept of activation (Broughton, 1982; in press) is given by the circadian rhythm literature wherein objective and subjective measures of sleepiness are dissociated from each other as well as from various rhythmic autonomic functions (Folkard, Hume, Minors, Waterhouse & Watson, 1985; Mistlberger & Rusak, 1989). Examples include the disparity between the circadian rhythmicity of sleep latency and both that of VAS scores (Monk, 1987) and AD-ACL scores (Clodore et al., 1986), the phase advanced peak in subjective alertness (VAS) in relation to the temperature rhythm (Monk & Leng, 1983), the correlation of the subjective arousal (VAS) rhythm with performance (Monk, 1989), which in turn is

dissociated from autonomic (oral temperature and pulse rate) rhythms (Froberg, 1977), and the spontaneous "internal desynchronization" of sleep/wake and temperature rhythms in environments lacking time cues (Wever, 1975; Dinges, 1989; Czeisler & Jewett, 1990).

As the circadian variation in some autonomic measures such as EDR and HR is very dificult to detect (Gale, Harpman & Lucas, 1972), and that for the pupil has not been sufficiently detailed, the temporal relationship of these measures to other autonomic indices of alertness remains unknown.

However, considerable evidence exists to support the notion that alertness/sleepiness and autonomic arousal are distinct phenomena which may not be universally accessed through existing measures. What is now needed is a series of comparative studies which focus on the relationship(s) of the pupil to various other autonomic indices and in turn on their associations with traditional measures of sleepiness. Given the number of individuals afflicted with the disabling symptom of EDS, continued research along this line is a very worthwhile endeavor.

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Appendix A
Patient Table

Age	Sex	SA	CA	SP	HH	EDS	PMS	AP	Med
44	F	X	X	–	–	X	NA	NA	–
42	F	X	X	X	X	X	0	.63	M/A
62	F	X	X	X	X	X	NA	NA	–
70	F	X	X	X	X	X	NA	NA	M
54	M	X	X	X	–	X	NA	NA	M/C
46	M	X	X	X	X	X	23	3.9	M/C
42	M	X	X	X	X	X	NA	NA	–
59	M	X	X	X	–	X	NA	NA	M
46	M	X	X	–	X	X	NA	NA	M
21	M	X	X	X	X	X	NA	NA	M/C

SA = Sleep attacks
CA = Cataplexy
SP = Sleep paralysis
HH = Hypnagogic hallucinations
EDS = Excessive daytime sleepiness
PMS = Periodic movements in sleep (%)
AP = Sleep apnea index (# per hour)
Med = Usual medication
M = Methylphenidate
C = Chlomipramine Hydrochloride
A = Amytripityline
NA = Not Available

Appendix B

Analysis of Ranks Summary Table SSS Ratings across Groups, Days, and Time.

Source of Variance	df	H Statistic
Group (N vs C)	1	106.32 **
Day (one vs two)	1	29.50 **
Time (0830–1830)	20	35.15 *
Group x Day	1	00.04
Group x Time	20	19.82
Day x Time	20	33.04 *
Group x Day x Time	20	10.20

* $p<.05$

** $p<.001$

Appendix C

Analysis of Ranks Summary Table for Day 2. SSS Ratings across Groups, Time, and Sessions.

Source of Variance	df	H Statistic
Group (N vs C)	1	5.35 *
Time (Pre vs Post)	1	4.27 *
Session (1 to 5)	4	5.10
Group x Time	1	3.55
Group x Session	4	1.30
Time x Session	4	2.52
Group x Time x Sess	4	1.80

* $p<.05$

Appendix D

ANOVA Summary Table
MSLT : Latency to Stage 1

Source of Variance	SS	df	MS	F Value
Group	1539.35	1	85.52	13.10 *
Session	52.23	4	13.06	13.06
Gr x Sess	54.29	4	13.57	13.57

* $p<.05$

Appendix E

ANOVA Summary Table
MSLT : Latency to Stage REM

Source of Variance	SS	df	MS	F Value
Group	1623.65	1	90.20	29.57 **
Session	96.19	4	24.05	1.78
Gr x Sess	96.19	4	24.05	1.78

** p<.001

Appendix F

ANOVA Summary Table
MSLT : Latency to Stage 2

Source of Variance	SS	df	MS	F Value
Group	2309.33	1	128.30	.08
Session	209.50	4	52.37	1.89
Gr x Sess	60.48	4	15.12	.55

Appendix G

ANOVA Summary Table
MSLT : Latency to Stage 3

Source of Variance	SS	df	MS	F Value
Group	11.41	1	.63	.04
Session	1.92	4	.48	.76
Gr x Sess	3.15	4	.79	1.24

Appendix H

ANOVA Summary Table
Dark-Adapted Pupil Diameter

Source of Variance	SS	df	MS	F Value
Group	170.31	1	9.46	.68
Session	3.45	4	.86	1.88
Gr x Sess	2.29	4	.57	1.24

Appendix I

ANOVA Summary Table
PLR : Latency to Constriction

Source of Variance	SS	df	MS	F Value
Group	27.02	1	1.50	2.22
Session	.51	4	.13	.40
Stimulus	.56	9	.06	.49
Gr x Sess	.60	4	.15	.47
Gr x Stim	1.34	9	.15	1.16
Sess x Stim	4.72	36	.13	1.07
Gr x Sess x Stim	3.99	36	.11	.90

Appendix J

ANOVA Summary Table
PLR : Extent of Constriction

Source of Variance	SS	df	MS	F Value
Group	192.81	1	10.71	.19
Session	1.23	4	.31	.58
Stimulus	.69	9	.08	.54
Gr x Sess	1.31	4	.33	.62
Gr x Stim	1.52	9	.17	1.18
Sess x Stim	6.12	36	.17	1.28
Gr x Sess x Stim	4.56	36	.13	.95

Appendix K

ANOVA Summary Table
PLR : Rate of Constriction

Source of Variance	SS	df	MS	F Value
Group	190.54	1	10.59	.17
Session	2.14	4	.54	.66
Stimulus	1.38	9	.15	.93
Gr x Sess	1.48	4	.37	.46
Gr x Stim	1.54	9	.17	1.04
Sess x Stim	6.21	36	.17	1.02
Gr x Sess x Stim	6.25	36	.17	1.03

Appendix L

ANOVA Summary Table
PLR: Constriction Velocity

Source of Variance	SS	df	MS	F Value
Group	18.78	1	1.04	.84
Session	.46	4	.12	.78
Gr x Sess	1.26	4	.31	2.13

Appendix M

ANOVA Summary Table
PLR : Maximum Redilated Diameter

Source of Variance	SS	df	MS	F Value
Group	1685.21	1	93.62	.17
Session	22.77	4	5.69	1.14
Stimulus	8.93	9	.99	3.16 *@
Gr x Sess	5.35	4	1.34	.27
Gr x Stim	1.11	9	.12	.39
Sess x Stim	24.32	36	.68	1.74
Gr x Sess x Stim	12.49	36	.35	.89

* $p<.05$
@ Geisser-Greenhouse $F(4, 70) = 3.16$, $p = .02$

Appendix N

ANOVA Summary Table
PLR : Rate of Redilation

Source of Variance	SS	df	MS	F Value
Group	12.25	1	.68	.35
Session	.52	4	.13	1.76
Stimulus	.11	9	.01	.89
Gr x Sess	.07	4	.02	.24
Gr x Stim	.10	9	.01	.84
Sess x Stim	.61	36	.02	.95
Gr x Sess x Stim	.61	36	.02	.94

Appendix O

ANOVA Summary Table
PLR: Redilation Velocity

Source of Variance	SS	df	MS	F Value
Group	2.27	1	.13	.67
Session	.14	4	.04	2.19
Gr x Sess	.04	4	.01	.55

Appendix P

ANOVA Summary Table
Pupillary Orienting Response to Tones

Source of Variance	SS	df	MS	F Value
Group	15.79	1	.88	1.13
Session	.54	4	.13	.66
Stimulus	8.11	10	.81	3.99 **@
Gr x Sess	.10	4	.02	.12
Gr x Stim	2.43	10	.24	1.20
Sess x Stim	5.19	40	.13	.62
Gr x Sess x Stim	5.63	40	.14	.68

** $p<.001$
@ Geisser-Greenhouse $F(5, 93) = 3.99$, $p = .002$.

Appendix Q

Analysis of Ranks Summary Table
Frequency of Spontaneous Oscillations

Source of Variance	df	H Statistic
Group (N vs C)	1	21.27 **
Session (1 to 5)	1	1.10
Group x Session	4	1.97

** $p<.001$

Appendix R

t-test Summary Table
REM vs NREM Sleepiness

Pupillary Variables	t	2-tailed Prob.
Baseline diameter	.47	.64
Latency to constrict	.11	.91
Extent of constriction	-.12	.91
Rate of constriction	.18	.86
Maximum redilation	.58	.57
Rate of redilation	1.03	.31
Pupillary OR to tones	.09	.93
Spontaneous oscillations	-.24	.81