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PSYCHOPHYSIOLOGICAL MEASURES OF EXCESSIVE DAYTIME SLEEPINESS (EDS) IN SLEEP APNEICS, NORMALS AND SLEEP DEPRIVED NORMALS

City University of New York PH.D. 1986

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PSYCHOPHYSIOLOGICAL MEASURES OF EXCESSIVE DAYTIME SLEEPINESS (EDS) IN SLEEP APNEICS, NORMALS AND SLEEP DEPRIVED NORMALS.

by

Gila Hertz

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Abstract

PSYCHOPHYSIOLOGICAL MEASURES OF EXCESSIVE DAYTIME SLEEPINESS (EDS) IN PATIENTS WITH SLEEP APNEA, IN NORMALS, AND IN SLEEP DEPRIVED NORMALS.

by

Gila Hertz

Advisor: Professor Gad Hakerem

Excessive Daytime Sleepiness (EDS) is a condition of being persistently sleepy during the day, having a tendency to fall asleep at almost any time during the waking state. EDS is a major symptom in patients with sleep apnea and the most disabling one. Daytime sleepiness is also experienced by healthy individuals who underwent experimental sleep deprivation. Monitoring the pupil behavior (pupillometry) and measuring the tendency to fall asleep (MSLT) in sleepy individuals, were found to be effective tools in evaluating sleepiness in normals and in patients with other disorders of sleepiness. The present study was designed to use pupillometry in conjunction with MSLT to assess sleepiness in apnea patients, and to determine whether these tools are useful in differentiating EDS in sleep apnea from the sleepiness experienced by sleep deprived normals.

Pupil signs of sleepiness were measured in 10 untreated apnea patients and were compared to the pupillary behavior of age matched normal controls. The control group was tested twice: once following adequate night's sleep, and once following sleep deprivation night. The protocol,

which was the same for all subjects, involved the recording of pupil size in darkness for two minutes , followed by the presentation of 15 low intensity, short duration light stimuli. This procedure was repeated just prior and immediately following 4 MSLT trials ,at 10:00 , 12:00, 14:00 and 16:00. On each MSLT trial, subjects were allowed to sleep for 10 minutes or to stay in bed for 20 minutes. In addition , the subjects filled out the Stanford Sleepiness Scale (SSS) eight times during the day before and after napping.

Results showed that the sleep deprived normals were significantly sleepier than apneics on the SSS and on the latencies to sleep stages 1 and 2. Pupil variability, was significantly greater in the two "sleepy" groups compared to the well rested nomals, indicating that the instability in pupillary size is a general measure of sleepiness. The apneics, however, had a significantly less extensive light reflex, and a slower pupillary contraction in response to light compared to the two normal groups. Suprisingly, though, the reflex in apneics recovered to almost normal shape following napping. Such recovery combined with the MSLT and SSS findings, indicated that it is likely that the apnea patients demonstrated an adaptation to their situation of chronically having a disrupted sleep.

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REVIEW OF LITERATURE

Excessive Daytime Sleepiness

Definition

Excessive daytime sleepiness (EDS) is the main symptom of a group of functional and organic conditions collectively called the Disorders of Excessive Somnolence (DOES), which is directly related to an increase in sleep behavior (Association of Sleep Disorders Centers, 1979). The definition is based on the notion that sleepiness is a physiological drive state produced by sleep loss (Dement, 1978). This condition of being persistently sleepy during the day , and the tendency to fall asleep quickly in the waking state, should be distinguished from physical tiredness or loss of mental alertness without an increase in sleep behavior. Among the conditions which are characterized by EDS are transient disruption of the sleep-wake cycle such as in the case of experimental sleep deprivation or in a response to a recent traumatic event. Other variables have been implicated in affecting daytime sleepiness: sleep fragmentation, circadian rhythms, CNS pathology and the use of drugs and alchohol (Roth, Roehr, & Zorick , 1982). The majority of patients, however, who experience EDS are those who suffer from sleep related disorders, such as narcolepsy and sleep apnea. Most often these patients, not being aware of their pathological sleep , confuse the condition with being overtired or fatigued. Consequently, they are being treated wrongly for other conditions such as hypoglycemia . In other cases they simply avoid seeking medical advice

untill after their quality of life deteriorates markedly.

Undiagnosed sleepiness is very often associated with being labeled as lazy or unmotivated. Without treatment EDS can cause poor performance both in the professional as well in the social aspects of life due to an inability to remain functionally alert. In children, EDS disorders are even more often misunderstood because in many cases sleeping too much is not considered a problem. (Guilleminault, 1978).

Sleep Deprivation

Most people experience sleep loss to some degree during their life, and the subjective complaints of fatigue, irritability, sensations of heaviness of eyelids and burning of the eyes is familiar after sleep loss of one or two nights. A common approach to evaluate waking performance and sleepiness has been a controlled sleep deprivation based on the drive reduction definition of sleepiness. Experimental data on sleep deprivation have shown that both total and partial sleep deprivation cause decreased daytime functioning (Webb et al 1972).

Total sleep deprivation. - in this type of study subjects are being kept awake for controlled periods of time. Psychological effects of sleep loss for several days involves subjective sensation of headaches, fatigue , irritation and an inability to concentrate (Lubin,1967). Objective psychological tests , however, have been less consistent. Confounding variables such as motivation and the atmosphere of experimental situation make these tests difficult to interpret, especially those that involve

personality changes. Performance is also confounded with time variables i.e., circadian rhythm (Lubin, 1967). Certain perfoemance tests were found to be sensitive indices of the effects of one night's loss of sleep, depending upon a number of properties such as the duration of the test and its level of complexion (Wilkinson, 1965). Among those tests the one hour vigilance test was reported as the most sensitive index of sleep loss. The performance on this test was significantly impaired by the loss of one night's total sleep deprivation (Wilkinson, 1970; Glenville , Broughton, Wing and Wilkinson, 1978).

Neurologically, short term sleep deprivation has resulted in hand tremor, neck flexion, visual discomfort which may progress to visual hallucinations and an increase in vulnerability to pain (Sassin, 1970). Slurring of speech, disorientation in time, and immediate memory loss have also been reported (Kollar, Namerow, Pasnau, & Naitho, 1968).

Polygraphic signs of sleep deprivation have indicated a slight decrease in alpha rhythm in the EEG, which has been explained as a lowered level of arousal (Luce & Segal, 1969). Other studies reported that sleep deprivation increased seizure susceptibility by enhancing spontaneous sleep abnormalities associated with seizure disorder. Brain wave tracing have shown abnormalities after 24-48 hours of sleeplessness, which resemble minor seizures (Luce & Segal, 1969; Shouse & Sterman ,1982). In general, though, most studies support the hypothesis that the behavioral, physiological and autonomic signs of total sleep deprivation indicate a

general decrease in arousal rather than a change of a specific state of consciousness.

Selective sleep deprivation. - Selective sleep deprivation refers to depriving a subject of a sleep stage instead of total sleep. This can be done by monitoring the sleep record and arousing the subject whenever the polygraph indicates that he is entering that stage. REM sleep deprivation has been studied extensively. (Dement, 1960). Upon recovery from selective stage REM deprivation, the subject will revert to an excessive amount of that sleep stage . In addition, when a subject is REM deprived for several nights , more and more times are required to arouse him. These two phenomena are the result of an hypothetical REM pressure. (Dement, 1960). There is no evidence of psychological abnormalities following REM deprivation . In fact , it has been suggested that REM deprivation may be beneficial for depressed patients (Vogel, Traub, Ben Horin, & Meyers, 1968).

Chronic sleep reduction. Partial sleep deprivation studies have shown a decrement in performance which was dependent on the amount of sleep loss. An impaired performance has been noticed in response to as little as two hours of sleep loss (Roth et al., 1982). Two hours of nocturnal sleep loss in children have also been found to decrease the latency to sleep during the day measured by MSLT (Carskadon , 1981). However, the study of the effects of chronic sleep reduction, of more than one hour less sleep per day, on daytime sleepiness revealed that there were no major

difficulties during the day, except for some initial tiredness which subsided after a couple of weeks. There was, however, a significant decline in sleep onset latency (Webb et al, 1974; Horne & Wilkinson, 1985).

Excessive Daytime Sleepiness And Sleep Apnea

A sleep induced apnea syndrome is diagnosed if during nocturnal sleep of 6-7 hours at least 30 episodes of cessation of air flow are observed. (Guilleminault, 1978). A few apneic episodes of short duration (less than 10 seconds), are common during the course of the night in a normal population. In apnea patients, however, apneic episodes are prolonged and closely follow one another. Towards the end of each episode EEG signs of arousal, such as K-complex, alpha activity or merely a change to a lighter sleep stage are seen in the record. Full awakening does not always happen, although it occurs periodically throughout the night. In most cases the patient is not aware of his breathing difficulties or the body movements which accompany each episode.

Three types of apneas have been described: a central apnea is defined as the cessation of airflow at the level of nose and mouth, accompanied by the absence of abdominal and thoracic respiratory movements. In obstructive or upper airway apnea there is no airflow in spite of respiratory efforts measured at the abdominal and thoracic level. In a mixed apnea the lack of airflow is followed by later respiratory effort (Guilleminault, 1978).

Excessive daytime sleepiness (EDS) is the most common and the most

disabling symptom associated with sleep apnea. Sleepiness is prolonged and persistent throughout the day compared to the short "sleep attacks" experienced by narcoleptics patients. In addition, naps are not refreshing and are accompanied by postnap fogginess .

The subjective measurement of EDS in sleep apnea presents a special problem because of the patient being too sleepy for an accurate estimation, or because of his tendency to deny his sleepiness (Dement, 1978). Objective measures of sleepiness, such as the Multiple Sleep Latency Test (MSLT), were less affected by subject variables. Sleep latency measured by MSLT was shorter in sleep apneics compared to normals. (Roth, 1980).

The cause of the severe sleepiness found in apneics is unclear, but several possibilities have been suggested: CNS involvement has been implicated because of the dependency of the respiratory responses to different inputs on the state of the brain, namely the sleep-wake cycle (Cherniack, 1981). Although sleep related respiratory problems often occur secondary to different neuropathologies, there is no direct evidnece for CNS dysfunction in sleep apnea which could be responsible for the excessive daytime sleepiness. Nocturnal sleep disruption has also been implicated as the cause for daytime sleepiness. The fact that sleep apneics do not experience actual sleep loss but rather suffer from a continuous sleep disruption led to a study of the effects of sleep fragmentation on waking functioning. Roth , Hartse, Zorick, and Conway

(1980), reported that polygraphic measures of daytime sleepiness are highly correlated with nocturnal sleep disruption. They found that the number of respiratory related arousals was the best predictor of daytime sleepiness measured by sleep latency (MSLT). In a recent study by the same group, the relation between sleep fragmentation and daytime sleepiness was studied more systematically (Stepanski, Lamphere, Badia, Zorick, & Roth, 1984). In this study it was found that the number of arousals ,as well as the type of arousals during nocturnal sleep, are important factors in daytime sleepiness in these patients. These authors classified the arousals into four categories according to the level of sleep disruption. Level 1 indicated the least amount of measurable sleep disruption while level 4 indicated the most , namely an awakening from sleep for a period of 30 seconds or more.

Lower level arousals, with the least disruption to sleep , best predicted the daytime sleepiness index in apneics. This rather unexpected finding was explained by a possible increase in the arousal threshold in these patients. Similarly, in sleep deprived subjects, it was reported that the sleepier the subject was, namly deprived for longer period of time, the more intense stimulus was required to aroue him (Hartse, Roth, & Zorick , 1981). Stepanski et al (1984), concluded that the sleepiness of apnea patients , was directly related to the partial but chronic sleep deprivation due to the frequent sleep fragmentation .

Regulation of Sleep and Arousal

Passive vs Active Regulation of Sleep

The passive theory of sleep argued that the brain is normally inactive and sensory stimulation is needed to keep the brain awake. This theory gained its support from the experiments of Bremer (1935), who recorded EEG signs following transections at different levels of the brain.

Bremer found that if the midbrain of a cat is sectioned at the intercullicular level ("cereveau isole") below the third nerve nucleus, an EEG record showed high amplitude slow waves indicating sleep. A lower transection at the first cervical segment of the spinal cord ("encephale isole") produced EEG signs of wakefulness. Bremer (1937) believed that the first transection eliminated adaquate sensory stimulation necessary to maintain wakefulness, while in the lower transection the sources for sensory stimulation are intact and therefore responsible for retaining EEG signs of wakefulness.

The passive view of sleep was further supported by the discovery by Moruzzi and Magoun (1949) of the reticular activating system. They observed that electrical stimulation of the reticular activating system caused an EEG desynchronization of a sleeping cat. The reticular formation was believed to be the mechanism which causes an activation of the cerebrum when stimulated.

The passive view of sleep has been challenged by a series of studies utilizing electrical stimulation to specific brain regions, and selective

lesions. In a study by Batini, Moruzzi, Palestini, Rossi, and Zanchetti (1958), lesions in the midpontine region resulted in alternate signs of sleep and waking, although the animals had the same sensory input as the "cerevea isole" preparation in Bremer's experiments. Thus, it appeared that the brain's signs of wakefulness did not depend on sensory input and Bremer's conclusion was wrong. In later experiments, Clemente, Sterman, & Wyrwick (1963) reported that stimulation of areas in the pre optic basal forebrain produced synchrony of EEG similar to that seen in sleep.

Similar results were reported when the nonspecific nuclei of the thalamus were stimulated (Hess,1944) . Finally, the discovery of Rapid Eye Movement (REM) sleep as an "active" state (Aserinsky & Kleitman, 1955) which was different from slow wave sleep state further supported the need to search for centers controlling sleep and waking.

The main proponent of the active theory of sleep was Jouvet (1972), who suggested a neurochemical control mechanism to explain the REM-NREM cycle. Jouvet focused on mechanisms responsible for producing sleep and not simply the inhibition of the waking state. Specifically, he asserted that the serotoninergic neurons of the Raphe system are involved in NREM sleep and the noradrenergic neurons of the locus coeruleus control REM sleep and that these two systems are interelated. A different region of the brain stem , the nucleus of the solitary tract, was implicated in producing sleep signs (Magnes, Moruzzi, & Popeiano, 1961). Stimulation with low frequency current had a synchronizing effect on the EEG. Sites

such as basal forebrain, raphe nuclei, thalamus and reticular formations were all reported to exhibit unit discharge changes which were selective for either NREM or REM sleep.

In the mid 1970's, studies utilizing electrical recording from cells in the brain stem have shown that cholinergic neurons of the nucleus gigantocellular tegmental field (FTG) in the pons are the executive mechanism that initiates REM sleep. (McCarley & Hobson ,1975). These researchers found a reciprocal arrangement between the firing of the FTG cells and the neurons of locus coeruleus. These two mechanisms alternately become active and result in an alternate production of REM and NREM sleep. The Raphe system ,according to this theory , is responsible for suppressing the FTG cells during waking. The exact location of REM neurons was disputed among researchers especially on the grounds that most features of REM sleep persisted after lesions of the so-called Executive REM neurons. There is agreement, though, that the lower brain stem is sufficient for REM sleep control. Recently, the same group demonstrated that the enhancement of REM sleep signs by microinjection of cholinergic agonists was found in specific sites in the pons. The percentage and latency to onset of REM sleep were dependent upon the site of the injection. (Baghdoyan, McCarley, & Hobson, 1985). They implied that during REM sleep under physiological conditions, functional organization of these neural sites enables the production of the coordination of REM sleep.

Arousal Theory

The classical activation theory.

The main source of data demonstrating the physiological basis of sleepiness and arousal was brain wave activity (EEG). The discovery by Moruzzi and Magoun (1949) that the stimulation of the brain stem reticular formation produces cortical arousal, was the basis of the activation theory. It was established that the presence of large amplitude slow wave activity is prominent in the cortex during sleep and coma, while low voltage fast activity is a correlate of waking arousal,alertnesss and cosciousness .

According to the classical theory of activation, an increased excitation of brain stem reticular formation leads to an increased excitation in the nonspecific nuclei of the thalamus which causes in turn the excitation of cortical neurons and wakefulness. Lindsley (1952), who helped to advance this concept, speculated about a continuum of psychological phenomena which correspond to a similar continuum in EEG. According to this hypothesis, there is a wide range of patterns and EEG frequencies observed during the stages from drowsiness to excited emotion in a normal person. Lindsley also made a distinction between alpha rhythm and alpha activity. The former represents an optimal synchronization of electrical activity of cortical elements. A breaking up or disappearance of the alpha rhythm represents a desynchronization of neural activity. Alpha activity may still exist as one of these activities in the absence of alpha

rhythm (Lindsley, 1956).

The main point in regard to the activation theory was that arousal occurs in a continuum from a low point during sleep to a high point during a great effort or excitement. Evidence for this contention has been presented for autonomic measures such as skin conductance and muscle tension (Duffy,1962; Malmo, 1959). These authors further assumed that the unidimensional mechanism which controls behavioral arousal is expressed in aspects of intensity.

The multidimension theory of activation.

The concept of ascending reticular activating system has been criticized as being the sole activating mechanism. Lacy (1967) pointed out the studies which had resulted in very low correlations among autonomic and electroencephalographic variables. A dissociation has also been found among autonomic variables themselves. Lacy suggested that electrocortical arousal, autonomic arousal and behavioral arousal may be considered different forms of arousal.

Anatomically, it has been shown that brain areas outside the reticular formation participate in the activating response , i.e, the hippocampus and other limbic structures (Vanderwolf, 1969).

Behaviorally, the arousal theory of vigilance postulated that the performance decrement found in vigilance tasks results from a progressive reduction in arousal over time. It has been shown ,however, that physiological arousal declines in almost any situation of prolonged

testing not necessarily those situations involving vigilance tasks.

Many psychophysiological measures have been employed to correlate behavior with physiological arousal. It became evident that in different behavioral situations there was a dissociation of the indicators of arousal. Vanderwolf and Robinson (1981) reviewed the evidence which showed that the reticulocortical pathways, involved in cortical and hippocampal arousal, actually consist of two distinct subsystems which correspond to two different types of behavior. Dissociation of somatic and behavioral arousal could be produced pharmacologically. In the atropinized cat, EEG waves similar to those seen in sleep appear in the record even though behaviorally the cat is awake . On the other hand , cholinergic agents such as eserine produce EEG activation without waking up the animal (Longo, 1971). The discovery of REM sleep constituted the major evidence proving that although this state is characterized by cortical activation , behaviorally the animal is sound asleep , and in many cases arousal threshold is highest in this state. Furthermore, decorticated cats retained signs of quiet sleep as well as signs of active (REM) sleep, suggesting that cortical activity is irrelevant to the main phenomena of sleep (Villablanca & Marcus, 1972).

Autonomic Correlates of Sleep and Arousal

During sleep many changes in autonomic phenomena are consistent with the overall lowered activity of bodily function. There are, however, differences in the autonomic phenomena during REM and NREM sleep. During

NREM sleep there is an increase in the parasympathetic activity combined with a slight decrease in tonic sympathetic activity. This is reflected in a slower, shallower respiration, slowing of the heart, pupil miosis and an increase in skin resistance (Oswald, 1962). Other measures, such as gastric motility, change according to ultradian rhythm almost independent of sleep cycle. During REM sleep, the main autonomic change is a decrease in tonic sympathetic activity. Thus, the pupil becomes more constricted and there is a decrease in sympathetic vasoconstriction outflow and tonic sweating. Other variables show an increase in variability: respiratory rate and amplitude are irregular, as well as muscle twiches indicating phasic increase of muscle tone which is tonically depressed. This variability is caused by phasic changes due to randomly increased sympathetic activity or phasic decrease in parasympathetic activity (Parmeggiani, 1985). According to Permeggiani, autonomic phenomena during REM sleep are less precisely regulated due to the release of brain stem integrative mechanisms from hypothalamic regulatory influences. On the other hand, autonomic phenomena during NREM sleep are "the result of closed loop operations preserving homoestasis at a lower level of energy expenditure than during wakefulness" (pp. 389). Berlucci, Moruzzi, Salvi and Strata (1964) found that in the sleeping cat pupillary constricrion was frequently interrupted by rapid dialtion. These dilations occurred in association with phasic rapid eye movements.

Autonomic correlates of sleepiness.

The autonomic manifestations of sleepiness, or fatigue, are the result of a shift in the autonomic nervous system equilibrium which occurs from moment to moment due to disorganization of corticodiencephalic activity (Lowenstein, Feinberg & Loewenfeld, 1963). The changes which occur during fatigue involve almost every somatic and physiological function in an oscillatory fashion between sleep and wakefulness. Because of the dynamic characteristics of these changes autonomic phenomena are difficult to monitor.

Specifically, Lowenstein and Loewenfeld (1963) describe the pupil as a unique organ which could accurately reflect the momentary imbalance of the autonomic nervous system. Sleep loss was also found to increase heart rate and respiration (Kleitman,1923), to increase GSR (Malmo, 1958) but to decrease palmar sweating and frontalis muscle tension (Ax & Luby, 1961).

Autonomic dysfunction in patients with primary disorders of sleep.

There is some evidence of autonomic abnormalities in patients with primary sleep disorders. In a recent study, patients with sleep apnea, narcolepsy and idiopathic hypersomnolence showed frequent cardiac abnormality and high adrenergic tone, measured by 24 hours of urinary epinephrine and norepinephrine excretion. (Boudoulas et al. 1983).
Cardiac abnormality was greater in sleep apnea than in patients with narcolepsy or hypersomnia. However, this could be explained by the fact

that apnea patients were significantly older and much more obese compared to the other groups. The high adrenergic tone which was found in this study contradicts the notion of catecholeamines involvement in cortical arousal. It is possible that high adrenergic tone in these patients reflects the stressful condition of being continuously sleep disrupted.

In an earlier study, narcolepsy was associated with attenuation of some cardiovascular reflexes (Sachs & Kaijser, 1982). In this study, patients with sleep apnea showed greater autonomic variability compared to narcolepsy, suggesting a more heterogeneous group.

Current Views of the Regulation of Sleep and Arousal

In summary, it appears that although there is some strong evidence supporting the existence of certain areas in the brain which control sleep and waking, the picture is not complete . Since we still do not know the function of sleep there is no information to determine whether sleepiness is caused by a dysfunction in the mechanisms that produce sleep (as a result of an impaired sleep) or, by a dysfunction in the arousal mechanisms which maintain wakefulness.

The current view of sleep and arousal does not percieve NREM sleep, REM sleep and wakefulness as three unitary states controlled by specific executive centers. Rather, there is more and more evidence supporting the existence of different mechanisms which temporarily coincide to control various phenomena in a specific state. REM state of sleep , for example, consists of a cluster of phenomena such as desynchronization signs of the

EEG, atonia of the skeletal muscles, theta ryhthm within the hippocampus, rapid eye movements, irregularity of breathing and phasic muscle twitches. There is accumulating evidence indicating that each of these phenomena is controlled by a separate brain stem mechanism (Vertes, 1984). Jouvet (1962) showed that caudal pontine transection abolished REM atonia without changing other signs of REM sleep. The specific area responsible for muscle atonia was recently found as the ventral area to locus coeruleus (Morrison, 1979). Other events of REM sleep were also studied in detail and it was found that EEG desynchronization is generated by midbrain reticular formation (Robert & Steriade, 1981), and rapid eye movements by an area anterior to the abducens nucleus (Siegel & Tomaszewski, 1983) . Sleep spindles which characterize stage 2 of NREM sleep could be eliminated by lesions to ventrobasal and ventrolateral complex of the thalamus while the EEG rhythm of stage 2 remains intact (Steriade, 1981). These lines of evidence support the existence of specific control mechanisms of sleep events, but the fact that somatic, autonomic and behavioral events show changes in activity during sleep states also implies the integrated activity of these systems in the transition from state to state.

A recent attempt to organize sleep events into an operational model proposed the nonspecific thalamus, in particular the intralaminar nuclei, as a "center" which coordinates sleep as well as vigilance events (Koella,1985). This hypothetical "central coordinating component" includes

wake and sleep programs with two subprograms for REM and NREM sleep, and many hypothetical connections between various subcomponents.

The use of EEG in analyzing sleep phenomena is helpful because it provides an ordinal classification of the events of sleep. It is clear , however,from the variety and the complexity of the events which take place in sleep and wakefulness that other physiological dimensions such as autonomic or somatic events of sleep should be systematically studied. Since sleep states are influenced by a general decrease in CNS activation and arousal, in turn, is influenced by almost any physiological phenomenon, it is important to identify those variables which are correlated with sleep states and distinguish them from those variables which are directly involved in causing state changes.

Indices of sleepiness and activation

Electroencephalography (EEG)

Electroencephalography (EEG), refers to the measurement of changes in electrical potentials in the brain which are detected by electrodes attached to various locations on the scalp. In general, the EEG of sleep is different from that of wakefulness. In wakefulness the record is made up of fast frequencies low voltage , while that of sleep is of high voltage slow frequencies waves. Investigation of EEG during various kinds of mental activity helped to develop the concept of physiological arousal . The electrical activity of the cortex when a subject is awake and relaxes is characterized by a synchronized wave form at a frequency of 8-10 cps known as alpha rhythm. The most commonly observed EEG correlate of alertness is desynchronization of the alpha rhythm with the production of "blocking" response or reduced amplitude.

EEG and sleep stages.

The changes which take place in EEG from the waking to the sleep state were first described by Loomis, Harvey and Hobart (1935). Loomis et al. (1937), proposed a classification of the EEG to stages A to E according to the increasing of sleep depth. Stage A is the stage of drowsiness when some alpha rhythm is still present. As the person falls asleep alpha rhythm slowly disappears. EEG of stage B consists of low voltage 4-6 cps waves and indicates light sleep. In stage C, sleep is deeper and the EEG signa are accompanied by K-complex (biphasic wave form), and spindles

wave forms at frequency of 12-15 cps. Stages D and E indicate deep sleep and are characterized by slow, high amplitude delta waves .

The discovery of Rapid Eye Movements (REM) sleep (Aserinsky & Kleitman, 1953), pointed out to the fact that the transition to sleep is not a continuous process of sleep stages but rather consists of two different states: REM and Non-REM (NREM) sleep. Thus, the changes which occur across the night reflect 4-5 cycles of NREM sleep which last about 90-110 minutes and followed by REM state . NREM sleep consists of 4 stages beginning with stage 1 of light sleep, through stage 2 which is characterized by K-comlexes and spindles and finally stages 3 and 4, during which delta waves occupy the major part of the record (Rechtschaffen & Kales, 1968)

EEG and the Measurement of Daytime Sleepiness: The Multiple Sleep Latency Test (MSLT)

The multiple Sleep Latency Test (MSLT) is a useful technique for the measurement of sleepiness by directly measuring the EEG signs accompaning sleepiness. In this test a subject is being given 4 or 5 opportunities to fall asleep during the day and his sleep is polygraphically recorded. Sleep latency or the time in minutes to sleep onset is measured as the first of three consectutive epochs of stage 1, or the first to any other stages (Richardson et al., 1978). An important advantage of this technique is the accuracy in which sleep onset can be detected. Another advantage of the technique is the detection of abnormality in sleep signs ,such as the extremely short REM latency observed in narcoleptics. The

technique has been used in a variety of conditions which involve sleepiness. In measuring pathological sleepiness, 5 minutes to sleep onset is considered abnormal (Richardson et al., 1978). In testing sleepiness in apnea patients compared to normal controls, the patients had an average of 2.6 min latency to stage 1 compared to 12.9 min of normal controls (Roth et al., 1980).

The Use of Pupillography in the Measurement of Sleepiness

Pupil stability.

The observation that the pupil diameter decreases in size when a person is tired and increases when he is awake and alert initiated the study of pupillometry as a tool to measure fatigue . In an initial pupillometry study of fatigue and arousal , Lowenstein and Loewenfeld (1951) observed that the pupil may remain stable for a long period of time if a person is alert, but become unstable with spontaneous waves of dilation and contraction when the person becomes tired. The more the subject is fatigued the deeper and more frequent these waves become. Pupil size is determined by the reciprocal association of sympathetic innervation responsible for pupil dilation and parasympathetic pathways responsible for pupil constriction . Thus, in a fatigued subject the system oscillate between wakefulness and sleep or waves of arousal (dilation) and sleepiness (contraction).

The difference between pupillary movements during acute and chronic fatigue was studied by Lowenstein, Feinberg and Loewenfeld (1963). Two main types of oscillations were observed in the pupil of normal healthy

but tired subjects: slow waves of dilations and contractions measuring up to .5 mm, and fast inextensive oscillations of .1 to .3 mm. Subjects who were chronically fatigued, but with no neurological deficits, also showed these two types of pupillary movements. However, these signs appeared earlier , in an exaggerated manner, and were removed by rest. In patients with chronic fatigue due to organic dysfunction, pupil fluctuations were even more marked and occurred in less than two minutes. They were caused without apparent previous effort or activity, and were not reversed by rest. In general, Lowenstein et al (1963) concluded, that the difference between acute sleepiness, chronic physiological sleepiness, and chronic pathological sleepiness is a quantitative rather than a qualitative one.

Pupil instability was reported in patients with primary sleep disorders. Yoss, Moyer and Ogle (1969) described narcoleptics patients as having smaller and unstable pupils with frequent alterations in size due to waves of pupillary constriction and dialation. In a recent study, Schmidt (1982) measured pupil instability in narcoleptics and in a group of patients of other disorders of excessive somnolence (DOES). He compared the two groups on the number of oscillations in pupil size which exceeded .5 millimeter. A decrease in the number of oscillations was observed after a 5 minutes' recording in the narcoleptics group. The DOES group, however, had a progressive increase in the number of oscillations. Schmidt (1982) explained this observation as a decreasing ability to "correct lapses in sympathetic (arousal) tone" (pp. 163), or to oscillate, which characterizes the severity of sleepiness in the narcoleptics group.

The increase with time of the number of oscillations in the DOES group indicated their ability to correct such lapses. Although sleep apnea patients were included in the DOES group in this study, they did not make an homogeneous sleep apnea group.

Pupil instability, defined as standard deviation of 900 data points collected for 90 seconds, was measured for narcoleptics and control normals (Connolly, 1984). In this study, pupil measures were taken before and immediately following MSLT trials. There was no significant difference between the two groups before naps indicating similar stability of the pupil. After naps , however, the normal subjects showed a decrease in standard deviation even though they spent most of the nap time resting instead of sleeping. The narcoleptics did not have a decrease in standard deviation indicating an inability of their pupil to recover after napping.

Light reflex.

The normal integrated pupillary reflex to light stimuli depends on an intact parasympathetic reflex arc (which includes retinal afferent impulses transmitted to the Edinger Westphal (EW) nucleus and back to the iris sphincter), as well as several inhibitory mechanisms which modulate the E.W. nucleus' output (Zinn, 1972).

The light reflex of a normal subject consists of two movements: contraction and redialation. The contraction movement consists of two phases: a fast primary phase caused by parasympathetic activity and a slower secondary phase due to sympathetic inhibition. Similarly, the

redialation phase consists of primary fast recovery due to parasympathetic relaxation and a secondary weaker dialation caused by sympathetic antagonism (Lowenstein & Loewenfeld, 1952).

In an early study, Lowenstein and Loewenfeld (1951) observed in normal subjects that upon repetition of light stimuli, the reflex shape deteriorates reflecting a gradual process of fatigue. The authors explained this deterioration as the result of disintegration of the central mechanisms which control the light reflex. Specifically, different shapes of light reflex corresponded to the site of weakness in the control mechanisms. The four major types of reflex shapes described by Lowenstien and Lowenfeld (1952) for normal subjects are:

a. normal reflex - a well integrated shape in which parasympathetic and sympathetic systems are well balanced.
b. W and V reflex shapes- which appear when weak sympathetic stimulation interferes with weak parasympathetic reflexes. This type of response is caused by disintegration at the cortical level.
c. Tonohaptic, a square shape- caused by sympathetic weakness. This response involves disintegration in the posterior hypothalamus level.
d. Sluggish, inextensive shape- a further weakening of both sympathetic and parasympathetic systems results in a sluggish, response until the response is completely eliminated.

Parasympathetic weakness caused by interruption to the pretectal area, third nerve nucleus or ciliary ganglion also results in an inextensive and sluggish reflex shape with low and delayed contraction and recovery. All

these changes occur in normal subjects who were given high intensity light stimuli. The changes are temporary and reversible as soon as stimulation occurs or following a rest period. Accordingly, Lowenstein and Loewenfeld (1964) termed these changes as "physiological fatigue" in contrast with "pathological fatigue" which is permanent and irreversible following a rest period.

Abnormal reactivity of the pupil to light has been found in schizophrenic patients. They had a significantly smaller extent of contraction, although their pupil diameter was normal. (Hakerem, Sutton & Zubin , 1963; Lee & Knopp ,1968). The characteristics of the pupil in these patients indicated a deficient inhibition on the Edinger Westphal (EW) nucleus which was evident in the faster contraction time in schizophrenics. This has led to the hypothesis that there is an uncoupling of the subcortical inhibitory systems which exert their effects on the EW nucleus (Knopp & Hakerem,1973).

Pupillary reactivity to light in patients with primary sleep disorders was not extensively studied. In patients with narcolepsy, the pupillary response to light was reported normal although their pupillary instability was documented (Yoss, Moyer & Ogle, 1969). In another study , however, narcoleptics had abnormal reaction to low intensity light stimuli ranging from very low to absent (Schmidt, 1982). The patients in the latter study had small and unstable pupils reflecting a shift toward parasympathetic predominance, while at the same time these patients showed minimal response to light indicating heightened inhibition of thr EW nucleus.

Schmidt (1982) explained these paradoxical results by postulating an uncoupling of the mechanisms which exert their effects on EW nucleus similarly to those postulated in schizophrenics. Specifically, Schmidt suggested "an uncoupling of cortical (sympathetic) stimulating influences as well as an uncoupling, or out of phase activity, of the two subcortical supranuclear inhibitory modulators" (pp.134).

In patients with other Disorders of Excessive Daytime Sleepiness (DOES), their response to light stimuli was reported as normal. Patients with chronic insomnia showed a reflex response slope which was very steep , and was correlated with the complaint of sleepiness. Normal subjects were also reported to have typical V and W reflex shapes with increased sleepiness (Schmidt & Fortin, 1984)

Quantification of Self Estimation of Sleepiness.- Stanford Sleepiness Scale (SSS)

One of the methods of quantifying the intensity of sleepiness is the Stanford Sleepiness Scale (SSS). The subject himself is asked to determine his degree of sleepiness by selecting a score ranging from one to seven. The subject is told that score 1 refers to being very alert and energetic, while scores 7 indicates that the person is actually sleeping. (Hoddes, Zarcone, Smythe, Phillips & Dement ,1973).

The validity of this scale was reported to be high in normal subjects, and was found to be sensitive to as little as 2 hours of sleep loss, when rating were made every 15 minutes during the day. (Hoddes et al 1973). SSS

scores in normal subjects were also highly correlated with sleep latency when taken at 15 minutes prior to lights off. (Carskadon and Dement 1975).

In patients with Excessive Daytime Sleepiness, however, the Stanford Sleepiness Scale (SSS) has not been as sensitive to an increased tendency to fall asleep. Motivational factors, as well as the condition of chronic sleepiness, affects the way these patients rate themselves on the SSS, mostly in the direction of denying sleepiness (Dement, 1978). The relation between SSS scores and objective measures of sleepiness has been investigated in apnea patients. Dement (1978) found that a sleepiness index, measured as the averaged sleep latency on the MSLT, was uncorrelated with the SSS ratings in these patients, whereas a significant negative correlation was found in a normal control group.

Rationale for the Present Study

Sleepiness is a common condition in a variety of clinical entities ranging from everyday experience following lack of adequate sleep to the excessive sleepiness experienced by patients with primary sleep disorders. Excessive daytime sleepiness (EDS) is a major symptom of patients with sleep apnea, and the most disabling one. The subjective estimation of sleepiness providesn an inaccurate measure, especially in these patients, mainly because of the possibility of wrongly being labeled as lazy or unmotivated. The development of tools which objectively and reliably assess sleepiness initiated extensive research into the etiological factors of sleep deisorders. Thus, changes in the autonomic system balance, which are indicators of sleepiness and alertness, can be accurately detected by measures of pupil behavior (pupillometry). Studies have shown that even small signs of sleepiness are reflected in pupillary changes (Lowenstien et al., 1963; Yoss et al., 1970; Schmidt et al.). The precise technique of continuous infrared scanning of the pupil is usful in reliably and accurately detecting these signs. Furthermore, the form and the extent of pupillary reflex are indicators of neural abnormality as well as of sleepiness. The Multiple Sleep Latency Test (MSLT) is another objective technique which directly measures EEG signs associated with sleepiness. Both of the above techniques have been previously used to assess sleepiness in different "sleepy" groups. Few of these studies, however, have examined the usefulness of these tools in patients with sleep apnea.

The present study has two purposes: the first is to use these tools to

objectively assess EDS in sleep apnea. The second is to use pupillometry in conjunction with MSLT to determine whether EDS in sleep apnea could be, qualitatively or quantitavely ,differentiated from sleepines experienced by sleep deprived normals. There is an accumulating evidence, as previously discussed, that EDS in sleep apnea is related to nocturnal sleep distruption, and the tendency to fall asleep in these patients is similar to that of sleep deprived normals. One way to test the difference between pathological sleepiness due to neural dysfunction, and that which result from sleep loss, is to see whether sleepiness signs are reversed after a period of sleep.

This study will examine pupillary behavior in darkness , as well as in response to light . Pupil measures will be taken at different times during the day before and immediately after MSLT trials .

Hypotheses and Predictions

Comparisons Between Sleep Apneics and Well Rested Normals

The purpose of these comparisons was to provide information about daytime sleepiness in sleep apneic patients as compared to that of normal, age matched controls, utilizing the Multiple Sleep Latency Test (MSLT) , the Stanford Sleepiness Scale (SSS) and pupillometry.

Pupillary tests and the Stanford Sleepiness Scale were administered at four times during the day just before and immediately after an opportunity to take a nap.

It was predicted that:

a. Apnea patients would show indications of sleepiness in pupil measures while normals would not. Also that in apnea patients pupil instability would be greater, pupil size would be smaller, reactivity to light would be less extensive, there would be shorter latency to constriction and a longer time for the pupil to recover after light stimulation. On the MSLT, sleep latency of patients would be shorter than that of normal, and otherwise there would be no abnormal polygraphic signs. It was also predicted that SSS scores would be higher in the apnea group, indicating less alertness for these subjects.

b. Pupil measures and MSLT scores would not show changes at different times of the day in the apnea group, but would indicate slightly more sleepiness in the afternoon session (14:00) in the normal group.

c. Pupil measures indicating sleepiness would show a recovery after a short rest (or sleep) period in both groups.

These predictions were based on the following assumptions:

a. Under condition of adequate sleep the autonomic nervous system is well balanced and the pupillary measures indicate stability and integration of the sympathetic and parasympathetic systems.

b. Following sleep loss, there is an imbalance in the autonomic system, in which there is an increase in the activity of the parasympathetic system with a weakening of sympathetic activity.

c. A period of sleep shifts the systems into equilibrium, but the chronic need to sleep soon brings back parasympathetic predominance.

d. Sleepiness increases as a result of sleep loss. EDS in apneic patients

reflects a partial but chronic sleep deprivation due to highly disturbed nocturnal sleep. Consequently, daytime sleepiness is persistent throughout the day. Normal subjects experience a slight dip in alertness in the early hours of the afternoon.

Comparisons Between Well Rested Normals and Sleep Deprived Normals

The purpose of these comparisons was to provide quantified information about daytime sleepiness level utilizing the above three methods in a group of normal subjects under two conditions: under the first condition, subjects had adequate sleep on the night prior to testing. Under the second condition the subjects were sleep deprived for 24 hours prior to the day of testing.

The prediction of this study were:

a. There would be indications of an increased sleepiness under the condition of sleep deprivation. Specifically, the sleep deprived would have smaller initial pupil diameters ,greater pupil instability, an increase in extent of constriction (V and W shapes) in response to light , a shorter reflex latency, and a longer time for the pupil to recover . On the MSLT, it was predicted that following sleep deprivation , the latency to sleep would be shorter than for subjects who were well rested.

b. Following either a period of rest or sleep, measures of sleepiness in the sleep deprived subjects would returned to normal patterns.

These predictions were based on the following assumptions:

a. Sleepiness which results from acute sleep deprivation (24 hours) indicates a predominantly parasympathetic activity, and a slight decrease in sympathetic activity.

b. Rest (or sleep) period shifts the parasympathetic system back to equilibrium with the sympathetic system.

Comparisons Between All Three Groups: Sleep Apnea, Sleep Deprived Normals And Well Rested Normals

These comparisons were based on the available data from the previous studies and compared the measures of sleepiness in three groups: sleep apneic patients, sleep deprived normals and normals who had sufficient sleep before being tested.

The predictions were:

a. There would be a continuum of the degree of sleepiness ranging from very sleepy to alert in the following order: Sleep apnea (SA), the normal group under the condition of sleep deprivation (SD) and the normal group under the condition of adequate rest (AR). Specifically, pupillary measures would show the following direction:

Initial diameter- AR>SD>SA

pupil variability -AR<SD<SA

Extent of constriction - SD>AR>SA

Response latency- AR>SD>SA

Pupil recovery - AR<SD<SA

Maximum contraction speed (MCS)- SD>AR>SA

On the MSLT , it was predicted that time to sleep latency would follow this order - AR>SD>SA.

b. It was predicted that following MSLT trials , there would be a recovery of all pupil measures, but with the same order as the pretrial measures.

The assumption underlying these predictions was that the sleepiness due to partial but chronic sleep deprivation is more intense than that which is caused by a short deprivation period.

METHOD

Subjects

Two groups of subjects participated in the experiment:

Sleep apnea patients.

Criteria for selecting patients were: Patients who were diagnosed as having sleep apnea by the Sleep-Wake clinic at Montefiore Hospital, and who had a cummulative apnea and hypopnea index (AHI) of 30 or greater. All patients were male, had a mean age of 52 (SD= 6.4; range 43-61), and were free of any medication for at least one month prior to testing. (see Appendix for subjects data).

Control group.

Normal control subjects were selected from those who responded to advertisements calling for males ,ages 40-60, who were non-smokers and non-users of alcohol, drugs or medication. The mean age of the subjects in the control group was 47 years old (SD=8.5; range 33-63).

Procedure

Subjects arrived at Queens College psychophysiology laboratory by 9:00 a.m. The procedures were explained to them, and electrodes for measuring sleep patterns were applied. These included:

electroencephalograph (EEG)- from C3 or C4 placements with reference to A2 or A1 respectively . These placements were selected because they are the best locations for recording sleep spindles and K-complexes. In addition, by maximizing the distance between the EEG electrode and the reference point, a better recording of slow wave amplitude is achieved.

Electrooculogram (EOG) for measuring eye movements - two recording channels from the right and the left eyes were recorded from electrodes placed above and slightly lateral to the right and left outer canti. Both eyes were referred to the contralateral ear to produce an out of phase deflection on the two channels.

Electromyograph (EMG) for measuring chin muscle tone- from two electrodes placed under the chin .

At 9:30 the testing began:

The subject entered a quiet dark room for collecting pupillary data. He was seated in a comfortable chair ,and asked to focus his eyes on a dim fixation light positioned six feet away. This light was of very low intensity, and was insufficient to evoke any pupillary response.

Both a preprepared bite board (with the subject's dental impression on it) and a headrest were adjusted to the subject to stabilize the pupil, and to prevent head movements. A TV camera was then focused on his left eye.

it was connected by coaxial cable to the pupillometer control unit (Whittaker TV pupillometer HV-16S) located outside of the dark room and in direct view of the experimenter. At this time the subject was instructed about the exact testing procedure and the experimenter left the dark room.

Following five minutes of dark adaptation, the pupil diameter was recorded for two minutes in complete darkness with the exception of an infrared light (Kodak Wratten filter R79. Cut off at 780 millimicron), which illuminated the pupil. Pupil diameters digitized at a rate of 10 datapoints per seconds were collected and were stored 1200 data points on a floppy disk (Heathkit H8 digital computer).

After recording the pupil diameter for 2 minutes, the subject was presented with a series of 15 light stimuli of low intensity and of duration of 200 msec for each stimulus. These stimuli evoked an averaged pupillary contraction of .75 mm in young healthy normal subjects during our preliminary pilot data collection . The sequence of events for each of the 15 trials was as follows:

- A tone (beep) served as the signal to focus on the fixation light indicated the beginning of the trial.
- 115 data points were collected at a rate of 50 points per second. At data point 20 (after 400 msec) the stimulus was presented for 200 msec.
- A second tone signaled the end of the trial.

Multiple Sleep Latency Test (MSLT). Following the pupillary data collection, subjects were taken to the sleep room. Electrodes were

connected to a polygraph located outside the sleep room to record sleep signs. (Grass Instruments Polygraph model 78).

EEG from C4/A1 (or C3/A2) channel, along with two channels of EOG (F3/A1; F4/A1) and one channel of EMG (01/02), were recorded on paper moving at a speed of 10 mm/sec.

Subjects comfortably lying on the bed were then asked to close their eyes and to try to fall asleep . The time the lights went out time was marked on the record to indicate the beginning of the test.

MSLT trials allowed 20 minutes for subjects to fall asleep. Once sleep signs appeared on the record they were allowed 10 minutes of sleep. If, however, sleep occured just few minutes before the 20 minutes period and the subject woke up for one minute or more during the post 20 minutes period, the trial was terminated even without completing the 10 minutes period. In other words, the time that a subject was allowed in bed ranged from 10 minutes, in case he fell asleep right away ,to 30 minutes in case he fell asleep on the 20th minute.

Post MSLT procedure. Following the completion of the nap, the lights were turned on and the subjects were asked again to rate their sleepiness level on the SSS scale. The subjects were then taken ,without delay, to the pupillometer room where pupil testing was repeated.

The same procedures were repeated another three times during the day: 12:00 p.m; 2:00 p.m; and 4:00 p.m. In between sessions, subjects waited in a nearby room . They were allowed to have a decaffinated drink or/and snack (Lunch after the 12:00 p.m session), to go to the bathroom and to

engage in reading or other similar activity but, were not allowed to nap. Subjects were prevented from eating for an hour prior to each session.

Repeated conditions. The normal subjects repeated the above procedure on two different days: Once , following an adequate sleep on the night prior to testing (well rested condition), and once following a total of 24 hours of no sleep. (sleep deprived condition). Under the sleep deprived condition, the subjects arrived at Queens College in the evening before testing after a normal working day, and had been asked to avoid taking naps during that day. During the night before testing, they were accompanied at all times by an experimenter, were permitted to read, listen to radio or have snacks and decaffeinated drinks, but were not permitted to lie down.

Testing began at 9:00 A.M. following the same procedure described above. Five subjects were tested under the sleep deprived condition on the first day of testing ,whereas the other five were tested in the reversed order.

Data Analysis

Pupillometry.

Measurement was made of the following during the two minutes recording :

Mean pupil diameter- A computer program calculated the pupil mean diameter as the average pupil diameter of 1200 data points (pupil diameter was digitized at a rate of 10 data points per second).

Pupil variability- The same program also calculated the standard

deviation of the 1200 data points.

A total of fifteen light stimuli were presented on each session for the light response experiment . An analysis program detected and rejected trials with artifacts due to blinking and eye movements . This program also calculated the average, standard deviation, and first derivative for each data point across all fifteen trials. The following variables were extracted from the data:

Initial dianeter- was determined by taking the median value of the pupil diameter from data point 10 (200 msec) to data point 20 (400 msec) (immediately prior to stimulus presentation), averaged for 15 trials.

Extent of constriction- was determined by the substraction of the smallest diameter from the initial diameter (averaged for 15 trials).

Constriction latency- was determined as the point in time after the onset of the stimulus where the pupil begins to contract.(The point in time when the speed of contraction exceeded 10 mm/sec was arbitrarily selected as the point of latency)

Maximal constriction speed (MCS)- was defined as the largest value of the first derivative between the latency point and the smallest diameter. This value was multiplied by 50 to be transformed to mm/sec.

Maximal recovery speed (MRS) - defined as the largest value of the first derivative between the point of the smallest diameter and the end of the trial.

Multiple Sleep Latency Test (MSLT)

The determination of sleep latency and sleep stages was made from the polygraph data. An epoch (a page) lasts for 30 seconds at a paper speed of 10 mm/sec. Sleep signs were determined by the conventional standardized criteria published by Rechtschaffen and Kales (1968).

The following dependent variables were extracted:

Sleep Latency to stage 1- was defined as the time in minutes from lights out to first signs of sleep stage 1, which lasted at least three epochs (90 sec).

Sleep latency to stage 2- was defined as the time from lights out to the presence of at least 3 epochs with well defined spindles or K-complexes.

Statistical Analysis

Statistical analysis was performed on an Apple Macintosh computer using the GANOVA-General analysis of variance program (Statsoft, Tulsa OK), serial no. 2005.

1. Comparisons between apnea patients and well rested normals- The design for these comparisons was a three way factorial design with repeated measures , with one grouping factor (Sleep apnea, normals) and two repeated measures: Time of the day (10:00; 12:00; 2:00; 4:00), and levels (pre MSLT, post MSLT).

The same procedure was applied for all dependent variables previously specified, except for the analysis of SSS for which a Kruskal Wallis ANOVA by ranks was applied (Statfast statistical package release 2.0

serial no. B2.0 by Statsoft).

Comparisons between well rested and sleep deprived conditions in normals- The design for these comparisons was a three way ANOVA with no grouping factor and with three repeated measures: conditions (well rested, sleep deprived), time of the day (10:00;12:00;2:00;4:00) and levels (prenap, postnap). Again a nonparametric Kruskal Wallis was used for the analysis of SSS scores.

Comparisons between apnea patients and sleep deprived normals- The design for these comparisons was three way ANOVA with one grouping factor (apnea patients, sleep deprived normals) and two repeated measures: Time of the day and levels (prenap, postnap).

Pearson product moment correlations were computed between all sleepiness variables using Statfast- statistical package by Statsoft (serial number B2.0).

RESULTS

Comparisons Between Well Rested Normals And Sleep Apnea Patients

Stanford Sleepiness Scale (SSS)

As shown in Table 1 sleep apnea patients (P) rated themselves as significantly less alert than well rested normals (N), on total SSS score combined for all 8 measures, as well as on the prenap trials and the postnap trials. These findings are consistent with the prediction that sleep loss would be reflected in a reduction of subjective alertness.

Multiple Sleep Latency Test (MSLT)

The apnea patients had significantly shorter latencies to the onset of sleep stages 1 and 2 compared to the well rested normals (Table 2). The mean latency across 4 naps to stage 1 was 11 minutes for the well rested normals, whereas the latency for apnea patients was 4.38 min. Similarly, the latency to stage 2 was 15.2 min for the well rested normals, but only 7.53 min for the apnea group. A 2x4 ANOVA with repeated measures revealed that both of these differences were significant (F=15.3, df=1,16 p<.0025 and F=17.69, df=1,16 p<.001 for sleep latency to stage 1 and sleep latency to stage 2 respectively), indicating that the apneics fell asleep more readily than did well rested. A significant time-of-the-day effect was found in the analysis of latency to stage 2. Planned comparisons between the means in each group showed that the latency to stage 2 was significantly shorter in the 2:00 o'clock nap compared to the other three naps, indicating a post lunch "dip" in both

apneics and well rested normals. These findings are consistent with the prediction that the apnea patients would fall asleep more readily than well rested normals . The afternoon dip was predicted, however, in the well rested group only.

Pupil Data

The means and standard deviations of the different pupil parameters are presented in Table 3. A three way ANOVA with repeated measures was computed using times of the day and prenap postnap scores as the two repeated dimensions and groups as the between factor.

Prenap condition: On the prenap condition, apnea patients had significantly greater pupil variability than well rested normals(F=5.11, df=1,18 p <.05). In addition, the patients had a significantly smaller resting pupil diameter (F=6.87, df=1,18 p<.025). The two groups also differed on measures of pupillary response to light stimulation. Specifically, the patients had a lower contraction speed (F=5.26, df=1,15 p <.05), a lower recovery speed (F=5.54, df=1,15 p <.05), and a longer latency to contraction (F=5.12, df=1,16, p <.05). While the patients had a smaller extent of contraction, this difference was not significant (F=3.76, df=1,16 p <.06). Comparisons between groups are presented in Table 4.

Postnap condition: Following MSLT naps, the apnea group exhibited significant changes in some of the pupil measures . Thus, resting pupil diameter increased significantly and the latency to pupil contraction decreased significantly after naps. Consequently, there were no significant differences between the two groups on these measures in the

postnap condition. On other pupil measures, however, there were significant differences between the groups in the postnap condition. Thus, the apnea patients had significantly greater pupil variability (F=4.38, df=1,18 p <.05), smaller extent of pupil contraction (F=6.4, df=1,16 , p<.025), and lower pupillary contraction speed (F=5.26, df=1,15 p <.05). The results are therefore consistent with the prediction that after naps the apnea patients would have an increased alertness level as measured by some of the pupil changes , but would not reach the alertness level of the well rested normals.

Comparisons Between Well Rested Normals

And Sleep deprived Normals .

Stanford Sleepiness Scale (SSS)

The sleep deprived normals rated themselves as being significantly less alert than the well rested normals on the prenap condition, on the postnap condition and on all eight trials combined . Mean SSS scores and standard deviations are presented in Table 5. The results of the SSS measure supports the prediction that subjective feeling of sleepiness increases with sleep loss.

Multiple Sleep Latency Test (MSLT)

Following a sleepless night, subjects fell asleep significantly faster compared to the time it took them to fall asleep following a night with adequate sleep. A two way ANOVA with repeated measures was computed using well rested and sleep deprived conditions and times of the day as the two repeated measures.

As shown in Table 6 the mean latency across 4 naps to stage 1 was 3.1 minutes for the sleep deprived group compared to 11 minutes for the well rested subjects (F=38.75, df=1,8 p<.001). Similarly, the latency to stage 2 was 4.8 minutes and 15.2 minutes for the sleep deprived normals and the well rested normals respectively (F=34.31, df=1,8 p<.001). This supports the prediction that following sleep loss, there is an increase in the tendency to fall asleep as measured by the latency to EEG sleep signs.

Pupil Data

Prenap and postnap conditions: Table 7 and 8 show that the pupil variability and latency to pupil contraction were the only pupil measures which significantly differentiated the sleep deprived normals from well rested normals. A three way analysis of variance with repeated measures was carried out using well rested and sleep deprived conditions, times of the day and prenap postnap levels as the three repeated dimensions. Under the condition of sleep deprivation, subjects had significantly greater pupil variability than under the well rested condition on the prenap level (.3 mm in the sleep deprived compared to .21mm in well rested normals), as well as on the postnap level (.33 mm in the sleep deprived compared to .17 mm in the well rested). On the latency to pupil contraction measure, there was a significant pre-post by conditions interaction. Computation of simple main effect indicated that the sleep deprived had a significantly longer latency to pupil contraction on the prenap level, but there was no such difference on the postnap level. On other measures, although not significant, the sleep deprived had a smaller resting

diameter, a lower contraction speed and a lower recovery speed. These findings indicate that most pupil measures are more robust than predicted and are not significantly affected by 24 hours of sleep deprivation.

Sleepiness Measures Which Differentiate Sleep Apnea Patients, Well Rested Normals And Sleep Deprived Normals.

Table 9 presents the mean scores and standard deviations of all the variables included in the study for all three groups: apnea patients, sleep deprived normals and well rested normals. The statistical comparisons between the groups are presented in Table 10. Plus signs designate a statistically significant difference. An examination of the variables which significantly differentiated the groups (Table 10), suggests that a classification of the variables into three classes could be made: The first class included those variables which significantly differentiated the two sleepy groups, apnea patients and sleep deprived normals, from well rested normals. These variables included sleep latency to stage 1, latency to pupil contraction on the prenap level and variability. The second class included those variables which differentiated all three groups from each other. The sleep deprived subjects had greater decreased alertness compared to the other two groups as measured by Stanford Sleepiness Scale (SSS), and by their longest latency to sleep stage 2. On pupil measures, however, the apnea group had the smallest resting diameter and the longest latency to pupil contraction on the postnap level. On these two measures significant differences were found between the well rested normals and the apneics, but not between sleep deprived and well rested

normals. The third class included those variables which differentiated the patients from the two "normal" groups, sleep deprived normals and well rested normals. These measures were: extent of pupillary contraction, maximum contraction speed, and maximum recovery speed on the prenap condition.

Time of the day effects. Figures 1 to 9 illustrate the fluctuations of sleepiness variables across the day, measured at 8 times before and after naps. An inspection of Figures 1-9 discloses no systematic differences between the 4 naps on most variables. Time of the day effect was evident, however, in sleep latencies. Figures 1 illustrates the afternoon dip formed by the lowest latencies to sleep stage 1 for both apneics and well rested on nap 3.

The changes in some sleepiness measures following napping, expressed by the prenap-postnap comparisons, were affected by the time of the day as seen in the pupil measures of initial diameter, variability and the speed of pupil recovery. Thus, in both well rested and sleep deprived, there was a significant increase in pupil initial diameter following the second, third and fourth naps, but there was no such change following the first nap (see Figure 6). This was evident in a time-of-day by pre-post interaction effect. (F=4.29, df=3,24, $p < .01$). Similarly, in both apneics and well rested groups there was a significant decrease in pupil variability following the third and the forth naps , but such decrease was not evident in the morning naps (see Figure 4). As shown in Figure 9, pupil recovery speed (MRS) increased significantly following the second

and the forth naps in both apneics and sleep deprived groups, whereas no such increase was evident following the first and the third naps. (A time-of-the-day by pre-post interaction effect was significant at $F=3.04$, $df=3, 42$, $p<.03$).

Prenap vs. Postnap Comparisons

Table 11 identifies the variables which changed significantly after nap compared to the prenap score in all three groups.

SSS Data

Apnea patients rated themselves as significantly less alert after nap. While well rested normals and sleep deprived normals also had a slight decrease in alertness level after naps as measured by SSS, this difference was not significant.

Pupil Data

In general, there was a significant change in pupil behavior following napping in both apneics and and well rested groups. In contrast, sleep deprived did not demonstrate such pupillary changes (Table 11). Specifically, both the apnea and the well rested groups had a significantly larger resting diameter , an increased pupil contraction speed , and a greater extent of pupillary contraction after naps compared to the prenap measures . There was a significant increase in the initial pupillary diameter after naps in the well rested group . Similarly, there was a slight increase in the initial pupil diameter following napping in the patient group, though this difference was not statistically significant. Only the patient group showed a significant decrease in pupil variability

on the postnap trials compared to the prenap trials. The other two groups demonstrated the expected decrease in pupil variability after naps, though the differences were not significant. Only the sleep deprived group had a significant shorter latency to pupil contraction after naps. Again, the other two groups showed the changes in pupil contraction that were in the expected direction, but no significant differences were found . There was no significant change in pupil recovery speed (MRS) following napping in any of the groups.

It is evident from the results of the present study that following MSLT trials, there were significant change in the pupillary behavior of the well rested subjects. Since this group spend at least half of the MSLT trials without falling asleep, the question which arises is whether sleep is necessary in order for these measures to recover, or rest itself is sufficient for such recovery. An analysis was performed in the well rested group in which naps which ended with sleep were compared to naps in which no sleep occurred. (see Table 15). Sleep was found to be necessary for the increase in pupil resting diameter and pupil initial diameter, while rest by itself was sufficient for the pupillary reflex to become more extensive, as measured by a greater extent of contraction as well as by higher contraction speed.

Correlations Between Sleepiness Indicators

To determine if a relationship exists between sleepiness indicators, pearson product moment correlations were computed between all sleepiness variables in each of the three groups.

Relation Between SSS scores And MSLT Scores. MSLT and SSS scores did not seem to be related in any of the groups. Sleep latency was not correlated with SSS scores in the prenap condition , in the postnap condition or with total SSS score.

Relation Between Prenap SSS scores And Postnap SSS Scores. Prenap SSS scores were highly correlated with postnap SSS scores in the well rested normals and in the patients. ($r=.65$ $p<.0001$ and $r=.66$ $p<.0001$ for the well rested normals and for the apnea patients respectively).

Relation Between MSLT And Pupil Measures . In the well rested group MSLT scores were positively correlated with maximum contraction speed ($r=.31$ $p=.045$), and with maximum recovery speed on the postnap measure only ($r=.33$ $p=.042$). In the sleep deprived normals sleep latency to stage 1 was negatively with pupil variability ($r=-.45$ $p=.005$ and $r=-.46$ $p=.004$ for the prenap and the postnap variability measure respectively), and with pupil contraction latency on the postnap condition. ($r=-.42$ $p=.01$). In the apnea group, there were no significant correlations observed between sleep latency and the pupil prenap and postnap measures.

Relation Between Pupil Measures

Generally, pupil measures appeared to be highly correlated with each other in the well rested group. There was less association among pupil measures in the sleep deprived group, and almost no association among pupil measures in the sleep apnea group. Tables 12, 13 and 14 identify the pupil variables which were correlated with each other in the well rested

normals, sleep deprived normals and sleep apnea respectively.

As expected, significant correlations were obtained in all three groups between extent of pupillary contraction and maximum contraction speed, on both prenap and postnap conditions. The following variables were significantly correlated with each other in the well rested normals group : extent of contraction, contraction latency, maximum contraction speed and maximum recovery speed (Table 12). In the sleep deprived group the extent of contraction and the contraction latency were not correlated with maximum contraction speed measure on the postnap measures. In addition, contraction latency was not correlated with maximum recovery speed on the prenap condition (Table 13). An examination of the correlations in the apnea group suggests that the pupil measures in that group are not correlated with each other. The only two measures which are correlated with each other in the patients group are: extent of pupillary contraction and the maximum of contraction speed (Table 14).

Table1. Stanford Sleepiness Scale (SSS): comparison between well rested normals and sleep apnea patients

[mean scores and standard deviations (in parenthesis) for SSS scores , computed as the averaged score for 4 prenap trials (pre), 4 postnap trials (post) and for all 8 measures combined (total).Between group analysis was made by Kruskal Wallis ANOVA by ranks, all compaisons preplanned.]

Variable	Well rested [a] normals (N)	Sleep apnea[b] patients (P)	N vs P
SSS-pre	1.9 (.96)	2.6 (.95)	p<.05
SSS-post	2.15 (1.32)	3.1 (1.05)	p<.05
SSS-Total	2.03 (1.14)	2.85 (1)	p<.05

[a]n=10; [b]n=10

Note. Stanford Sleepiness Scale (SSS)- self rating scale ranging from score 1 which is being alert, wide awake, energetic to score 7- cannot stay wake. sleep onset soon.

Table 2. **Multiple Sleep Latency Test (MSLT): comparison between well rested normals and sleep apnea patients.**
[Mean scores and standard deviations (in paranthesis)for sleep onset latency were computed across 4 naps. Between groups analysis was made by two-way ANOVA with repeated measures. All comparisons preplanned)

	Well rested [a] normals (N)	Sleep apnea[b] patients(p)	N vs P
SL-1	11 (6.67)	4.38 (3.6)	p<.001
SL-2	15.2 (5.58)	7.53 (4.48)	p<.001

[a]n=10; [b]n=10

Note. SL-1= Sleep latency to stage 1 measured in minutes; SL-2= Sleep latency to stage 2 measured in minutes

Table 3. **Pupil measures: mean scores and standard deviations (in parenthesis) for well rested normals and for sleep apneics.**
[Scores were averaged for 4 prenap trials (Pre), for 4 postnap trials (Post) and all 8 trials combined (Total).]

	Well rested normlas (N) n=10			Sleep apnea patients (P) n=10		
Variable	Pre	Post	Total	Pre	Post	Total
RD	5.52 (.92)	5.72 (.83)	5.61 (.89)	4.47 (1.01)	5.1 (.92)	4.57 (.88)
Var	.21 (.1)	.17 (.11)	.19 (.1)	.46 (.33)	.36 (.26)	.42 (.33)
ID	5.34 (1.04)	5.58 (1.01)	5.46 (1.03)	4.61 (1.15)	5.19 (1.0)	4.9 (1.08)
EC	.38 (.25)	.55 (.27)	.44 (.26)	.19 (.14)	.31 (.15)	.25 (.15)
CL	333 (65)	326 (46)	329 (55)	397 (71)	379 (64)	387 (67)
MCS	2.35 (1.15)	2.82 (1.17)	2.59 (1.16)	1.33 (.71)	1.83 (.73)	1.53 (.72)
MRS	1.11 (.31)	1.22 (.4)	1.17 (.36)	.86 (.35)	1.16 (.36)	1.00 (.35)

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm);ID= Initial diameter (mm); EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec).

Table 4. Statistical Comparisons of pupil measures between well rested normals and sleep apneics.
(Analysis was made by a three way ANOVA with patients and well rested normals as between groups factor and with time of the day and prenap postnap levels as the repeated measures factors. All comparisons preplanned.)

Variable	Prenap	Postnap	Total
RD	$p < .05$	n.s.	$p < .05$
Var	$p < .05$	$p < .05$	$p < .05$
ID	n.s.	n.s.	n.s
EC	$p < .05$	$p < .05$	$p < .05$
CL	$p < .05$	n.s	$p < .05$
MCS	$p < .05$	$p < .05$	$p < .05$
MRS	$p < .05$	n.s.	n.s.

Note. RD=Resting diameter (in mm); Var= Standard deviation of 1200 data points (in mm); ID= Initial diameter (in mm); CL= Pupil contraction latency (in msec); EC= Extent of contraction (in mm); MCS= Maximum contraction speed (mm/sec); MRS- Maximum recovery speed (mm/sec)

Table 5. Stanford Sleepiness Scale (SSS): comparisons between well rested normals and sleep deprived normals.

[Mean scores and standard deviations (in parenthesis) for SSS scores computed as the averaged score for 4 prenap trials (pre), for 4 postnap trials (post) and for all 8 trials combined (total). Between group analysis by Kruskal Wallis Anova by ranks. All comparisons preplanned.]

Variable	Well rested normals (N)	Sleep deprived normals (SD)	N vs. SD
SSS pre	1.9 (.96)	3.31 (1.11)	$p < .001$
SSS post	2.15 (1.32)	4.03 (1.57)	$p < .01$
SSS total	2.03 (1.14)	3.67 (1.34)	$p < .001$

Note. Stanford Sleepiness Scale (SSS)= self rating scale ranges from score 1-alert, wide awake, energetic to score 7- cannot stay awake. sleep onset soon.

Table 6. Multiple Sleep Latency Test: comparisons between well rested normals and sleep deprived normals.

[Mean scores and standard deviations (in paranthesis) for sleep latency were computed across 4 naps. (Between groups analysis was made by Two-Way ANOVA with repeated measures. All comparisons preplanned.]

Variable	Well rested normals (N)	Sleep deprived normals (SD)	N vs SD
SL-1	11 (6.67)	3.1 (2.81)	$p < .001$
SL-2	15.2	4.79	$p < .0001$

Note. SL-1= Sleep latency to stage 1 (in minutes); SL-2 =Sleep latency to stage 2 (in minutes)

Table 7. Pupil data: mean scores and standard deviations (in parenthesis) for well rested normals and for sleep deprived normals.

[Scores were averaged for 4 prenap trials (Prenap), for 4 postnap trials (Postnap) and for all 8 trials combined (Total)].

	Well rested normals(N)			Sleep deprived normals(SD)		
Variable	Prenap	Postnap	Total	Prenap	Postnap	Total
RD	5.52 (.92)	5.72 (.83)	5.61 (.89)	5.26 (1.04)	5.38 (1.08)	5.32 (1.06)
Var	.21 (.1)	.17 (.11)	.19 (.1)	.30 (.16)	.33 (.18)	.32 (.17)
ID	5.34 (1.04)	5.58 (1.01)	5.46 (1.03)	5.05 (1.16)	5.35 (1.07)	5.2 (1.11)
EC	.38 (.25)	.55 (.27)	.44 (.26)	.41 (.28)	.51 (.28)	.46 (.28)
CL	333 (65)	326 (46)	329 (55)	375 (72)	347 (56)	361 (64)
MCS	2.35 (1.15)	2.82 (1.17)	2.59 (1.16)	2.34 (1.28)	2.66 (1.18)	2.5 (1.23)
MRS	1.11 (.31)	1.22 (.4)	1.17 (.36)	1.24 (.49)	1.39 (.58)	1.31 (.53)

Note. RD= Resting diameter (mm); Var=Standard deviation for 1200 data points (mm); ID=Initial diameter (mm); EC=Extent of contraction (mm); CL=Contraction latency (msec); MCS=Maximum contraction speed (mm/sec); MRS=Maximum recovery speed (mm/sec).

Table 8. Statistical comparisons of pupil measures between well rested normals[a] and sleep deprived normals[b]. [Analysis made by three way ANOVA with well rested and sleep deprived conditions, time of the day and prenap postnap levels as three repeated measures. All comparisons preplanned.

Variable	Pre	Post	Total
RD	n.s.	n.s.	n.s.
Var	$p < .05$	$p < .01$	$p < .05$
ID	n.s	n.s	n.s
EC	n.s.	n.s.	n.s.
CL	$p < .01$	n.s	$p < .01$
MCS	n.s.	n.s	n.s.
MRS	n.s.	n.s.	n.s.

[a]n=10; [b]n=9.

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); ID= Initial diameter (mm);EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec).

Table 9. Summary Table of means and standard deviations (in parenthesis) of sleepiness measures computed for well rested normals, sleep apneics and sleep deprived normals.

	Well rested normals (n=10)			Sleep apnea patients (n=10)			Sleep deprived normals (n=9)		
Variable	Pre	Post	Total	Pre	Post	Total	Pre	Post	Total
RD	5.52 (.92)	5.72 (.83)	5.61 (.89)	4.47 (1.10)	5.1 (.92)	4.57 (.88)	5.26 (1.04)	5.38 (1.08)	5.32 (1.06)
Var	.21 (.1)	.17 (.11)	.19 (.1)	.46 (.33)	.36 (.26)	.42 (.33)	.3 (.16)	.33 (.18)	.32 (.17)
ID	5.34 (1.04)	5.58 (1.01)	5.46 (1.03)	4.61 (1.15)	5.19 (1.0)	4.9 (1.08)	5.05 (1.16)	5.35 (1.07)	5.2 (1.11)
EC	.38 (.25)	.55 (.27)	.44 (.26)	.19 (.14)	.31 (.15)	.25 (.15)	.41 (.28)	.51 (.28)	.46 (.28)
CL	333 (65)	326 (46)	329 (55)	397 (71)	379 (64)	387 (67)	375 (72)	347 (56)	361 (64)
MCS	2.35 (1.15)	2.82 (1.17)	2.59 (1.16)	1.33 (.71)	1.83 (.73)	1.53 (.72)	2.34 (1.28)	2.66 (1.18)	2.5 (1.2)
MRS	1.11 (.31)	1.22 (.4)	1.17 (.36)	.86 (.35)	1.16 (.36)	1.00 (.35)	1.24 (.49)	1.39 (.58)	1.31 (.53)
SSS	1.9 (.96)	2.15 (1.32)	2.03 (1.14)	2.6 (.95)	3.1 (1.05)	2.85 (1)	3.31 (1.11)	4.03 (1.57)	3.67 (1.34)
SL-1	11 (6.67)			4.38 (3.6)			3.1 (2.81)		
SL-2	15.2 (5.58)			7.53 (4.88)			4.79 (3.6)		

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); EC= Extent of contraction (mm); ID= Initial diameter (mm);CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec). SL-1= Latency to sleep stage 1. SL-2= Latency to stage 2.

Table 10. Summary table of the between groups comparisons (Plus signs indicate significant differences)

	Well rested normals vs. apnea patients			Apnea patients vs. sleep deprived			Well rested vs. sleep deprived		
Variable	pre	post	total	pre	post	total	pre	post	total
RD	+*	-	+*	-	-	-	-	-	-
Var	+*	+*	+*	-	-	-	+*	+*	+*
ID	-	-	-	-	-	-	-	-	-
EC	+*	+*	+*	+**	-	+**	-	-	-
CL	+*	-	+*	-	-	-	+**	-	+**
MCS	+*	+*	+*	-	-	+*	-	-	-
MRS	+*	-	-	+**	-	-	-	-	-
SSS	+*	+*	+*	+*	-	+**	+***	+***	+**
SL-1		+**			-			+***	
SL-2		+***			+**			+***	

*= p<.05. **=p<.01. ***=p<.001.

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); ID= Initial diameter(mm);EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec). SSS=Stanford Sleepiness Scale (score 1-7). SL-1= Latency to sleep stage 1. SL-2= Latency to sleep stage 2.

Table 11. Within group comparisons of sleepiness measures: prenap-postnap differences.
[Analysis made by t-test for dependent samples. (Blank= no significance)]

Variable	Well rested Normals (n=10)	Apnea patients(n=10)	Sleep deprived normals (n=9)
RD	p<.05	p<.05	-
Var	-	p<.05	-
ID	p<.01	-	-
EC	p<.05	p<.05	-
CL	-	-	p<.01
MCS	p<.01	p<.05	-
MRS	-	p<.01	-
SSS	-	p<.01	-

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); ID= Initial diameter (mm); EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec). SSS=Stanford Sleepiness Scale (Scores 1-7).

Table 12. Correlation coefficient for pupil measures in well rested normals
[Correlations were computed separately for the prenap trials (Pre) and for the postnap trials (Post)]

	RD		var		EC		CL		MCS		MRS	
Variable	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
RD -pre	.91 ***		-.29	-.22	.03	.08	-.22	-.16	.06	.11	.08	.01
RD-post			-.15	-.28	-.02	.06	-.23	-.16	.06	.17	.10	.10
Var-pre			.27		.09	-.03	.03	.03	.08	-.15	.04	.05
Var-post					-.25	-.18	.41 **	.14	-.33 *	-.3 *	-.26	-.34 *
EC -pre					.89 ***		-.82 ***	-.49 **	.8 ***	.62 ***	.69 ***	.73 ***
EC-post							-.78 ***	-.58 ***	.75 ***	.79 ***	.66 ***	.25
CI -pre								.5 ***	-.68 ***	-.66 ***	-.66 ***	-.58 ***
CL-post									-.37 *	-.41 **	-.38 *	-.42 **
MCS -pre										.69 ***	.76 ***	.26
MCS-post											.63 ***	.31 *
MRS-pre												.26

*=p<.05. **=p<.01. ***p<.001.

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec).

Table 13. **Correlation coefficients for pupil measures in sleep deprive normals.**
[Correlations were computed separately for the prenap trials (Pre), and for the postnap trials (Post)].

	RD		Var		EC		CL		MCS		MRS	
Variable	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
RD-pre			-.33 *	-.17	.21	.49 **	-.3	-.23	.41 *	.18	.25	.17
RD-post			-.19	-.17	.18	.42 **	-.3	-.19	.38 *	.17	.28	.14
Var-pre				.51 **	.04	-.12	-.005	.24	-.21	-.32	.2	.1
Var-post					.06	.02	.007	.05	-.16	-.06	.23	.11
EC-pre						.85 ***	-.75 ***	-.62 ***	.52 ***	.13	.33 *	.2
EC-post							-.75 ***	-.67 ***	.66 ***	.28	.45 **	.23
Cl-pre								.52 ***	-.43 ***	-.2	-.15	-.12
CL-post									-.31 *	-.04	-.08	-.02
MCS-pre										.67 ***	.56 ***	.34 *
MCS-post											.32 *	.36 *
MRS-pre												.37 *

*= p<.05. **=p<.01. ***=p<.001.

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); EC=Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec).

Table 14. Correlation coefficients for pupil measures in sleep apnea patients.
[Correlations were computed separately for the prenap trials (pre) and for the postnap trials (post)]

	RD		Var		EC		CL		MCS		MRS	
Variable	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
RD-pre	.41 **		.25	.32 *	.51 **	.3	-.06	-.07	.54 **	.4	.31	.16
RD-post			.00	-.13	.3	.18	.06	.01	.34 *	.22	.21	.17
Var-pre				.73 ***	-.16	-.34 *	-.34 *	-.44 **	-.2	-.27	.25	.12
Var-post					-.1	-.28	-.36	-.29	-.1	-.03	.12	.08
EC-pre						.71 ***	-.19	-.05	.95 ***	.55 ***	.31	.27
EC-post							-.04	-.1	.68 ***	.75 ***	.17	.09
CL-pre								.7 ***	-.09	.05	-.04	.09
CL-post									-.01	.1	-.1	.07
MCS-pre										.62 ***	.29	.13
MCS-post											.18	.1
MRS-pre												.35 *

*= p<.05. **=p<.01. ***=p<.001.

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec).

Table 15. **Comparisons of sleepiness measures between sleep-trials vs no sleep-trials in the well rested normals.** [Means and standard deviations (in parenthesis) of prenap measures and postnap measures for naps which resulted in sleep compared to naps where sleep has not occurred. Analysis by t test for dependent samples.]

	Sleep (n=27)			No-sleep (n=13)		
Variable	Pre	Post	p	Pre	Post	p
RD	5.64 (.95)	5.89 (.85)	<.05	5.25 (.68)	5.36 (.66)	n.s
Var	.21 (.1)	.17 (.11)	n.s	.20 (.09)	.17 (.07)	n.s
ID	5.52	5.79	<.01	4.93	5.11	n.s
EC	.32 (.2)	.49 (.22)	<.01	.48 (.29)	.65 (.26)	<.05
CL	337 (48)	334 (47)	n.s	326 (72)	309 (44)	n.s
MCS	1.89 (.79)	2.49 (.89)	<.001	2.56 (1.06)	3.21 (1.32)	<.05
MRS	1.04 (.26)	1.15 (.34)	n.s	1.24 (.33)	1.37 (.45)	n.s.
SSS	2 (1.07)	2.5 (1.7)	n.s	1.69 (.86)	2.3 (1.4)	n.s

Note. RD= Resting diameter (in mm); Var= Standard deviation for 1200 data points (mm); ID= Initial diameter (mm); EC= Extent of contraction (mm); CL= Contraction latency (msec); MCS= Maximum contraction speed (mm/sec); MRS= Maximum recovery speed (mm/sec). SSS=Stanford Sleepiness Scale, score 1-7.

Figure 1. Mean sleep latencies for control, apneics and sleep deprived.

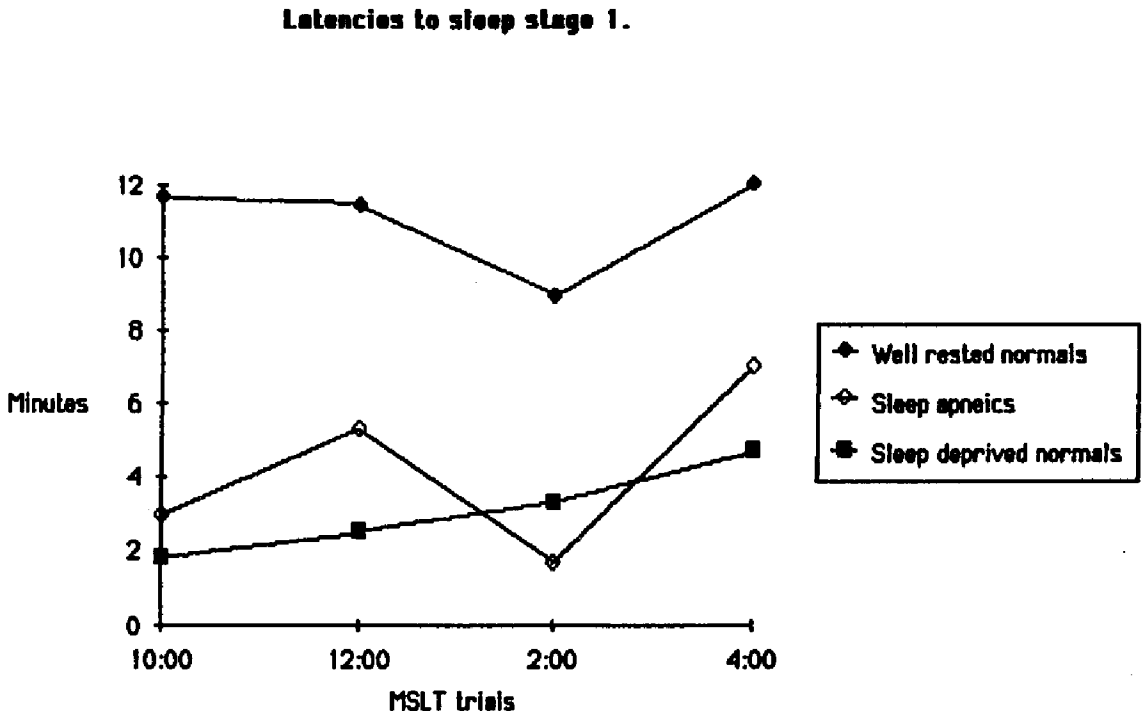


Figure 2. Mean Stanford Sleepiness Scale (SSS) scores for the three groups.

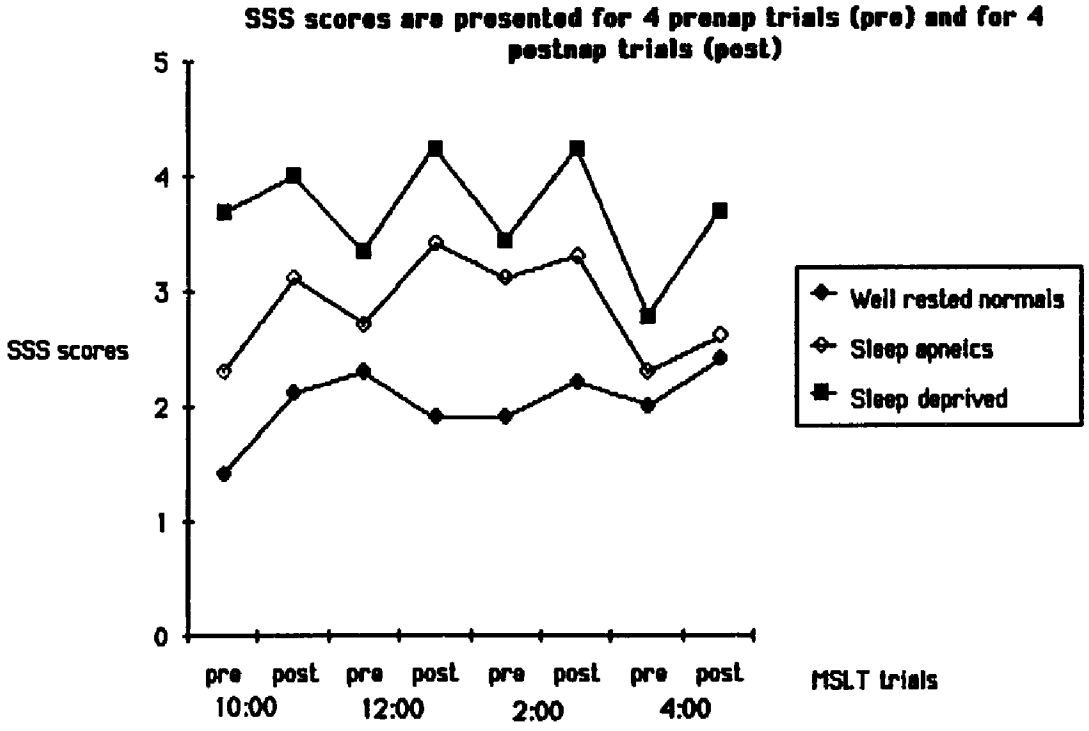


Figure 3. Mean pupil resting diameter scores for the three groups

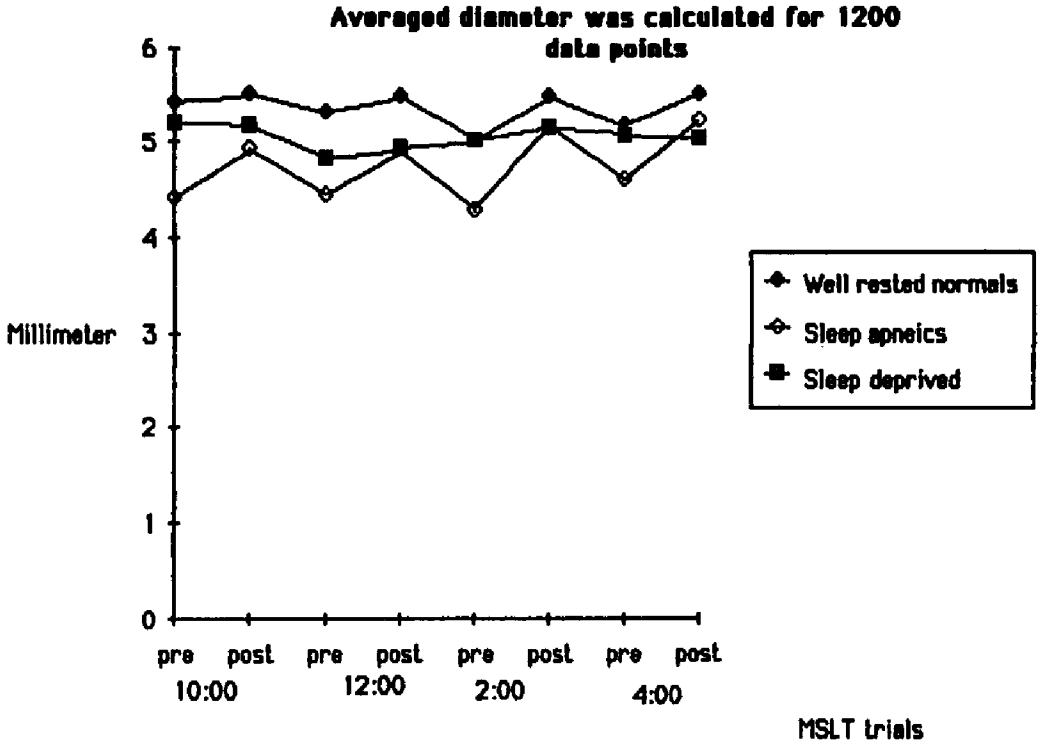


Figure 4. Pupil variability in control, apneics and sleep deprived

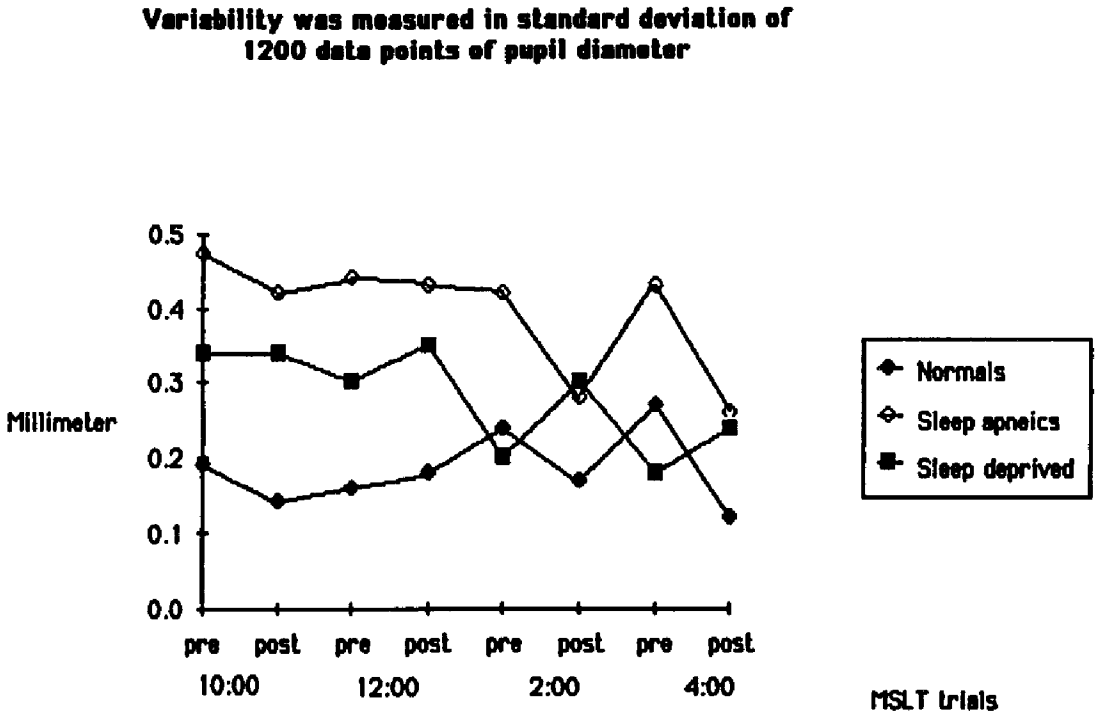


Figure 5. Mean latencies to pupil contraction (CL) in the three groups

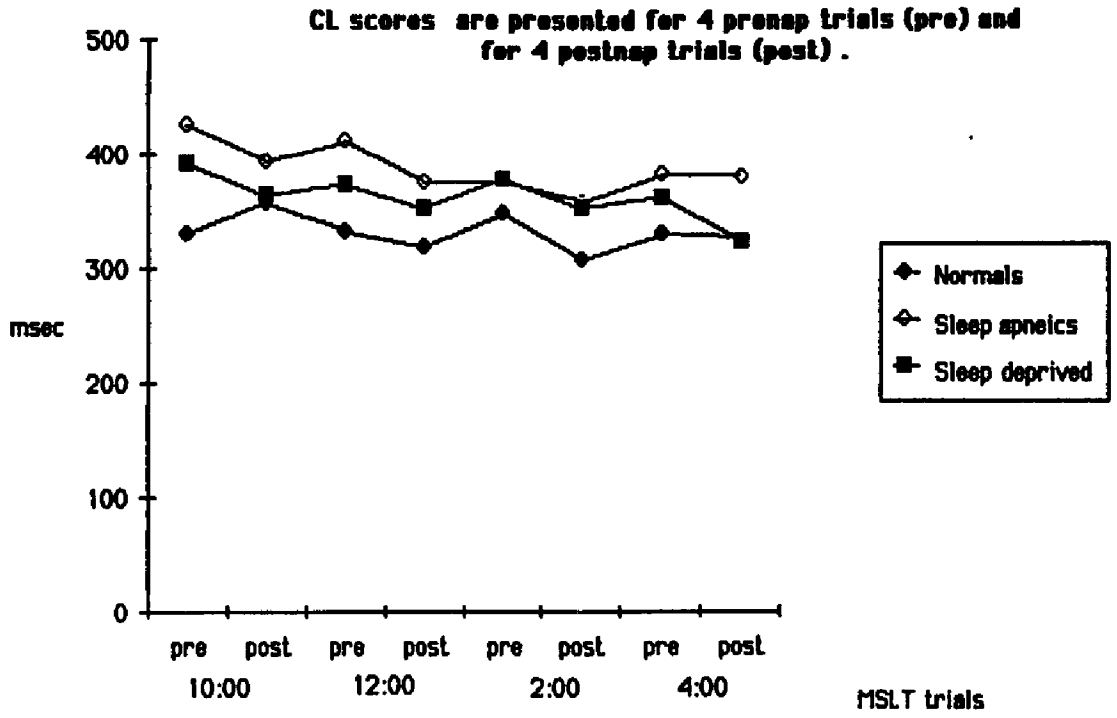


Figure 6. Mean scores of pupil initial diameter (ID) for the three groups.

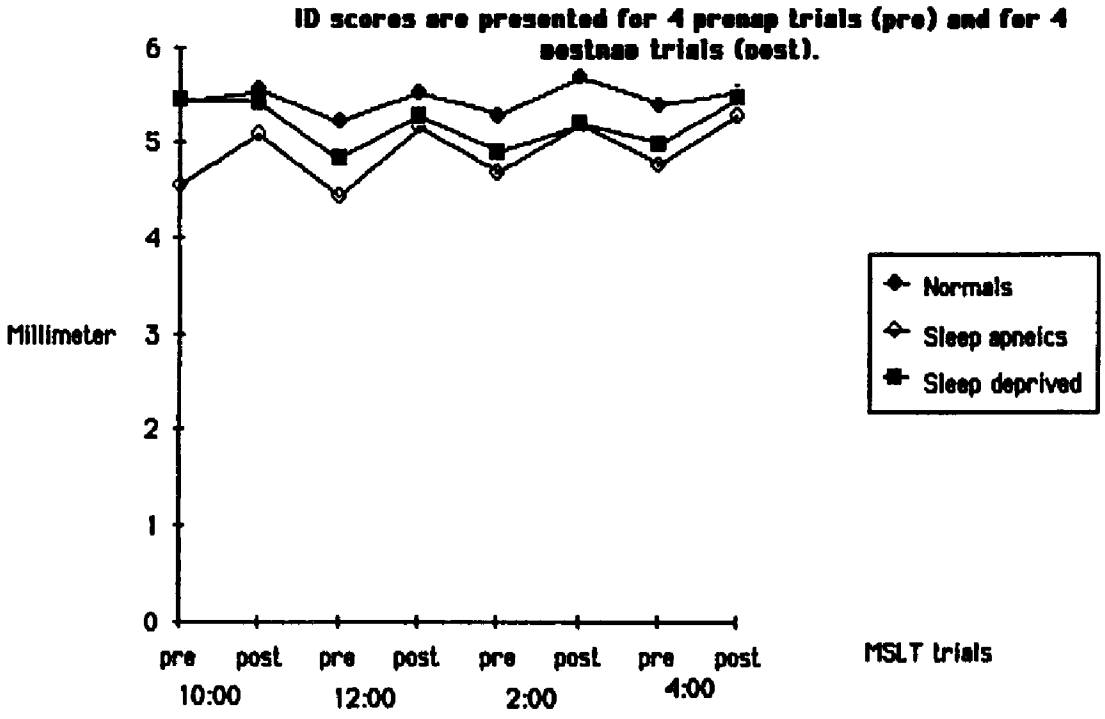


Figure 7. Mean scores of the extent of pupil contraction (EC) for the three groups

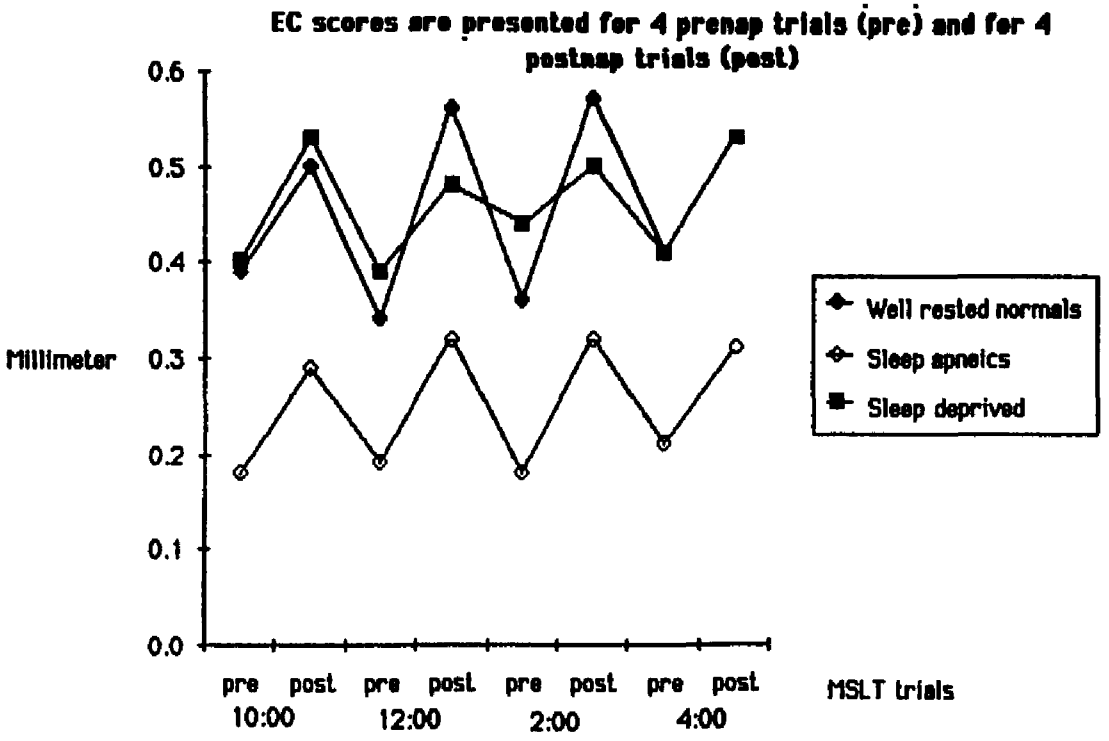


Figure 8. Mean scores of maximum pupil contraction speed (MCS) for the three groups

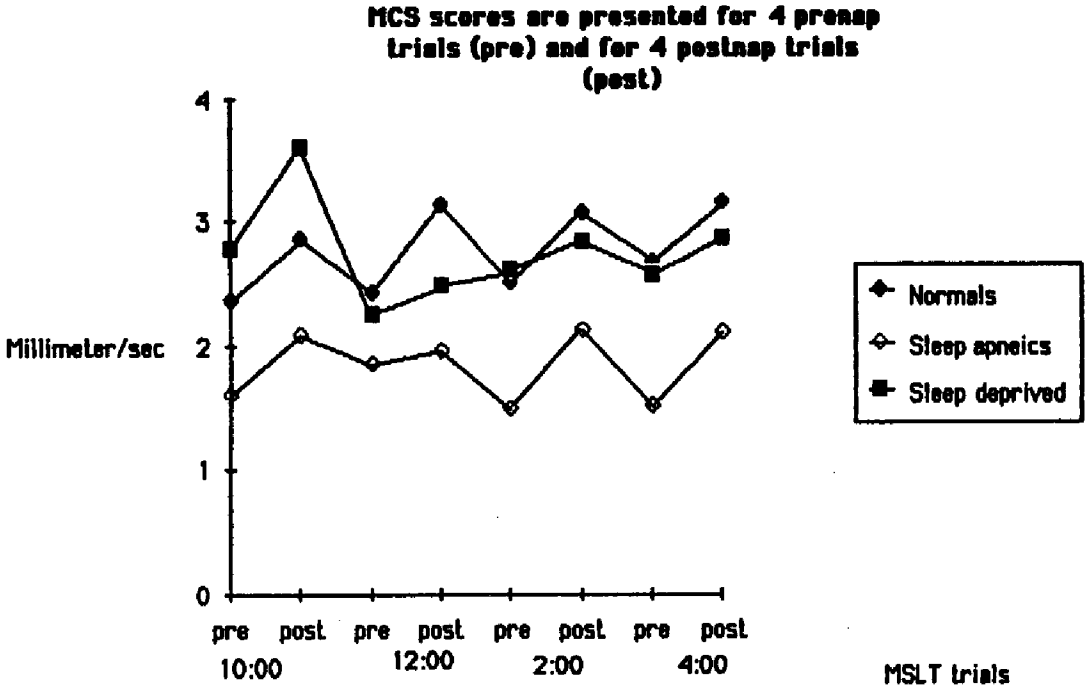
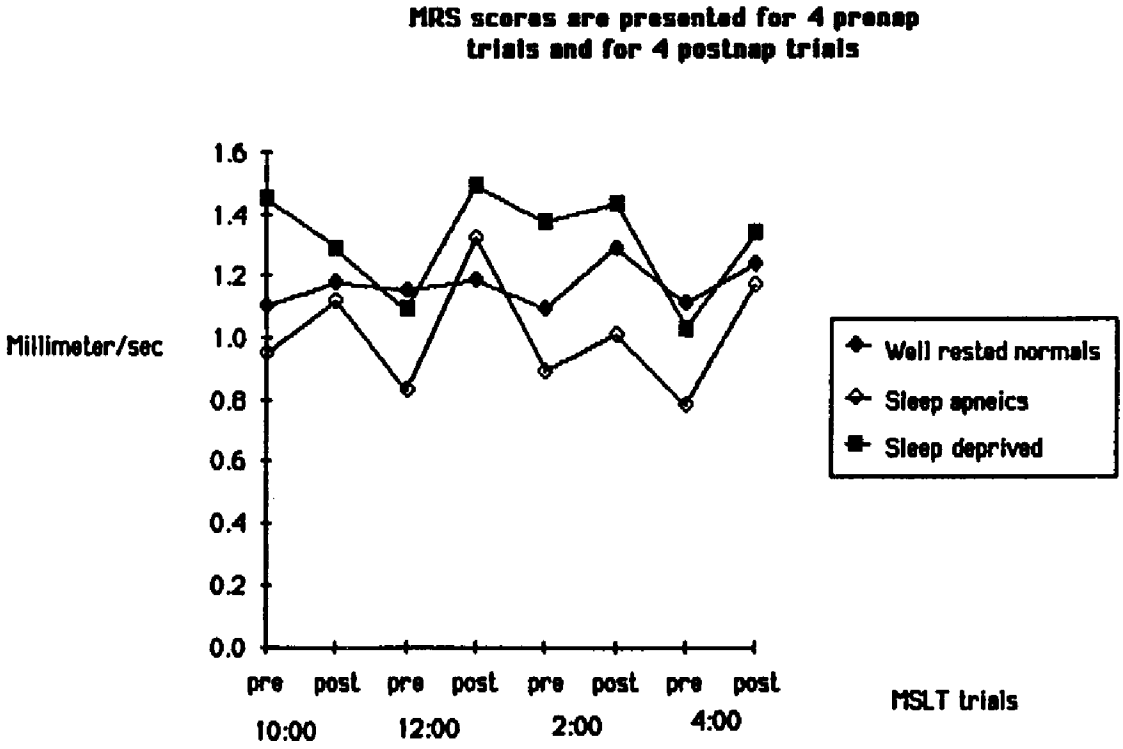


Figure 9. Mean scores of maximum pupil speed (MRS) for the three groups



DISCUSSION

In the present study EDS was measured using three different techniques: subjective assessment (SSS), Multiple Sleep Latency Test (MSLT), and pupillometry. Pupillary data indicated that the pupil of sleep apneics is significantly more fatigued than the pupil of the well rested and the sleep deprived normals. However, on other measures of sleepiness, i.e., on the Stanford Sleepiness Scale (SSS) and the Multiple Sleep Latency Test (MSLT), the sleep deprived normals were the sleepiest group. These results contradict the prediction that all three sleepiness measures would indicate that the sleep apneics are the sleepiest group.

The high validity of SSS reported in normal subjects (Hoddes et al, 1973) has not proven itself in patients with sleep disorders. As discussed previously, the subjective quantification of sleepiness presents a special problem in sleep apnea patients. These patients are chronically tired and therefore lose their frame of reference for their actual alertness leve (Dement, 1978). In addition, a denial of the extent of the condition also contributes to the inaccuracy of their judgement (Guilleminault, 1978). Unreliability of patient's own evaluation of their state of wakefulness has also been reported in narcoleptics (Yoss,1969). Furthermore, when compared to sleep deprived normals, narcoleptics rated themselves as less sleepy on the SSS (Pressman, 1982; Connoly, 1984). Thus, it appears that the SSS loses its sensitivity as a measure of sleepiness in conditions of

chronic sleepiness.

In comparing SSS scores before naps to those after naps, all three groups reported of being sleepier after MSLT trials as compared to the pre MSLT condition. However, this difference was statistically significant in the patient group only. Once asleep, the apnea patients were very difficult to arouse, and upon awakening they reported fogginess and disorientation. This finding was expected since one of the essential features in the diagnosis of sleep apnea, according to the Outline of Diagnostic Classification of Sleep and Arousal (1979), is the typical occurances of naps which tend to be prolonged and unrefreshing. As for the other two groups, there was no significant difference in the subjective assessment of sleepiness between the prenap and the postnap conditions, although both groups reported of being less alert following the MSLT trials. Of interest in the subjective assessment of sleepiness is the difference that sleep had on the reports in these groups. Statistical analysis was conducted on the data from the well rested normals to determine whether the actual occurrance of sleep was necessary in order to feel sleepier after MSLT trials. The analysis revealed that the well rested normals reported the same slight decrease in alertness level after MSLT trials regardless of whether they actually fell asleep, or simply had a period of rest. It appears, therefore, that a short period of time (20 minutes) was not sufficient for the subjects to feel refreshed.

Prenap scores of SSS were highly correlated with postnap SSS scores in the well rested normals and in the patients, indicating that the degree

sleepiness reported before the nap predicted the sleepiness level after nap. Similar results were previously reported in normal subjects, and were interpreted as reflecting the daily fluctuation in SSS ratings (Carskadon, 1975).

In none of the groups was there a significant correlation between SSS scores and the MSLT scores. The lack of correlation in the well rested and in the sleep deprived normals was unexpected , since previous studies in normal subjects found SSS scores to be highly correlated with MSLT scores (Carskadon, 1975). In the well rested normals, and in the sleep, deprived normals, the lack of correlation could be explained by their wide range of sleep latencies compared to their tendency to repeatedly score their sleepiness at the same SSS level at different times of the day. In the patient group, however, the lack of correlation between SSS scores and MSLT scores is in agreement with previous studies in apnea patients who rated themselves as alert yet literally fell asleep in front of the experimenter's eyes (Roth, Hartse, Zorick & Conway, 1980). Similar results were reported in patients complaining of EDS (Dement , 1978), as well as in patients with narcolepsy (Schmidt & Fortin, 1982).

Between group comparisons on MSLT measures were able to shed more light on the differences between the three groups. Sleep latency to stage 1 differentiated the well rested normals from the two "sleepy" groups. There was no significant difference in sleep latency between the sleep deprived normals and the patients, though the sleep deprived group were slightly sleepier than the patients. On the other hand, sleep latency to stage 2 significantly differentiated all three groups from each other, placing the sleep deprived as the sleepiest group. Of interest is the significant

difference between the patients and the sleep deprived normals in view of the lack of such difference between the two groups on sleep latency to stage1. A possible explanation is the difference in sleep structure between normals and apneics. Sleep apneics have been reported to have more sleep stage 1 and less sleep stage 3-4 compared to normals (Roth et al, 1980). Presumably, this is because the apnea patients do not reach stage 2 for long periods of time due to the frequent arousals associated with apnea episodes. Therefore, at least in these patients, latency to stage 1 more accurately measures sleepiness level. Accordingly, it appears that sleep latency (to stage 1) reflects sleepiness in general, but does not differentiate "normal" sleepiness due to sleep deprivation from sleepiness associated with sleep apnea. Still, the fact that sleep deprived normal had shorter latencies to both stage 1 and stage 2 might indicate a higher degree of alertness in the apnea group. In this context it is also likely that the patients' higher scores on the SSS compared to the sleep deprived normals, actually reflected their elevated degree of alertness , rather than the loss of frame of reference. One can postulate then, that the chronic disruption to sleep, such as that experienced by sleep apnea patients, produced a higher state of arousal than in normals who experienced a total loss of sleep.

. Webb & Agnew (1974) deprived subjects with as much as 21/2 hours of sleep loss a night for 60 nights, in a study which examined the effects of chronic sleep reduction o daytime performance. These authors found that such sleep loss did not result in major behavioral consequences, except for drowsiness which was reported in the initial period of the experiment, but returned to baseline level after the second week. Other studies reported

that the restriction of sleep to 1 to 1.5 hours less than the normal sleep, had minimal adverse effects on psychological performance and subjective assessment of daytime sleepiness, unless sleep was less than about 6 hours per day down from 7.5-8 hours per day whereupon problems occurred (Horne & Wilkinson, 1985). Furthermore, during a 3 month follow up , subjects still continued with about 1 hour reduction of their previous normal sleep. It seems, then, that the extension or reduction of the usual sleep length within limits is relatively easy , depending upon factors such as changes in man's productivity, energy conservation and seasonal daylight changes (Horne, 1983). An actual higher arousal level as a result of sleep reduction was observed by Tyler et al (1947), who studied the effect of experimental insomnia on EEG signs. They found that the changes produced by prolonged wakefulness were similar to those produced by an increased alertness level, such as that which is required for solving problems. These changes consisted of reduced alpha activity and augmented fast activity. Thus, it is likely that the apnea patients adapted to the situation of being chronically deprived of some degree of sleep loss, which was expressed in subjective feeling of being relatively alert, as well as in their longer sleep latency compared to the sleep deprived normals. The data provided by the pupil measures offer additional support for this hypothesis.

The results provided by pupil data present a different picture of sleepiness degree in the three groups. Sleep apnea patients were

significantly sleepier than the well rested normals as measured by the signs of pupillary fatigue. Similarly, they were significantly sleepier than the sleep deprived subjects on most pupil measures.

Pupil variability, reflecting the stability of pupil size, was significantly greater in the two "sleepy" groups compared to the well rested normals. This was in agreement with previous studies of pupillary fatigue which demonstrated a decrease in the stability of the pupil in sleepy normal subjects, as well as in patients with sleep disorders. Lowenstein, Feinberg & Loewenfeld (1963) described the manner in which the pupil of a normal subject becomes unstable and waves of pupillary dilations and contractions appear at the end of a long work day. Pupil instability has also been documented in narcoleptics (Yoss, 1970; Schmidt, 1982) , in patients of Other Disorders of Somnolence (DOES) (Schmidt, 1982), and in patients with pathologic fatigue due to organic dysfunction (Lowenstein et al, 1963).

Resting pupil diameter was significantly smaller in apneics compared to the well rested normals. The sleep deprived normals had a slightly, but not significantly, smaller pupil diameter compared to the well rested normals. A decrease in pupil size as a result of increased sleepiness level is consistent with findings in narcoleptics (Yoss & Moyer, 1969; Schmidt, 1982), as well as in normal sleepy subjects (Lowenstein et al 1963). Thus, it can be concluded that the decrease in the ability to maintain large pupil, as well as the decrease in pupil size are general, but sensitive indicators of decreased alertness.

In addition to the decrease in pupillary size and stability, the apnea

patients showed a reduced, less extensive response to light compared to the "normal" groups. Specifically, the extent of pupillary contraction was significantly smaller and the speed of pupil contraction and pupil recovery were significantly slower in the apneics than in both normal groups. The sleep deprived normals demonstrated a slightly, but not significantly, more extensive reflex than the well rested normals. The latency to pupillary contraction was significantly longer in the two sleepy groups compared to the well rested normals. There is an inconsistency in the literature regarding the relation between sleepiness and the pupillary reaction to light stimuli. An inextensive sluggish response to light light was described by Lowenfeld and Lowenstein (1963) in fatigued normals at the end of a work day . In contrast, Schmidt and Fortin (1983) observed that in normal subjects, the response slope of the light reflex is steep and the extent of contraction was excessive with increased sleepiness. In the present study , the sleep deprivrd subjects similarly showed a steeper, more extensive reflex. The protocol used in the study of Loewenfeld and Lowenstien involved the presentation of long series of light stimuli, with higher intensity and longer duration for each stimulus presentation, thus monitoring the rate of pupil fatigability. On the other hand, the protocol in the present study as well as in Schmidt's studies called for a short series of stimuli reflecting momentary signs of pupil fatigue.

The pupillary reaction to light in patients with sleep disorders has primarily been studied in patients with narcolepsy. Yoss, Moyer and Hollenhorst (1970 observed normal responses to light in their narcolepsy patients. Utilizing a similar procedure , Schmidt (1982) found that the pupil response in narcoleptics ranged from very small to almost absent. In

that study, the narcoleptics also had a significantly smaller and unstable pupil compared to normals indicating higher parasympathetic activity. Schmidt noted that the small extent of pupillary contraction in narcoleptics is paradoxical in light of the obvious parasympathetic predominance. He speculated that these findings are the result of a disintegration of the suprenuclear systems impinging upon Edinger Westphal (EW) nucleus, thus producing a sleepy cortex due to a decrease in cortical inhibition, but an aroused brainstem, due to an increased brainstem inhibition of EW nucleus.

The data provided by the present study are in agreement with those reported by Schmidt (1982). The presence of pupil instability and a small pupil resting diameter in both the patient and the sleep deprived groups, suggested a parasympathetic predominance . However, whereas the sleep deprived normals demonstrated the expected increase in pupil response to light, the apnea patients had a decreased, inhibited reflex.

A probable explanation for the inhibited reflex in apnea patients is that, with progressive sleepiness, the weakening of both the sympathetic and the parasympathetic systems is evident, in a fashion similar to that described by Lowenfeld and Lowenstein (1952) in normal fatigued subjects. An alternative explanation is that the minimal response found in apneics, is the result of an increased supranuclear sympathetic inhibition of the EW nucleus. Such increase in sympathetic influences upon EW nucleus could be attributed to either cortical, hypothalamic or brain stem

influences (Zinn, 1972). The present experiment , however, provided no direct evidence about any specific inhibitory system or systems which affects EW nucleus. One way to provide an answer to that question is to design an experiment which will measure the degree of pupil dilation in response to different arousal stimuli, thus measuring directly the sympathetic changes which follow an increase in the sleepiness level. Nevertheless, there is some evidence which points to the possibility that central disintegration of pupillary reflex activity and as a result an "out of phase" activity of the systems modulating pupil reaction, is responsible for the reflex dilation seen in apnea patients. Examination of correlations between pupil measures in the three groups of the present study reveals that a gradual decrease in the number of measures being significantly correlated with each other, was observed with increased sleepiness. Thus, in the well rested normals all measures of pupillary light reflex were significantly correlated with each other. In the sleep deprived normals, some of the measures were not correlated with others. Specifically, extent of contraction and contraction latency were not correlated with maximum contraction speed on the post nap trial. In the patients group , except for the obvious correlation of extent of contraction and maximum contraction speed, none of the measures were significantly correlated with each other.

The nature of the disintegration of central mechanisms is not known but several speculations have been forwarded: Lowenstein and Loewenfeld (1952) described the various levels at which central nervous system

disintegration occurs according to the stage of pupil fatigue. They stated the general rule of fatigue manifested in pupillary reflex as "central in origin, that sympathetic centers fatigue before parasympathetic centers, and cortical before subcortical centers" (pp.19). A decreased cortical inhibition out of phase with brainstem hyperactivity had been postulated to account for the small pupil reaction seen in narcoleptics (Schmidt,1983). Pillipson et al (1980) demonstrated, in dogs, that sleep fragmentation per se rather than sustaining sleep deprivation was sufficient to induce an impaired arousal response while not affecting ventilatory response to hypoxia and hypercapnia. They suggested that "sleep fragmentation appears to have produced a dissociation between brain stem (ventilatory) response and more rostral (arousal) response, perhaps in the reticular activity system or its cortical projections" (pp.286).

Thus, it appears that central disintegration of neuronal networks is possible with increased sleepiness. As mentioned before, the design of the present experiment permits only speculation about the nature of such central disintegration in sleep apnea. There is some evidence, however, which indicates an increased brainstem activity in apnea patients. In a study which analyzed rapid eye movement density in sleep apneics, an accumulation of REM activity during episodes of apnea, and a higher proportion of REM activity compared to normal controls were reported (Hertz, Sampson & Baker , 1985). In normals, one of the changes observed following REM sleep deprivation is hightened neural excitability (Cohen et al 1970). In fact, REM sleep deprivation, known to increase monoamine

neuronal activity, was also found to improve depression (Vogel, Traub, Ben Horin & Meyers, 1975). REM activity has been proposed as a sensitive indicator of CNS dysfunction because of the diffuse nature of the systems which are involved in the production of REM sleep (Foster & Kupfer, 1976). Sleep apneics, while not being deprived completely of REM sleep ,suffer a significant decrease in the amount of REM sleep.

Studies which investigated the effect of sleep loss on autonomic arousal do not shed more light on that form of arousal in apnea patients. Malmo (1958), suggested that sleep deprivation produce higher state of autonomic arousal arousal as measured by GSR. Ax and Luby (1961) who studied the effect of 123 hours of sleep deprivation on normal subjects, found a decline in arousal state measured by the fall in palmar sweating and frontalis muscle tension, which indicated a profound fatigue of central sympathetic centers and a predominance of the parasympathetic system. In the same study, however, respiration rate gradually increased indicating higher sympathetic activity. In patients with primary sleep disorders, high adrenergic tone measured by urinary norepinephrine excretion, was reported (Bodoulas et al, 1984). In yet another study, sleep apnea patients demonstrated a decrease in cardiovascular reflexes (Sachs & Kaijser, 1982). The interpretation of these findings is difficult because of the different reflexes reported and because of the complex nature of the CNS involvement in these reflexes.

The possibility that a central nervous system dysfunction is involved in sleep apnea has been raised by Guilleminault, Cunniskey & Dement (1980) and by Guilleminault (1982), based on a spectrum of clinical findings

which included physiological, psychological, and behavioral manifestations. In a study of evoked potentials in apneics, however, there was no immediate or cummulative effect on the functioning of of the neurons that subserve the middle latency evoked respose (Mosko, Kniper, Sassin & Donnelly, 1984). In addition, while one of the pupil indicators of pathological sleepiness due to neural dysfunction is whether pupillary fatigue signs could be reversed after a short rest period (Lowenstein et al 1964), the results of the present study indicated that both the well rested group as well as the apnea group demonstrated such recovery following MSLT trials. However, some postnap measures in the patient group i.e., pupil diameter and pupil variability, although recovered after napping, were still significantly different from postnap measures of well rested normals. These results suggest that the restored equilibrium in the apnea group, shown in the recovery of pupillary fatigue signs following napping, has been shifted to a lower functional level. The autonomic phenomena during slow wave sleep in normal subjects similarly indicate a closed-loop operations functioning at a lower level of energy than during wakefulness (Parmeggiani et al 1985).

The sleep deprived did not demonstrate signs of pupillary recovery after naps, which is not consistent with the prediction that all three groups would show a recovery of pupil measures. It is clear that the sleep deprived did not suffer any permanent dysfunction since they were tested following normal night sleep ,as well as following deprivation night. It is probable ,however, that whereas the autonomic nervous system in the apneics adapted to the situation of chronic sleep disruption by functioning

at a lower level, the autonomic system of the sleep deprived, overwhelmed by the acute sleep loss, did not manifest such adaptation. It should be emphasized at this point, that any conclusion regarding the comparison between sleepiness in apnea patients and that in sleep deprived normals should be drawn cautiously, since the sleepiness level of these patients was qualitatively not only quantitatively different from that of sleep deprived normals. Apnea patients suffer chronic sleep fragmentation rather than total sleep loss. Bonnet (1985), attempted to model the sleep disruption effects of apnea in normal adults by performing standardized awakenings after each minute of sleep. The disruption procedure resulted in poor performance on the Wilkinson addition test and rated themselves on the SSS as sleepier than on baseline. Unfortunately, the subjects in this study underwent sleep disruption procedure for 2 nights only. It would be interesting to monitor pupillary signs of sleepiness in normal subjects following many nights of continuous sleep disruption similar to that experienced by apnea patients.

An examination of those measures of sleepiness which differentiated the three groups from each other suggests that a classification of the sleepiness measures into three groups could be made: the first group are those measures which significantly differentiated the well rested normals from the two "sleepy" groups indicated high degree of sensitivity to sleep loss. Included in this group are pupil variability, latency to pupillary contraction in the prenap condition and the latency to sleep stage 1.

The second group of sleepiness measures include those measures which differentiated all three groups from each other, indicating a gradual

change with increasing sleepiness. Pupil resting diameter, SSS and latency to sleep stage 2 represent this group. Pupil resting diameter was slightly but not significantly smaller in sleep deprived normals compared to well rested normals, but became significantly smaller in the patient group.

The third group of sleepiness measures are those measures which significantly differentiated apnea patients from the well rested normals and the sleep deprived normals. The extent of pupillary contraction, speed of pupillary contraction and speed of pupillary recovery on the prenap condition are included in this group.

Figure 10 illustrates a proposed model of sleepiness measures based on the above classification. This model involves the differential sensitivity of pupil parameters to acute and chronic sleepiness. According to that model, pupil variability , contraction latency and latency to stage 1 are sensitive to both acute and chronic sleepiness. The measures of resting diameter, SSS and latency to stage 2 are indicate sensitivity to and differentiate acute from pathological sleepiness. The pupil response to light, however, seems to be more resistent to acute sleepiness.

One implication of this model is that the pupil parameters are controlled by different rather than common mechanisms, and that these mechanisms are state dependent. Another implication is that in conditions with chronic sleepiness, there is an adaptation of some of the pupil measures preserving the ability of the pupil to recover after rest. This was demonstrated in the present study by the recovery of pupil measures in apnea patients compared to the lack of such recovery in the sleep deprived

subjects.

Although the suggested model uses the term pathology in refering to the parameters which differentiated apneics from the normal groups, it should be emphasized that pathology in this case does not necessarily imply neural dysfunction in the patient group.

A future testing of this model should include more controlled studies which would measure various pupil parameters under conditions of controlled period of sleep loss, ranging from a minimal restriction of sleep to a maximum possible sleep deprivation. An induction of long term sleep fragmentation in normal subjects would be helpful in the understanding of the effects of sleep fragmentation on daytime sleepiness.

Figure 10. A proposed model for the classification of sleepiness measures.

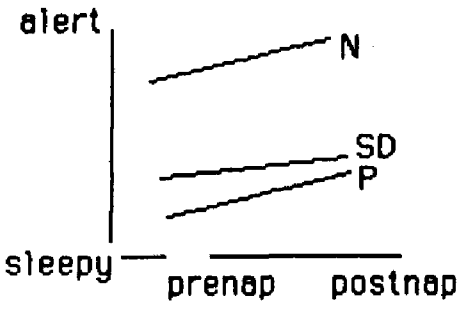
General sleepiness measures

(differentiated both sleepy groups from well rested normals).

Latency sleep stage-1

Variability

Latency to contraction



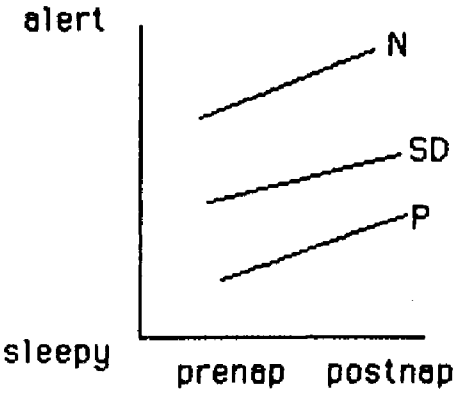
Specific sleepiness measures

(Differentiated all three groups from each other)

Pupil resting diameter

Latency to sleep stage-2

Stanford Sleepiness Scale (SSS)



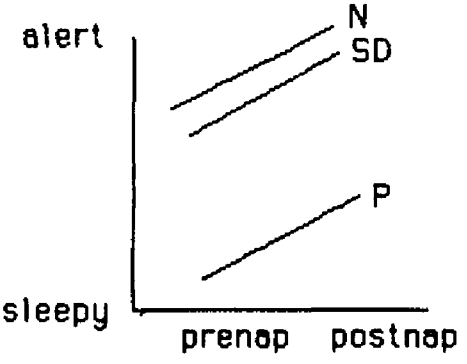
Pathology sleepiness measures

(Differentiated the patients from the two normal groups)

Extent of pupillary contraction

Maximum contraction speed

Maximum recovery speed (?)



N- well rested normals

SD- Sleep deprived

P- apnea patients

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