THE EFFECT OF SLEEP FRAGMENTATION ON DAYTIME FUNCTION

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ABSTRACT

Sleep fragmentation is the term used to describe brief awakenings or microarousals from sleep which are less than 15 seconds long and often occur without the awareness of the sleeping subject. Arousals is the collective term for awakenings >15 seconds and microarousals < 15 seconds. Patients with sleep apnoea/ hypopnoea syndrome (SAHS) have recurrent upper airway obstructions during sleep usually terminated by arousals and decreases in oxygen saturation. They suffer from impaired daytime function which correlates weakly with their nocturnal hypoxemia and sleep fragmentation. These are interrelated making it difficult to distinguish which is the cause of daytime dysfunction in SAHS patients. This thesis examines the impact of sleep fragmentation alone on daytime function by inducing sleep fragmentation in normal subjects and studying their subsequent daytime function.

A problem associated with studying sleep fragmentation is its poor definition. Current arousal definitions use a combination of a greater than 1 second increase in EEG frequency with or without increased EMG activity depending on sleep stage. This can lead to difficulties in comparing results between studies. Although the American Sleep Disorders Association (ASDA) has published guidelines on visual scoring of arousals they have not been validated or compared with other arousal definitions currently in use. Therefore 3 different arousal definitions and 1 definition of awakening were compared in SAHS patients. The definitions were (1) ASDA (3 seconds), (2) ASDA modified to 1.5 seconds, (3) Cheshire 1.5 second. The awakening was defined as a Rechtschaffen and Kales' stage shift to wakefulness. There were significantly more arousals of any kind than awakenings, and significantly more 1.5 second arousals by either definition than ASDA arousals. However not all apnoeas and hypopnoeas were terminated by visible EEG arousals with at best, 83% of respiratory events being terminated by 1.5 second ASDA arousals. There were weak but significant

relationships between microarousals scored by any definition and daytime sleepiness on the multiple sleep latency test (MSLT).

The first sleep fragmentation protocol examined the effects of one night of induced visible EEG arousals on the daytime function of normal subjects. The subjects were objectively sleepier during the day after fragmentation as measured by both the MSLT and the maintenance of wakefulness test (MWT). Subjects had altered mood on the UWIST mood adjective checklist following sleep fragmentation; energetic arousal was diminished all day except at 12.00, hedonic tone was decreased at 10.00, and tense arousal was increased at 08.00 and 10.00. Subjects had impaired performance on 2 tests of cognitive function; Trailmaking B, a test of mental flexibility, and on PASAT 4 seconds, a test of sustained attention. These deficits were similar to those seen in SAHS patients prior to CPAP therapy.

There are subgroups of patients with sleep apnoea whose apnoeas and hypopnoeas occur when they are lying supine or when they are in REM sleep. This allows them to obtain periods of uninterrupted sleep which may be sufficient to overcome any daytime dysfunction that may have occurred due to their REM or posture related sleep apnoea. Therefore 2 fragmentation paradigms were compared; regular fragmentation every 90 seconds of sleep, and clustered fragmentation every 30 seconds for 30 minutes every 90 minutes. There was no difference in arousal frequencies between study nights. There were no differences in daytime function despite significantly less stage 2 and more slow wave sleep on the clustered fragmentation night. This suggests that deficits in daytime function are dependent on sleep fragmentation and not stage 2 or slow wave sleep.

Not all apnoeas and hypopnoeas are terminated by visible EEG arousals but are terminated by transient increases in blood pressure. The impact of these transient increases in blood pressure on daytime function are unknown. Therefore daytime function was compared after an undisturbed night's sleep and one night of sleep fragmentation to cause blood pressure elevations alone without coincident visible EEG arousals. There was

significantly less slow wave sleep on the fragmented study night but there was no difference in visible EEG arousals between study nights. Non-visible sleep fragmentation made subjects sleepier during the day on the MSLT and MWT, and decreased hedonic tone upon awakening. There was no effect on cognitive function.

Finally changes in EEG frequencies during visible EEG arousals were examined using Fast Fourier Transformation (FFT). There were significant increases in all physiological frequencies of human sleep within 5 seconds of the start of an arousal. During the non-visible fragmentation night alpha EEG power was determined with FFT. There was a significant increase in peak alpha power within 5 seconds of a tone whether that tone produced a visible EEG arousal or not. This suggests that computerised analysis of the EEG may be useful in measuring sleep fragmentation.

For Hugh

DECLARATION

I declare that I have been the principal investigator in all the studies presented in this thesis and that the contents of this thesis are my own work. I have been assisted in aspects of these studies by various members of staff of the sleep laboratory whose contributions have been noted in the acknowledgements section.

This work was performed in the sleep laboratories within the Rayne Laboratory, City Hospital, Edinburgh and the Royal Infirmary, Edinburgh between 1994 and 1997.

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ABBREVIATIONS

AHI	Apnoea+ Hypopnoea Index
ASDA	American Sleep Disorders Association
BMI	Body Mass Index (kg/ m^2)
CPAP	Continuous Positive Airway Pressure
ECG	Electrocardiograph
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalograph
EMG	Electromyograph
EOG	Electrooculograph
ESS	Epworth Sleepiness Scale
FFT	Fast Fourier Transformation
HAD	Hospital Anxiety and Depression scale
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
PLMS	Periodic Limb Movement Syndrome
PTT	Pulse Transit Time
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
SAHS	Sleep Apnoea/ Hypopnoea Syndrome
SaO2	Oxygen Saturation
SDB	Sleep Disordered Breathing
SSS	Stanford Sleepiness Scale
SWS	Slow Wave Sleep
UAR	Upper Airway Resistance
UPPP	Uvulopalatopharyngoplasty

Chapter 1

Sleep apnoea/ hypopnoea syndrome (SAHS); background and treatment.

1.1 Background

The sleep Apnoea/Hypopnoea syndrome (SAHS) is a relatively common condition in the general population (Young et al 1993) whereby the sufferer's upper airway is repetitively completely (apnoea) or partially (hypopnoea) sucked closed during sleep. Patients suffer from SAHS for a variety of reasons, outlined in more detail in the following introduction. When the SAHS patient falls asleep combinations of factors lead to their upper airway gradually becoming obstructed. During an apnoea the patient keeps trying to breathe against the obstructed airway but has to undergo some degree of arousal from sleep in order to clear the obstruction. Once the upper airway is open, in the more severe cases, the patient will fall straight back to sleep only for the cycle to repeat itself. This tends to result in highly disrupted or fragmented sleep which can leave the patient feeling very sleepy during the day. In addition these patients may suffer from impaired daytime mood and performance. The focus of this introduction is to describe SAHS and the factors that contribute to it, to outline previous research on sleep apnoea and daytime function, and to describe previous research on sleep disruption in normal subjects.

1.2 Uncovering Sleep Apnoea

Apnoea literally means absence of breath during sleep. It was first described polygraphically by Gastaut et al (1965, 1966), and independently by Jung et al (1965), in patients suffering from the Pickwickian syndrome. It was characterised as repetitive upper airway obstructions during sleep terminated by electroencephalograph (EEG) defined arousals from sleep and associated with decreases in arterial oxygen saturation. These patients also suffered from excessive somnolence. Although this led to better

understanding of the pathophysiology of Pickwickian syndrome it also provoked interest in the study of breathing during sleep alone without associated cardiorespiratory problems. A symposium on sleep related respiratory problems in Europe drawing together the fields of neurology and respiratory medicine (Sadoul and Lugaresi 1972) served to recognise sleep apnoea as a primary disorder not necessarily associated with obesity or cardiorespiratory problems, both of which are characteristics of the Pickwickian syndrome.

Gastaut et al (1965, 1966) described 3 types of apnoea as episodes of complete cessation of airflow for more than 10 seconds associated with; (1) cessation of respiratory effort (central), (2) continued respiratory effort (obstructive), and (3) initial cessation of respiratory effort which resumes midway through the event (mixed). True central sleep apnoea is rare and will not be dealt with in this thesis. In an early published series of 62 patients with sleep apnoea, Guilleminault et al (1976) found that most had obstructive or mixed apnoeas during sleep.

1.3 Obstructive Apnoea- Sequence of Events

During sleep muscle tone decreases throughout the body which, as it includes the upper airway dilating muscles, invariably results in narrowing of the upper airway. In patients with disorders of breathing during sleep this loss of muscle tone in the upper airway dilating muscles leads to narrowing of the upper airway. This may result in increased upper airway resistance, snoring or, in patients with sleep apnoea, the generation of increasingly negative intraluminal pressures in the upper airway so that it occludes. During the resulting apnoea increasingly negative intrathoracic pressure is generated with each occluded inspiratory effort until a critical level is reached (Gleeson et al 1990) and the patient arouses from sleep and clears the upper airway obstruction. The patient resumes breathing, returns to sleep and in severe cases the cycle begins again instantly. Most apnoeas and

hypopnoeas terminate in visible EEG arousals from sleep. In addition apnoeas and hypopnoeas terminate in transient increases in arterial blood pressure (Shepard 1986) regardless of whether there is an EEG arousal or not. This is reflected in the finding of Rees et al (1995) that even if respiratory events do not terminate in a visible EEG arousal there are increases in computer detectable EEG frequency. Upper airway obstructions may be accompanied by decreases in arterial oxygen saturation in older or more overweight patients which, due to a combination of delays, both physiological and within the technique of measuring oxygen saturation, reach their nadir after breathing has resumed.

1.4 Symptoms of Sleep Apnoea

The most common symptoms of sleep apnoea include snoring, uncontrollable daytime sleepiness, nocturnal choking attacks, restless and/ or unrefreshing sleep, personality changes, poor concentration and memory and decreased sex drive (Guilleminault et al 1976, Whyte et al 1989). Patients with sleep apnoea cannot be diagnosed on their symptoms but need to have objective evidence from overnight monitoring. Hillerdal et al (1991) demonstrated that heavy snorers and patients with SAHS could not be separated on the basis of their symptoms alone. Amongst these symptoms this thesis will focus on the daytime sleepiness, impaired mood and cognitive function that are found in SAHS patients. The relative contributions of nocturnal events to these impairments are discussed in greater detail in chapter 2 dealing with SAHS and daytime function.

1.5 Defining Sleep Apnoea

The term sleep apnoea covers a broad range of disease. The relationships between nocturnal indicators of SAHS i.e. number of apnoeas and hypopnoeas, and daytime sleepiness are poor (section 2.7) and therefore combining patient symptoms and objective evidence from nocturnal monitoring to define the condition is important in the determination of who receives treatment.

Early definitions of sleep apnoea included 30 apnoeas in 7 hours of sleep (Guilleminault et al. 1976), 5 apnoeas per hour of sleep (Guilleminault et al 1978) and 10 apnoeas per hour of sleep (Lavie 1983). Apnoeas were defined as a minimum of 10 seconds in duration. These definitions were largely arbitrary and as most patients referred to sleep apnoea clinics at that time had hundreds of apnoeas in any night's sleep, were not often implemented as exclusion criteria for treatment (Guilleminault et al 1976).

As awareness of the disorder and the numbers of patients referred to sleep centres who had symptoms of sleep apnoea, but milder forms of the syndrome, increased, (Whyte et al 1989) definition of sleep apnoea became more crucial. Lugaresi et al (1983) recognised the need for describing the less severe forms of sleep apnoea. They suggested that trivial snoring was the beginning point and severe sleep apnoea the end point along a continuum of disease progression. They divided this continuum into 4 stages based on objective monitoring of respiration during sleep and daytime sleepiness. The stages were: preclinical; with sporadic apnoeas, initial; when apnoeas occurred during stage 1, 2 and REM sleep, overt; apnoeas throughout all stages of sleep, and complicated; when alveolar hypoventilation persists during wakefulness. Interestingly they also divided patients into 4 stages of daytime somnolence, however the nocturnal and daytime observations did not match.

Gould et al (1988) recognised that some patients with clinical features of sleep apnoea did not have apnoeas but had recurrent nocturnal

hypoventilation with arousal. These events were termed hypopnoeas and a definition of greater than 50% decrease in thoracoabdominal movement for at least 10 seconds was validated in a series of patients. This led to a definition of the sleep apnoea/ hypopnoea syndrome (SAHS) as more than 15 apnoeas + hypopnoeas per hour of sleep (AHI) associated with 2 major symptoms out of those outlined previously.

The above definition of hypopnoea is not universal with some laboratories requiring a 50% decrease in oronasal airflow rather than thoracoabdominal movement. Many laboratories require a 4% decrease in arterial oxygen saturation associated with either of the above. The above definitions are based on polysomnography evaluation of sleep and breathing and although sleep apnoea can be diagnosed using limited sleep studies which concentrate on respiratory and/ or oxygen saturation signals, their reliability in accurate diagnosis of milder forms of sleep apnoea remains questionable (Douglas et al 1992, Gugger et al 1995).

1.6 Epidemiology of SAHS

Sleep apnoea syndrome is only 30 years old as a medical disorder. Since the first description by Gastaut et al (1965) clinicians dealing with this condition have reported exponentially increasing numbers of patients being referred for treatment (Whyte et al 1989). However epidemiological studies have only recently begun to estimate the true prevalence of this disorder in the general population. Indeed the UK has lagged behind the USA and Australia in the recognition and diagnosis of sleep apnoea (Shapiro et al 1981) which has led to the early suggestion that there may be fewer sleep apnoea patients in this country. Data from Stradling and Crosby (1991a) however suggests that this is not the case.

There are methodological difficulties in performing such epidemiological studies. Definitions of what constitutes clinically significant sleep apnoea have moved forward considerably from suggestions of 5

apnoeas per hour of sleep (Guilleminault 1976). The significance of partial breathing pauses (hypopnoeas) (Gould et al 1988) and the subsequent elucidation of minimum criteria for diagnosis of SAHS (AHI>15 with 2 major symptoms) has been somewhat superseded by the findings that patients with milder sleep apnoea can benefit from treatment (Engleman et al 1997). Some laboratories use oximetry to diagnose sleep apnoea (Stradling and Crosby 1991a), however this technique has been reported to miss some 33% of patients with significant SAHS (Douglas et al 1992). In addition there is the argument that patients only have sleep apnoea when they suffer from symptoms, in addition to having a positive diagnosis on objective nocturnal measures of oximetry, breathing pattern and/ or sleep (Young et al 1993). This should be interpreted with caution as patients may not have an insight into their "symptoms". This applies in particular, to two of the major symptoms of sleep apnoea, snoring and daytime sleepiness. Snoring is often reported by the bedpartner, as the snorer is unaware because they are asleep, and SAHS patients may deny daytime sleepiness as they have lost their frame of reference (Dement et al 1978). Studies can also be biased by selection procedures. Patients consenting for polysomnography in studies of this nature may do so because they suspect that they have a sleep disorder.

Early epidemiological studies in Italy (Franceschi et al 1982) and Israel (Lavie 1983) found that 1.1% of hospital inpatients, and 1.0% of industrial workers had sleep apnoea. These percentages may have been underestimated due to the relatively strict diagnostic criteria used in these studies of greater than 10 apnoeas per hour of sleep. In the Israeli study Lavie points out that results may have been biased by the large percentage of subjects with EDS who consented to polysomnography (26% of subjects who had polysomnography had EDS) compared with 8% of the total sample suffering from EDS. Both these studies included a wide age range and subsequent studies have focused on middle aged subjects as most patients referred to sleep clinics with sleep apnoea are in this age group.

Cirignotta et al (1989) found that 3.3% of their male sample (aged 30 to 69) had an apnoea index greater than 10 per hour of sleep, but concluded that only 0.5% had symptomatic apnoea requiring treatment. Stradling and Crosby (1991a) found a similar number of subjects with severe symptomatic sleep apnoea (0.3%). This study circumvented the problem of self interest in its selection process for polysomnography by performing home oximetry on 900 middle aged men. They found that 46 (5%) subjects had 4% oxygen desaturation dip rates >5/hour, and of these, 3 had severe symptomatic sleep apnoea and a further 18 had sleep apnoea when supine only, giving a prevalence rate of 2%. This may be an underestimation as polysomnography failed technically in 15 subjects and oximetry may underdiagnose patients with sleep apnoea (Douglas et al 1992). In America, Young et al (1993) found that 4% of men and 2% of women had AHI > 5 + daytime sleepiness but that 24% of men and 9% of women had AHI > 5 alone. The high ratio of men: women (2:1) with sleep disordered breathing in this study is similar to that found by Jennum and Sjol (1992) in Denmark. This is similar to Bearpark et al (1995) who reported a high prevalence of sleep apnoea in Australia. Twenty four percent of middle aged men had respiratory disturbance indices (RDI; equivalent to AHI) > 5, however only 3% of subjects had RDI>5 and coexisting daytime sleepiness.

In summary these studies show that severe symptomatic sleep apnoea may have a prevalence of approximately 3/ 1000 middle aged men, but that milder forms of the syndrome are relatively common (3 to 4/100 middle aged men).

These findings in women (Young et al 1993, Jennum and Sjol 1992) are of particular interest as this is a considerably higher proportion of women in the population with sleep apnoea than has been seen in sleep apnoea clinics where the ratios of men: women was approximately 8:1 (Whyte et al 1989). It is unclear why a greater proportion of men than women are referred for evaluation in sleep apnoea clinics. There is however some evidence that women present with different symptoms at the clinic more indicative of

insomnia (Ambrogetti et al 1991) and that they underreport classic sleep apnoea symptoms such as snoring, nocturnal gasping and witnessed apnoea (Redline et al 1994).

1.7 Mortality in Sleep Apnoea

Untreated sleep apnoea is associated with increased mortality and treatment with tracheostomy improves survival. However the data for survival after treatment with uvulopalatopharyngoplasty (UPPP) or continuous positive airway pressure (CPAP) (see section 1.12, 1.13) are ambiguous. Partinen et al (1988) found that out of 198 patients who were followed up after 5 years there were 14 deaths. These deaths all occurred in the patients who had been conservatively treated, with encouragement to lose weight, as opposed to those who had had a tracheostomy. He et al (1988) found that mortality was higher in untreated patients with an apnoea index greater than 20 compared with those less than 20. This was true whether patients were older or younger than 50. In the treated patients significantly more patients who had had UPPP died (8 deaths) than those who had had CPAP or a tracheostomy (0 deaths). Keenan et al (1994) however found no difference in long term survival over 6 years between CPAP and UPPP treated SAHS patients. These latter 2 studies had low numbers of deaths for reliable comparison between UPPP and CPAP. Performing long term prospective studies assessing CPAP or UPPP for reducing mortality in SAHS is ethically impossible as patients with SAHS cannot be diagnosed and left untreated.

1.8 Mild SAHS, Snoring, Increased Upper Airway Resistance

Patients with mild sleep apnoea may only have respiratory events during REM sleep or when they are lying supine. Apnoeas during REM sleep were originally dismissed by Guilleminault et al (1976) as non-pathologic due to the inherent respiratory instability found in REM sleep (Douglas 1994). In

addition REM sleep occurs every 90 minutes during nocturnal sleep and therefore patients with REM-sleep apnoea may have time in between REM periods where they have relatively uninterrupted sleep. This sleep will include slow wave sleep (SWS) which has been suggested as the sleep required for adequate cerebral functioning (Horne 1988). In postural related sleep apnoea respiratory events may occur during time spent asleep in the supine position. If the patient alternates between body positions there will be periods during the night when they obtain uninterrupted sleep. It is unclear whether these periods of uninterrupted sleep are sufficient to allow normal daytime functioning. The question of how much sleep and of what type is required to be restorative is dealt with in the section on sleep deprivation and disruption (section 2.11).

In recent years the rigid definitions of SAHS have become less fixed with the recognition that some patients with the clinical indications of sleep apnoea nonetheless have AHI <15 (Young et al 1993). Engleman et al (1997) found that patients with mild sleep apnoea (AHI; 5 to 15 per hour of sleep) can benefit from CPAP therapy, the treatment of choice for sleep apnoea. It has also emerged that patients may become symptomatic for sleep apnoea when they do not have even mild sleep apnoea, i.e. AHI< 5 per hour slept, but suffer from heavy snoring or even increases in upper airway resistance (Guilleminault et al 1991, Guilleminault et al 1993). These findings lend support to the theory of Lugaresi et al (1983) that snoring is the initial phase and severe sleep apnoea the end phase of a continuum of disease which has common pathophysiology. Increased upper airway resistance may occur prior to the development of snoring. Collectively increased upper airway resistance (UAR), snoring and sleep apnoea syndromes of varying severities have become known as sleep disordered breathing (SDB).

1.9 Risk Factors for SAHS

The obese middle aged man has long been the classical image of the sleep apnoea patient and in early clinical reports this description fitted a large number of the patients (Guilleminault et al 1976). Indeed in all of the above epidemiological studies, apart from Lavie (1983), obesity was significantly associated with the incidence of sleep apnoea. Although sleep apnoea is common in middle age, evidence on the relationship between age and the incidence of sleep apnoea is inconclusive. Bearpark et al (1995) and Young et al (1993) did not find any significant relationship between age and SDB whereas Jennum and Sjol (1992) and Stradling and Crosby (1991a) did. In a similar fashion Jennum and Sjol (1992) found significant contributions of both smoking and alcohol intake to the incidence of SDB but Bearpark et al (1995) and Lavie (1983) did not. Stradling and Crosby (1991a) found that alcohol intake but not smoking was a small (1%), but significant, independent predictor of the 4% oxygen desaturation index.

1.10 Neck Circumference and the Upper Airway

The main risk factors for SAHS of male sex and obesity may be linked. Men generally deposit adipose tissue centrally around the trunk and abdomen whereas women deposit it around the periphery (Edwards 1951). Vague (1956) termed excess fat deposition in these areas android and gynoid obesity respectively and suggested that the region over the first three cervical vertebrae was the area where at equal body weights men have more fat than women. A large proportion of women with SDB are postmenopausal (Redline et al 1994) which may be related to their increased central fat deposition (Edwards 1951).

It can be argued that measuring neck circumference would be a good indicator of fat deposition around the first 3 cervical vertebrae. Studies in normal subjects suggest that for equal body mass indices (BMI; kg/m^2) men and women have significantly different neck circumferences (Martin et al

1994) with the regression lines for each relationship approximately parallel. Stradling and Crosby (1991a) found that neck circumference was the best predictor for the incidence of sleep apnoea (r^2=7.9%) in the epidemiological study described in section 1.6. In SAHS patients, Katz et al (1990) found that external neck circumference was a better predictor for severity of sleep apnoea than BMI or age, and Davies et al (1992) found that neck circumference was the single best predictor for SaO2 dip rate. Neck circumference accounted for 29% (Katz et al 1990) and 35% (Davies et al 1992) of the variance in severity of disease.

Eller Shelton et al (1993), using magnetic resonance imaging (MRI), measured fat deposition in the neck. They found that SAHS patients had increased volume of adipose tissue adjacent to the upper airway compared to normals and that this correlated significantly with AHI. Although the authors did not control for BMI, there was no relationship between BMI and adipose tissue volume suggesting that SAHS patients have an increased tendency to deposit fat in the neck regardless of obesity. This fat deposition in SAHS patients may increase mass loading of the upper airway which in turn may lead to increased upper airway resistance (Koenig and Thach 1988) and a greater tendency to occlusion. However the link between obesity and sleep apnoea cannot solely be caused by increased neck fat deposition leading to increased mass loading of the upper airway as Grunstein et al (1993) found that waist circumference was a better predictor of sleep apnoea severity than either neck circumference or BMI.

The upper airway of SAHS patients is already compromised even before any potential effect of mass loading around it can be taken into account. Studies measuring upper airway dimensions using acoustic reflection (Bradley et al 1986, Martin et al 1995), MRI (Rodenstein et al 1990, Schwab et al 1993) and cephalometry (Lowe et al 1986, Jamieson et al 1986, Yildirim et al 1991) have shown that SAHS patients have smaller internal upper airways than normal subjects while awake. In addition the upper airway in sleep apnoea patients appears to be 'floppier' than normal

subjects. Suratt et al (1985) found that SAHS patients' upper airways were more collapsible compared to normals, Brown et al (1985) that they were more compliant, and Brown et al (1987) that with the application of positive pressure SAHS patients had more distensible upper airways than normal subjects. Recent evidence suggests that during wakefulness SAHS patients defend their upper airway and that this loss of defense during sleep may contribute to upper airway collapse/ occlusion. Mezzanotte et al (1992) found that genioglossal EMG tone in SAHS patients is increased compared to normals, and we (Martin et al 1995) found that SAHS patients have a smaller decrease in the upper airway dimensions upon lying supine compared to snorers or BMI matched control subjects.

In addition to the upper airway of SAHS patients being smaller than non-SAHS patients and normals there is also evidence that SAHS patients have a differently shaped upper airway. Rodenstein et al (1990), and Schwab et al (1993) using MRI suggested that SAHS patients had upper airways with anterior- posterior alignment compared to normals whose airways were aligned in a lateral fashion.

1.11 Genetic Predisposition to SAHS

The altered bony structures in the upper airways of SAHS patients may have a genetic component. Strohl et al (1978) within one family noted the presence of sleep apnoea in more than one family member. The predominant risk factor for this family was obesity. Obesity itself runs in families (Stunkard et al 1986) which makes it difficult to interpret whether SAHS is truly a heritable disease. The finding in sleep apnoea clinics that not all patients with SAHS are obese suggests that there are other heritable risk factors for the presence of sleep apnoea. There are many genetic disorders that are associated with SAHS most notably Down's syndrome and Prader-Willi syndrome in both of which obesity is a common problem and may exacerbate their predisposition to SAHS.

Pillar and Lavie (1995) found that 47% of the offspring of SAHS patients had AHI > 5 and 13% had AHI>20. Redline et al (1995) found that 13% of relatives of SAHS patients, compared to 6% of neighbourhood control subjects had sleep apnoea (AHI> 15 + one major symptom). In this study however relatives were significantly older than controls and 83% of the index SAHS patients were obese, both of which may have predisposed the relatives towards having a greater incidence of sleep apnoea compared to control subjects.

Mathur and Douglas (1995a) performed a similar case control study but only used index SAHS patients with BMI<30 to factor out the familial effects of obesity. Relatives were matched for age, sex, height and weight with control subjects drawn from a GP register. They found that relatives had increased AHI, arousal indices and 2% and 3% desaturation indices, and more relatives had symptoms of sleep apnoea than controls. In addition relatives had altered craniofacial morphology similar to that found in SAHS patients (Lowe et al 1986, Jamieson 1986) compared to controls. This suggests that craniofacial abnormality may mediate the inheritance of SAHS in non-obese patients.

1.12 Treatment of Sleep Apnoea/ Hypopnoea Syndrome

Common treatments of sleep apnoea fall into four categories; conservative, surgical, mechanical devices, or continuous positive arway pressure (CPAP). Conservative therapy consists mainly of encouraging patients to lose weight, due to the relationship between body mass index (kg/m2) and severity of sleep apnoea as measured by the apnoea + hypopnoea index, and avoiding evening alcohol (Engleman et al 1993). Surgical treatments include tonsillectomy (mainly used in children), craniofacial surgery for correction of craniofacial abnormalities (Riley et al 1990) which can occur in SAHS patients (Jamieson et al 1986), and tracheostomy (Guilleminault 1976), which was the only treatment for sleep

apnoea until 1981. A further surgical treatment, uvulopalatopharyngoplasty (UPPP), was introduced for sleep apnoea by Fujita et al (1981) which involves the surgical removal of the uvula and part or all of the soft palate. There is burgeoning interest in mechanical devices for the treatment of sleep apnoea (Lowe 1994) which fall into 2 categories; (1) simple non-prescription devices for snoring which act by keeping the mouth closed and preventing mouth breathing (e.g. snoreguard) or increasing the nasal airspace to reduce nasal resistance (e.g.nosovent), (2) appliances which act by gradual advancement of the mandible to increase upper airway area which is smaller in patients with sleep apnoea (Yildirim et al 1991, Martin et al 1995). These latter devices are complex appliances currently under assessment for treatment of sleep apnoea (Lowe 1996).

Around the same time as Fujita et al (1981) described UPPP treatment for SAHS, Sullivan et al (1981) described continuous postive airway pressure therapy (CPAP) for sleep apnoea. This acts as a pneumatic splint holding the upper airway open. The CPAP machine pumps air at positive pressure into the upper airway via a mask held in place over the patient's nose with straps fitted over the back of the head. The pressure required by the CPAP machine to hold the upper airway open during sleep and prevent apnoeas and hypopnoeas occurring can be titrated in the sleep laboratory on an individual basis. The patient then takes the machine home with instructions to use it every night while sleeping.

1.13 Efficacy of Treatment

The goals of treatment for sleep apnoea are to produce a resolution of symptoms, notably snoring and daytime sleepiness, via minimising or eliminating apnoeas and hypopnoeas. Conservative therapy may be indicated for young patients for whom the intrusive nature of CPAP or its requirement as a therapy for life may discourage them from using it, or for those with milder sleep apnoea whose symptoms are not severe enough for

them to tolerate CPAP. However Partinen et al (1988) found that patients treated conservatively had almost a 5 times greater chance of vascular mortality than those treated with a tracheostomy. In addition Engleman et al (1993) found that conservative treatment did not improve daytime sleepiness in patients with sleep apnoea. Simple non-prescription devices for snoring may be attractive for some individuals due to their relative non intrusiveness compared to CPAP, however there is a lack of placebo controlled trials of their effectiveness in reducing apnoea + hypopnoea index or resolving symptoms (Lowe et al 1994). There is also a cost consideration in the U.K. as these devices are not generally available through the NHS.

CPAP is now accepted as the therapy of choice for sleep apnoea due to problems with UPPP. He et al (1988) found that the cumulative probability of survival after UPPP over 7 years was similar to that of untreated SAHS patients. Polo et al (1989) found that UPPP, while reducing apnoeas, actually led to an increase in hypopnoeas which may themselves be pathological (Gould et al 1988). Sangal et al (1992b) found that there was no significant reduction in respiratory events in 11 patients followed up within 1 to 6 months after UPPP. These results may be due to UPPP only dealing with upper airway obstruction in the nasopharynx, which does not include those patients who obstruct retroglossally or those who have upper airway obstruction in both areas of the upper airway (Chaban et al 1988, Shepard et al 1990). In addition patients who require further treatment for their sleep apnoea after UPPP may find use of CPAP difficult due to problems with mouth leak at higher CPAP pressures (Polo et al 1994).

1.14 Concluding Remarks

The aim of this chapter has been to give background information on the sleep apnoea/ hypopnoea syndrome. It has dealt with the recognition and definition of the syndrome, and its prevalence in the population. There are various risk factors leading to SAHS, including its heritability and how male sex and obesity affects it with increased neck circumference. The treatment of choice for sleep apnoea is CPAP therapy but there is controversy about whether it actually improves mortality in SAHS. The following chapter deals with daytime function in normal subjects and SAHS patients.

Chapter 2

Daytime function in patients with sleep apnoea hypopnoea sydrome and during sleep intervention studies in normal subjects.

2.1 DAYTIME FUNCTION

The rationale behind this thesis is the fact that patients with sleep apnoea/ hypopnoea syndrome suffer from impaired daytime function. They are pathologically sleepy during the day (Roth et al 1980) and have decrements in their neuropsychologic function compared to control subjects (Greenberg et al 1987). More recently Engleman et al (1994a) demonstrated that some of these decrements are reversible with CPAP therapy. This following chapter will focus on previous research in this area. This includes describing the methods available for measuring daytime function, sleep intervention studies in normal subjects (sleep deprivation, restriction and disruption), and studies of daytime function in patients with sleep apnea. This chapter will also focus on the relationships between nocturnal sleep and breathing variables and daytime impairments and on the resolution of SAHS patients' impairments with CPAP therapy.

2.2 Measuring Daytime Sleepiness

Sleepiness can either be measured subjectively, with questionnaires or objectively using sleep EEG. The most commonly used tests for daytime sleepiness in patients with sleep apnoea are:

Subjective

Stanford Sleepiness Scale (SSS) (Hoddes et al 1973).

This is a Likert type scale where a patient rates their sleepiness *at that moment* on a seven point scale, 1 being wide awake, and 7 being practically asleep.

Epworth Sleepiness Scale (ESS) (Johns 1991)

The scale consists of asking the patient whether they would never (0), have a slight chance (1), moderate chance (2), or high chance (3) of dozing in 8 daily situations. Patients are asked to answer the questions with reference to their "life in recent times" (see Appendix 1). The maximum of 24 indicates excessive sleepiness. This scale involves reflection over past experience rather than the instantaneous assessment of the SSS.

Objective

Multiple Sleep Latency Test (MSLT) (Dement et al 1978)

Subjects are asked to lie down in bed in a dark room and try to sleep for 20 minutes, 4 or 5 times during the day, at 2 hourly intervals. Sleep is monitored with polygraphically recorded EEG in 30 second epochs. Sleep onset is determined as the time to the first epoch of any stage of sleep including stage 1 (Thorpy 1992). An epoch is scored asleep if at least 50% of that epoch is indicative of any sleep stage. The sleep onset latency was originally the time to 3 consecutive epochs of stage 1 sleep or the first epoch of any other sleep stage (Carskaddon et al 1986) but was changed as some sleep apnoea patients have apnoeas as soon as they fall asleep and then arouse themselves and therefore never get 3 consecutive epochs of stage 1 sleep. The mean sleep onset latency is calculated as the mean of the individual sleep onset latencies from the 4 or 5 naps. Normal daytime sleepiness consists of a mean sleep onset latency of between 10 and 20 minutes. Pathological daytime sleepiness is less than 5 minutes with the grey area of undefined sleepiness between 5 to 10 minutes (Thorpy 1992).

Maintenance of Wakefulness Test (MWT) (Mitler et al 1982)

(Repeated Test of Sustained Wakefulness)

Subjects are asked to sit upright in a bed or an armchair, in a dimly lit room and are asked to try to remain awake for 40 minutes, 4 times during the day,

again at 2 hourly intervals. They are not allowed to read, sing, exercise their limbs or do anything physical which may help them stay awake. Again sleep is monitored with polygraphically recorded EEG and the sleep onset latency is the time to the first epoch of any sleep stage. This test was originally described by Mitler et al (1982) with 20 minute naps, and by Hartse et al (1982) with 30 minute naps. This was extended to 40 minutes by Poceta et al (1990a, 1990b) to minimise ceiling effects. Again mean sleep onset latency is calculated from the individual sleep onset latencies over the 4 naps.

The effect of instructing subjects to remain awake and to sit upright rather than lie down increases the sleep onset latency on the MWT compared to the MSLT in normals (Hartse et al 1982). In patients referred to a sleep clinic for their daytime sleepiness instructing them to remain awake increases their sleep onset latency from 8.4 minutes on the MSLT to 26.5 minutes on the MWT. The MWT has not been used nearly as extensively as the MSLT and therefore validated data as to what constitutes normal or pathological sleep onset latencies on this test are not available yet.

2.3 Measuring Mood

Patients with sleep apnoea may suffer from alterations in personality, notably increased irritability (Whyte et al 1989). There is controversy over whether sleep apnoea alone can lead to clinical depression (see section 2.14) however it is clear that SAHS patients can have clinically significant scores on questionnaires which are used in clinical settings to aid diagnosis of anxiety and depression (Cheshire et al 1992). In the series of studies presented in this thesis sleep fragmentation is being modeled in normal subjects in whom it is difficult to mimic the chronicity of sleep apnoea and its subsequent effect on mood and personality. Therefore instantaneous measurements of mood as described by Matthews et al (1990) were used.

Thayer (1989) postulated that arousal, that is wakefulness as opposed to arousal from sleep, was a basic component of mood which could not be described in a single way but involved interaction between more than one process. This led to the idea of 2 different ways of describing arousal; energetic arousal and tense arousal which varied in orthogonal directions to one another to produce well documented mood states; e.g. tense-tiredness (high tense arousal, low energetic arousal), and calm-energy (low tense arousal, high energetic arousal). Matthews et al (1990) refined measurements of mood to produce the UWIST (University of Wales Institute of Science and Technology) mood adjective checklist (UMACL) using factor analysis of items from various mood scales. In addition to the original energetic arousal and tense arousal dimensions of mood, which were not interrelated, they added a pleasure- displeasure dimension termed hedonic tone, which had moderate relationships to both arousal dimensions.

Thayer (1989) suggested that arousal as a component of mood has its basis in biological systems, with energetic arousal mediated by the reticular activating system, which also mediates arousal stimuli from the brainstem to the cortex during sleep, and tense arousal by the autonomic nervous system. Studies by Gold et al (1995), Hepburn et al (1995) and Hepburn et al (1996) tested this hypothesis using acute insulin induced hypoglycaemia as a biological stressor. These studies showed that hedonic tone and tense arousal alterations in mood closely followed the autonomic activation seen in response to hypoglycaemia whereas energetic arousal changes mirrored the changes in cerebral function seen in response to hypoglycaemia.

In a similar fashion the sleep fragmentation protocols presented in this thesis in chapters 5 and 6 could be described as interventions aimed at the reticular activating system and the autonomic nervous system respectively.

2.4.1 Daytime Sleepiness in Sleep Apnoea; Subjective

Hypersomnolence has long been associated with sleep apnoea. In the categorisation of Pickwickian syndrome the concurrence of daytime sleepiness and nocturnal apnoea was noted (Gastaut et al 1965). Quantitative assessment of this problem has traditionally been difficult due to the apparent lack of insight that the sleep apnoea patient has into their own sleepiness (Dement et al 1978), and the patients' fears that admissions of sleepiness, particularly related to driving, may jeopardise their job. Although there is a significant relationship between polygraphic sleep onset and Stanford Sleepiness Scale (SSS) score (Hoddes et al 1973) in normal subjects, this relationship is uncoupled in SAHS patients (Dement 1978). Roth et al (1980) found that SAHS patients rated themselves as alert as normal subjects on the SSS and anecdotally reported that some patients rated themselves as being fully alert whilst to the observer they were practically asleep. These poor results may be due to the nature of the SSS which is instantaneous and does not allow for sleepiness in different daily situations. Patients with sleep apnoea often report that if they are performing a stimulating task then their sleepiness can be overcome but it is when they are in a monotonous or relaxing situation that their sleepiness may be overwhelming. In addition patients with sleep apnoea, who may have been suffering from excessive sleepiness for a prolonged time may have adjusted their frame of reference so that they cannot accurately rate their own sleepiness.

The development of the Epworth Sleepiness Scale (ESS) (Johns 1991, 1992, 1993) has addressed these problems by asking questions that are specifically related to sleepiness and require discrete answers about the patient's recent experience (Appendix 1). Johns (1991) found that patients with sleep disorders that included daytime sleepiness as a symptom scored significantly higher than normal subjects. There were significant relationships between respiratory disturbance index (RDI) and ESS in SAHS patients, and ESS and objective daytime sleepiness as measured by the multiple sleep

latency test (MSLT) in a group of patients diagnosed with sleep disorders. In a second study Johns (1992) found that there was no difference between two ESS scores of 87 medical students 5 months apart, confirming test-retest reliability. Also ESS improved with CPAP therapy in 54 SAHS patients to within the range scored by normal subjects (Johns 1992). This was confirmed by Hardinge et al (1995) in a recent report. Using factor analysis Johns (1992) found that one factor, sleepiness, accounted for most of the variance in ESS and that each question was internally consistent for that factor. Furthermore Johns (1993) found that the ESS could distinguish between snorers and patients with mild, moderate or severe sleep apnoea. However the problem of the unreliability of subjective assessment of sleepiness in sleepy patients remains. Kingshott et al (1995) investigated whether partner assessments of SAHS patients' ESS were more reliable than the SAHS patients own assessments. They found that partner ESS varied randomly with no overall consistent difference to patient ESS. They also found that there were no relationships between either patient or partner assessments of ESS and AHI, in contrast to Johns (1992, 1993). Therefore the ESS is an improvement on the SSS but is still imperfect.

2.4.2 Daytime Sleepiness in Sleep Apnoea; Objective

This problem of subjective assessment of sleepiness can be addressed by using objective tests of daytime sleepiness which polygraphically document the onset of sleep in a series of naps during the day. Those most commonly used are the MSLT (Carskaddon 1986, Thorpy et al 1992), and to a lesser extent the MWT (Poceta et al 1992). Although they are time consuming and expensive to perform they are useful in diagnosis of daytime somnolence, especially in narcolepsy, and in assessing patient response to treatment. In patients with SAHS this is of particular importance as daytime sleepiness is a presenting symptom of the syndrome and the incidence of road traffic accidents is significantly higher in these patients (Findley et al 1988).

Dement et al (1978) and Roth et al (1980) found that sleep apnoea patients were objectively sleepier than normal subjects on the MSLT. It is less clear however what causes daytime sleepiness in SAHS patients, whether it is nocturnal hypoxemia or the frequency of arousals from sleep suffered by SAHS patients. This is discussed in greater detail in section 2.7 however prior to this methods of measurement of arousals and their relevance in SDB shall be discussed.

2.5.1 Measuring Arousals (Sleep Fragmentation); Visual

Sleep fragmentation is the term used to describe the interruption of sleep with short (less than 15 seconds) increases in EEG frequency either occurring spontaneously or in response to respiratory events or tones. These short events are known as microarousals. Although there is general agreement that they exist and have important influences on sleep itself and daytime function there is not universal agreement on how they should be defined and scored (ASDA 1992, Cheshire 1992).

Initial guidelines from Rechtschaffen and Kales (1968) on measuring sleep disturbance deal only with scoring movement arousals which were equated with a stage shift to a lighter sleep stage or a stage shift to wakefulness. This has a minimum duration criterion of 15 seconds which is often too long to pick up the recurrent microarousals that often terminate apnoeas or hypopnoeas. In 1978 Phillipson and Sullivan drew the attention of sleep physiologists to the phenomenon that arousals (microarousals or >15 sec arousals) occur in response to apnoeas and hypopnoeas. Roth et al (1980) used increases in chin or leg EMG to score arousals subsequent to apnoeas or hypopnoeas. Zwillich et al (1981) looked for 5 second bursts of alpha rhythm on the EEG associated with an increase in EMG activity. Gould et al (1988) reduced the duration further to a 1.5 second increase in EMG activity accompanied by any increase in EEG frequency. This definition was altered by Cheshire et al (1992) to a return to alpha or theta on the EEG for

1.5 seconds accompanied by any increase in EMG activity, which improved the relationship between microarousal frequency and AHI. The American Sleep Disorders Association guidelines on the scoring of arousals (1992) suggest a 3 second increase in EEG frequency accompanied by a 3 second increase in EMG activity during REM sleep only. The increase in EMG activity in REM sleep is included in definitions because transient alpha intrusion into REM sleep is common and may not constitute an arousal.

Although all the above studies have aspects of their definitions in common and all use the sleep EEG, there has been no systematic comparison, and more importantly validation, of the definitions available in SAHS patients. In addition defining what constitutes a "normal" arousal frequency is contentious.

Mathur and Douglas (1995b) compared R&K awakenings with 3 microarousal definitions in normal subjects recruited from a general practice who had one night of polysomnography. The microarousal definitions used were from ASDA (1992), Cheshire (1992) and a modified ASDA definition to a shorter duration of 1.5 seconds. The modified ASDA scored the greatest number of microarousals, however, all definitions demonstrated that the upper limit of arousal frequency in these normal subjects was high (from 55 to 67 per hour of sleep). Either this is a true finding or the semi- invasive nature of polysomnography itself may be responsible for this high arousal frequency on the first night of polysomnography in these normals. Applying these data to SAHS patients suggests that microarousal scoring may be inaccurate due to polysomnography causing spontaneous microarousals. However these patients are sleepy anyway and thus may have fewer spontaneous microarousals caused by the polysomnography than a normal subject.

All these definitions rely on the accuracy and consistency of the human eye and there is currently no data on within or between rater reliability of arousal scoring by any definition.

2.5.2 Measuring Sleep Fragmentation; Non-Visual

Visual methods of arousal scoring are monotonous and time consuming and automation of the process is of clinical and research interest. Fast Fourier Transformation (FFT) is a widely used technique to generate frequency spectra from the sleeping EEG (Hjorth 1970, Necklemann and Ursin 1993, Oglivie et al 1991). It functions on the premise that the EEG can be described by a series of sine waves of different frequencies and that as EEG frequency decreases EEG amplitude increases. Resolution of the FFT depends on the duration of the window within which separate calculations of EEG power are made, power being the square of the EEG amplitude. It is possible to use a zero cross method to produce frequency spectra however this may lose some of the heterogeneity of the EEG.

Rees et al (1995) used FFT to produce EEG spectra in patients with sleep apnoea on a timescale short enough to distinguish between the beginning and the end of respiratory events. They found that median EEG frequency increased in the second half of an apnoea or hypopnoea compared to the first half and that EEG frequency increased at the end of a respiratory event regardless of whether there was a visible EEG arousal or not. They also found that EEG frequencies during visible EEG arousals at the end of respiratory events did not differ from frequencies at the end of events that did not terminate in visible EEG microarousals. In this study FFT was sensitive enough to isolate changes in the EEG which the human eye could not score as a microarousal.

Roberts and Tarassenko (1992) have applied fuzzy logic to the EEG by using an artificial neural network to analyse sleeping EEG. Davies et al (1993) fragmented normal subjects' sleep with tones to produce definite microarousals. Tones were also given which did not produce any visible change on the EEG. Artificial neural network analysis of the EEG by the Roberts technique found changes in the EEG in response to tones even when there was no visible EEG arousal.

Drinnan et al (1996) selected 4 microarousals at the end of respiratory events in 30 subjects with varying severities of sleep apnoea. Raw EEG data were passed through 3 automated EEG analyses which included zerocross and FFT methods. A point 8 seconds prior to the start of the arousal was compared to one 8 seconds after the start of the arousal. They found significant increases in EEG frequency during arousals at the termination of respiratory events demonstrating that automated EEG analysis can detect visible EEG arousals in response to respiratory events.

The above 3 studies all require the user to give the computer time markers to direct the various analyses in their search for increases in EEG frequency/ activity. The next step with non-visual methods of EEG analysis is to automate this process. Average increases in EEG frequency/ activity could be used as a threshold above which microarousals may be detected automatically and consequently validated against manual arousal scoring. However manual scoring of the EEG for visible microarousals may not be the best starting point for validating automatic arousal selectors for use in patients with sleep apnoea. Rees et al (1995) compared apnoeas that did terminate in visible microarousals with those that did not and found no difference between them in the chemical and mechanical changes that occurred either during the apnoea or at apnoea termination. The limiting factor is that EEG only records from the cortex and many apnoeas may well be resolved with brainstem arousal only.

An alternative is to use non-EEG methods of arousal determination. Acoustic stimulation that does not produce visible EEG arousals can cause transient blood pressure elevations (Davies et al 1993). However beat to beat blood pressure can only be monitored using an arterial catheter or by digital infrared plethysmography (Finapres) (Parati et al 1989) both of which are cumbersome and require good subject cooperation. Pulse transit time (PTT), the time interval between the ECG R wave and the arrival of the pulse at and extremity, usually the finger, is approximately inversely proportional to blood pressure (Geddes et al 1981).

Brock et al (1993) and Pitson et al (1994, 1995) have performed studies validating PTT as a more portable and reliable measure of changes in autonomic activity during sleep. PTT is measured as the time it takes for the pulse wave to travel from the aortic valve to a peripheral site. For ease of measurement this is usually the finger. PTT is approximately inversely proportional to blood pressure; as blood pressure increases the arterial walls become stiffer and the pulse wave can propagate faster, therefore PTT is shorter, and as blood pressure falls, arterial wall stiffness drops causing slowing of propagation of the pulse wave and a subsequent lengthening of PTT (Geddes et al 1981). Brock et al (1993) compared the blood pressure oscillations measured with the Finapres and swings in PTT that occur while awake during quiet breathing with a variety of inspiratory loads. There were similar arterial blood pressure oscillations and PTT swings in response to the same inspiratory load. In a subsequent study (Pitson et al 1995) PTT correlated well with inspiratory effort measured with oesophageal pressure in sleeping SAHS patients. In addition to this Pitson et al (1994) demonstrated that there were significant changes in PTT in normal sleeping subjects in response to tones regardless of whether they caused visible EEG arousals or not. These results suggest that PTT may be useful in screening for sleep apnoea. Its advantages are that it is not cumbersome like the Finapres and it is well tolerated by human subjects requiring only ECG monitoring and a finger oxygen saturation probe. It does not however give beat to beat information like the Finapres and it varies with the respiratory cycle. Its merits for use in the experiments in this thesis are discussed in chapter 3.

In normal subjects inspiratory effort prior to arousal is similar in individuals regardless of whether the stimulus to arousal is hypoxia, hypercapnia or increased ventilatory load (Gleeson et al 1990). Therefore PTT as an indicator of inspiratory effort may be useful in monitoring autonomic arousal in patients with sleep apnoea.

2.6 Arousals in Sleep Disordered Breathing

The original characterisation of sleep apnoea by Gastaut et al (1966) includes clear descriptions of EEG arousals that occur at the end of apnoeas but also includes a description of apnoeas that do not terminate in visible EEG arousals, the importance of which has only recently been re-identified as described above (Davies et al 1993, Basner et al 1995, Rees et al 1995). It is these EEG and non-EEG arousal phenomena, and their relative impacts on daytime function which are the focus for this thesis. Gastaut et al (1966) suggested 2 mechanisms for the severe daytime somnolence found in their 2 Pickwickian patients who had obvious sleep apnoea; a narcolepsy syndrome where obesity and somnolence are linked by a central defect in the brainstem, or that insufficient sleep at night causes the daytime somnolence. The initial theory is incorrect due to the fact that patients with sleep apnoea do not have to be obese (Mathur and Douglas 1995a). The latter theory is logical as feeling sleepy during the day following a shortened nocturnal sleep is a common experience. Evidence from sleep deprivation/ restriction studies has documented this objectively in normal subjects (se section 2.11).

Initial studies on daytime sleepiness in patients with sleep apnoea by Dement et al (1978) and Roth et al (1980) suggested that rather than quantity of sleep it was the quality or continuity of sleep, assessed by the number of arousals associated with apnoeas, that determined daytime sleepiness. The relationships between severity of sleep apnoea and consequent sleep fragmentation, and daytime sleepiness (as discussed in greater detail in section 2.7) are weak and do not fully explain the daytime sleepiness found in sleep apnoea patients.

Although the correlations between sleep fragmentation and daytime sleepiness are relatively weak (Roehrs 1989) or non-existent (Cheshire et al 1992) the relevance of sleep fragmentation as an additional variable to score in an overnight sleep study has increased somewhat in recent years. This is largely due to the referral of patients to sleep apnoea clinics who do not have

a concrete explanation for their symptom of daytime sleepiness, (AHI > 5/ hour of sleep, narcolepsy or periodic leg movement syndrome). The only problem that may show up on the polysomnography is an elevated microarousal index. Recent data from Mathur and Douglas (1995b) found high microarousal indices in normal subjects on a single night of polysomnography. Control subjects recruited from the general population had mean arousal frequency of 21, (95 th percentile; 56) per hour of sleep, and thus what constitutes a normal arousal index is unclear. Collard et al (1996) found contrasting results, that normal subjects had a mean arousal index of 13 (95th percentile; 24) per hour of sleep. This lower figure may have been due to 2 reasons; the subjects in this study were younger than those of Mathur and Douglas (1995b) who found that arousal index increased with age, and the arousal definition of Collard et al (1996) did not score events which showed a return to theta rhythm on the EEG.

Guilleminault et al (1991) noted that patients who did not have sleep apnoea per se but who suffered from daytime sleepiness had snoring associated microarousals and in a further study had increases in upper airway resistance associated with microarousals (Guilleminault et al 1993). Upon treatment with CPAP therapy in both studies the number of microarousals decreased coincident with an improvement in daytime sleepiness.

Thus microarousals, with snoring or increased upper airway resistance, can cause daytime sleepiness in certain patients. The converse of this, that subjects with high arousal indices will suffer from daytime sleepiness, (Mathur and Douglas 1995b) does not seem to be true. The mechanism(s) whereby similar microarousal indices, or AHI, will lead to daytime sleepiness, either subjective or objective, in one person and not another are not understood.

2.7 Daytime Sleepiness; Correlation with Nocturnal Variables

Apnoeas and hypopnoeas terminate in dips in oxygen saturation and brief arousals from sleep and therefore research has focused on investigating the relationships between indices of nocturnal hypoxemia and sleep fragmentation, and daytime sleepiness. Unfortunately the methods for quantification of the two parameters are not standardised in the literature although many authors use the number of 4% desaturations per hour for nocturnal hypoxemia (Stradling and Crosby 1991a, Douglas et al 1992) and some combination of 3 seconds or less increase in EEG frequency and/or EMG tone for sleep fragmentation (Cheshire et al 1992, ASDA 1992).

Orr et al (1979) compared 4 sleepy and 4 non-sleepy subjects with equal severity of upper airway obstruction and found that the sleepy subjects had lower PaO2 during sleep and upon awakening. They concluded that hypoxemia may cause daytime sleepiness in the sleep apnoea syndrome. However sleep was not scored and daytime sleepiness was assessed subjectively which is unreliable in the hypersomnolent patient (Dement et al 1978, Roth et al 1980).

Roth (1980), in 10 apneic subjects, only found one weak relationship between daytime sleepiness and nocturnal variables; between objective daytime sleepiness and the number of brief arousals associated with respiratory events. These were scored as respiratory events accompanied by increases in chin EMG or leg movements and did not include any EEG criteria. Stepanski et al (Sleep 1984) found that in a group of 55 subjects which included 15 with insomnia, 15 with periodic leg movement syndrome (PLMS), 15 with sleep apnoea and 10 normals, arousals explained 25% of the variance in objective daytime sleepiness measured by the MSLT. In the sleep apnoea patients alone there was no relationship between daytime sleepiness and arousals, results similar to Cheshire et al (1992). Stepanski et al (1984) attribute this to the small variability of daytime sleepiness within each group of subjects. Interestingly they found that longer total sleep time was significantly correlated with increased daytime sleepiness. They explain

this by suggesting that there is a minmum duration of sleep required for sleep to be restorative, an idea which Downey and Bonnet (1987) have also explored. This interruption of sleep may increase the drive to sleep and any extra sleep the subjects have will in turn be interrupted and thus not be restorative. Alternatively it may be a consequence of scoring sleep in 30 second epochs which will show no loss of total sleep even if the subject has had many brief (less than 15 second) arousals. The method of scoring of arousals in this study would go some way to dealing with this as the authors scored arousals according to 6 different categories from as subtle as less than 5 second increases in EEG frequency through to stage shifts and awakenings from sleep. There were however small numbers of subjects in these studies which may account for the poor relationships between various measures of sleep fragmentation and daytime sleepiness

Guilleminault et al (1988) found that, out of nocturnal variables including apnoea + hypopnoea index, nocturnal hypoxemia and sleep staging, only duration of stage 1 and slow wave sleep correlated significantly with daytime sleepiness measured by the MSLT. They did not measure microarousals but used stage 1 sleep duration as an indicator of sleep fragmentation. There is something of a methodological problem here as Rechtschaffen and Kales guidelines for sleep staging suggest that stage 1 has to be scored prior to scoring stage 2 sleep. In cases of severe sleep apnoea patients may often go straight into stage 2 sleep after awakenings due to apnoeas or hypopnoeas. The amount of stage 1 sleep that is scored depends on how strictly the particular sleep laboratory interprets the scoring guidelines. Microarousal scoring improves on this as it is event based and only requires 10 seconds of prior sleep as an interval between events (ASDA 1992, Cheshire et al 1992).

Bedard et al (1991a) found that in 20 SAHS patients only nocturnal hypoxemia correlated with MSLT. They did not score microarousals and they may have biased their patient sample by selecting only those with a minmum nocturnal O2 less than 80%. Roehrs et al (1989) in 466 patients, found that

both 3 second arousals associated with respiratory events and nocturnal hypoxemia were correlated with daytime sleepiness on the MSLT. These two variables were significantly interrelated and in multiple regression analysis microarousals came out as the single best predictor of daytime sleepiness. Cheshire et al (1992) unlike any of the previous studies, did not find any relationship between daytime sleepiness and nocturnal variables. This may have been due to the relatively low number of subjects; n=29 compared to n=466 (Roehrs et al 1989).

Using nocturnal hypoxemia as a predictor for daytime sleepiness in SAHS patients should be done with caution due to the significant relationships between age and obesity, and hypoxemia. Although SAHS patients tend to be middle aged and obese, awareness of the syndrome is increasing in the U.K. and with it referrals to sleep laboratories of younger, less obese patients who may have just as severe sleep apnoea as an older more obese patient but who do not have intermittent nocturnal hypoxemia.

The findings in the above studies that nocturnal variables such as sleep quality and nocturnal hypoxemia correlate with the MSLT suggests that the MSLT goes some way towards improving on the SSS in the assessment of daytime sleepiness. However Mitler (1993) has suggested that there may be a floor effect in excessively sleepy SAHS patients. In addition some normal subjects and SAHS patients may be particularly good at falling asleep on demand; the normal subjects because they may be 'sleepy' individuals (Harrison and Horne 1996a), and the SAHS patients because being excessively sleepy they may nap whenever they can get the opportunity. Mitler et al (1982) also suggested that testing the patients' ability to remain awake more closely approximates to their real life situations, and that successful treatment for a sleep disorder comprises alleviating this struggle to stay awake. For these reasons Mitler et al (1982) and Hartse et al (1982) introduced the MWT. Poceta et al (1992) used the MWT with 40 minute naps to test daytime sleepiness in patients with SAHS. Mean sleep onset latency was 26 minutes, considerably higher than that seen on the MSLT in SAHS

patients, which is often less than 10 minutes (Roehrs et al 1989, Cheshire et al 1992). In addition they found that the strongest nocturnal correlates of sleep onset latency on the MWT were respiratory associated arousals, apnoea + hypopnoea index and nocturnal hypoxemia. The major criticism of the MWT is that subject motivation is uncertain, and as this test is tedious, this may add significantly to its variability. This may explain why Sangal et al (1992a) found that 15% of SAHS patients had above average sleep latencies on the MSLT but were below average on the MWT. It is interesting to note that the amount of variance in daytime sleepiness explained by nocturnal variables (13%) is similar whether sleepiness is measured by the MSLT (Roehrs et al 1989) or the MWT (Poceta et al 1992).

In summary sleep fragmentation is the more reliable predictor of daytime sleepiness in SAHS patients whether it is measured by the MSLT or the MWT. However at best only 13% of the variance in daytime sleepiness is explained by sleep fragmentation.

2.8 Performance Measures; Driving

A potentially fatal consequence of daytime sleepiness is sleepiness whilst driving. Horne and Reyner (1995) found that sleep related vehicle accidents accounted for between 16 and 20% of accidents on major roads and motorways in England. Circadian rhythm influenced accident numbers with three peaks in the number of accidents related to time of day; 2 to 3 am, 6 to 7 am, and 4 to 5 pm. Leger (1994) estimated that in the U.S. the cost of sleep related vehicle accidents was somewhere between $29 and $38 billion in one year (1988). It is unclear what the relative contribution of sleep apnoea and its consequent daytime sleepiness is to these estimates. George et al (1987) found that SAHS patients had more than twice the number of vehicle accidents than controls. Findley et al (1988) found that 29 SAHS patients had a seven fold greater record of automobile accidents than did 35 control subjects, and had 2.6 times the rate of accidents than all licensed

drivers in one U.S. state. In a further study Findley et al (1989) found that patients with sleep apnoea performed significantly worse than control subjects on 2 driving simulators, consisting of a simulator car with road films, and a computer programme of a monotonous highway drive (Steer Clear). However Stoohs et al (1994) found a non significant increase ($p=0.14$) in the rate of accidents for comercial long haul truck drivers with sleep disordered breathing (SDB) compared to those without, although those with SDB were more obese than those without. There was no relationship between severity of SDB and accident rate in this sample. This is similar to a preliminary report by Flemmons et al (1993) who did not find any relationship between the number of objects hit on the Steer Clear programme (Findley et al 1989) and AHI or arousal frequency. Results from driving simulators should be interpreted with caution as few can truly mimic day to day driving.

2.9 Cognitive Function

Further evidence of the effects of sleep apnoea on performance come from cognitive function testing. The literature in this area focuses on whether potential cognitive deficits in SAHS patients are due to functional cerebral impairment caused by nocturnal hypoxemia or are secondary to the daytime sleepiness suffered by these patients.

Hypoxemia itself impairs cognitive function as demonstrated by altitude simulation studies (Gibson et al 1981). Attention has focused on patients with COPD, who suffer from chronic hypoxemia. These patients have deficits in cognitive function (Fix et al. 1982, Grant et al 1982), which get progressively worse with increasing severity of hypoxemia (Grant et al 1987). These patients should not be used as a model for the effects of hypoxemia alone on daytime function because they also have disrupted sleep (Calverley et al 1982) which itself can impair cognitive function (see section 2.11.3). In addition it is difficult to extrapolate results from studies on patients with COPD to patients with SAHS, because COPD patients are also

hypoxic during the day which may add to their cognitive impairment. Neuropsychological function in SAHS and COPD patients has been compared by Roehrs et al (1995). They found that performances were similar in both groups and were non-specific to tests related to sleepiness or hypoxemia, apart from 2 tests, where SAHS patients performed more poorly on a test related to sleepiness and COPD patients on a test related to hypoxemia.

Prior to investigating the relationships between performance measures in SAHS patients and nocturnal sleep and breathing variables it is important to demonstrate that deficits do exist. Various studies suggest that cognitive deficits exist in SAHS patients however few demonstrate this conclusively. Guilleminault et al (1976) noted that patients with sleep apnoea may suffer from impaired cogntive function in a description of cases of SAHS. Kales et al (1985) found that SAHS patients had cognitive deficits but only compared them with standardised scores, i.e. they did not use control subjects. It is vital in studies of this nature to use carefully matched control subjects because age and years of education themselves correlate with cognitive function.

Greenberg et al (1987) studied a wide range of cognitive functions in SAHS patients, patients with disorders of excessive somnolence (DOES), to act as sleepy controls, and age and educationally matched healthy controls. They found that SAHS patients had global neuropsychological impairment compared with both control groups and they performed significantly worse than either control group on 7 out of 17 psychometric tests. The authors point out however that SAHS patients' group mean performance was 1/2 a standard deviation lower than that of either control group. This may be a reflection of the 1/2 SD fewer years of education or the lower premorbid IQ intelligence (vocabulary) measures found in the SAHS patients. Furthermore objective daytime sleepiness was only measured in 2/14 SAHS patients and 7/10 DOES patients.

Neagale et al (1995) studied frontal lobe functions in 17 SAHS patients and 17 age and educationally matched controls and found that patients had significantly impaired performance on 11 out of 25 outcome measures. The patient sample was subsequently divided into moderately and severely apneic, and moderately and severely hypoxemic. Severely apneic patients had poorer performance on one test of frontal lobe function and severely hypoxemic patients also had poorer performance on one test of frontal lobe function. Furthermore logistic regression models identified specific functions, marked by the TOWER-3 (planning ability) and STROOP (mental flexibility) tests, which are particularly impaired in patients with sleep apnoea. Interpretation of these results should be done with care as the authors did not measure sleep fragmentation nor did they include any sleep EEG data into their logistic regression model.

2.10 Correlation with Nocturnal Variables

Several studies have correlated cognitive function in SAHS patients with nocturnal variables to investigate the relative contributions of nocturnal hypoxemia, respiratory and sleep variables to the cognitive impairment described above. Many of these nocturnal variables are interrelated and it is important to include them all in an analysis of this kind particularly as young, non-obese individuals can have a similar AHI to an older more obese individual but not have their severe nocturnal hypoxemia. In a similar fashion many outcome measures from the cognitive function tests are interrelated. Furthermore care must be taken to ensure that statistically significant correlations do not occur by chance due to the large numbers of nocturnal and cognitive variables available for a correlation analysis. Statistical methods that may help to achieve this are principal components analysis (Child 1990), multivariate analysis of covariance (MANCOVA), and multiple regression analysis (Bryam and Cramer 1994).

Greenberg et al (1987) found that psychomotor function, and Bedard et al (1991b) found that performance and verbal IQ correlated with nocturnal hypoxemia. Unfortunately there were no indices of sleep fragmentation measured in these studies. Greenberg et al (1987) did correlate REM and slow wave sleep, and cognitive function but found no significant relationships. Bedard et al (1991b) used multiple analysis of covariance to produce a 'vigilance' factor, consisting of; sleepiness on the MSLT, and alertness on the four choice reaction time task, to reflect sleep fragmentation and found that it correlated significantly with attention and memory impairment. This assumes that sleep fragmentation causes daytime sleepiness when at best sleep fragmentation only explains 13% of the variance in daytime sleepiness.

Berry et al (1986) also found that hypoxemia correlated with verbal and performance IQ, and memory. They did not report any correlations between cognitive function and sleep variables. Respiratory events, which correlate more significantly with sleep fragmentation than hypoxemia (Cheshire et al 1992), were entered into the analysis but did not show any significant relationships with cognitive function. In this study AHI was probably underestimated due to the requirement of a 10% desaturation in addition to a reduction in airflow for the scoring of an hypopnoea.

Cheshire et al (1992) correlated daytime sleepiness, mood and cognitive function with nocturnal variables including respiratory events, sleep staging and sleep fragmentation, and nocturnal hypoxemia. They controlled for age, as cognitrive function is related to age, and for HAD anxiety and depression as 40% of their patients scored in the significant range for anxiety or depression on this scale. In a multiple regression analysis AHI was the strongest predictor of performance with significant additional contributions from microarousal frequency (sleep fragmentation) and hypoxemia.

These results suggest that microarousals are an important contributary factor for daytime performance and strengthen the case for their inclusion in scoring of overnight sleep studies.

Yesavage et al (1985) and Hayward et al (1992) have performed studies in the elderly and have found that respiratory disturbance (AHI) correlates significantly with performance measures. The presence or absence of relationships between cognitive function and hypoxemia or sleep variables were not reported in either study which makes it difficult to assess their relative contributions. This is especially relevant as Hayward et al (1992) found that respiratory disturbance only accounted for 4% of the variance in cogntive function. In addition Hayward et al (1992) did not allow for the effects of age on cognitive function. The stronger relationships between respiratory disturbance and cognitive function seen by Yesavage et al (1985) may have been caused by their inclusion of 23 patients who had been referred to the sleep clinic. This would raise the level of cognitive impairment in their sample.

Findley et al (1986) approached this problem in a different way by isolating all other factors apart from hypoxemia. They compared cognitive function in hypoxemic and non-hypoxemic patients with sleep apnoea and found that hypoxemic patients had poorer performance on tests of attention, memory and vigilance. They did not report on whether the patient groups had similar AHI, which if they were different would have had an impact on their cognitive function. In addition these hypoxemic patients were also hypoxic during the day which alone may have added to their impairment.

As a slight digression the mechanism by which hypoxia may affect cerebral function has been described by Gibson et al (1981). The autoregulatory changes in cerebral blood flow which occur in response to hypoxia happen quickly enough to protect the intracellular energy supply (ATP synthesis) although not quickly enough for adequate neurotransmitter synthesis. Enzymes involved in neurotransmitter synthesis, in particular acetylcholine, are particularly sensitive to hypoxia and it is these which may be compromised by the intermittent hypoxemia seen in some SAHS patients. Interestingly Meyer et al (1980) demonstrated that brainstem-cerebellar blood flow was reduced below normal in patients with sleep apnoea when

awake and that this decreased even further during sleep. The authors suggested that there may be an impairment in the autoregulatory mechanism for increasing cerebral blood flow in response to hypoxia in SAHS patients.

In summary it is difficult to separate the relative effects of hypoxemia and sleep fragmentation on daytime function in SAHS patients using correlation analysis as they are interrelated.

Sleep deprivation and sleep disruption impair cognitive function also but only on performance tests that are of little interest to the subject and of relatively long duration. If the test is of short duration (less than five minutes) and complex enough subjects can uprate their performance over the course of that test (see section 2.11). This suggests that the cognitive impairment suffered by sleep deprived or sleep restricted subjects may be secondary to their daytime sleepiness. In patients with SAHS peformance is also impaired on short complex tests, e.g. Trailmaking B. This suggests that shorter complex tests may be affected by hypoxemia. However the sleep fragmentation studies (see section 2.11.4) of Bonnet (1987), Philip et al (1994), and Roehrs et al (1994) used monotonous performance tests. In the sleep fragmentation studies in this thesis we propose to use both monotonous and complex tests to cover a broad range of cognitive function.

2.11 INTERVENTION STUDIES IN NORMAL SUBJECTS

2.11.1 Sleep Deprivation

Patients with SAHS are not totally sleep deprived. They may have longer than average duration of time spent in bed in an attempt to overcome their daytime sleepiness. Although the focus of this thesis is on sleep fragmentation sleep deprivation studies can provide guidelines as to the kinds of performance tests that could be used in testing for daytime impairment in patients with sleep apnoea or sleep fragmented normal subjects.

The first reported sleep deprivation experiment in 1896 (Patrick and Gilbert) found that reaction time, letter reading and addition tasks were greatly impaired in 2 subjects. Williams et al (1959) sleep deprived normal subjects for 3 to 4 days and compared their performance with that of control subjects. Their performance measures were divided into tasks in which the subject controlled the pace of the experiment and those in which the experimenter controlled the pace or speed. On the subject paced tasks the authors concluded that, although the accuracy of performance was not affected by sleep deprivation, the speed of the response to a stimulus (e.g. reaction time to turn off a light that has switched on) was lengthened and that this corresponds to an increase in the frequency and duration of lapses in concentration. They defined these lapses as reaction times that are at least twice as long as the subject's baseline reaction time prior to sleep deprivation. More recently these lapses have been termed microsleeps (Horne 1988) although Bjerner (1949) introduced the idea of their association with falling asleep, finding that long reaction times were associated with decreases in alpha activity on the EEG. Similarly Wilkinson (1965) found that on a five choice reaction time test the number of gaps in between responses longer than 1.5 seconds, corresponding to Williams' lapses, was increased after 30 hours of sleep deprivation. On the experimenter paced tasks Williams et al (1959) found that subjects had increased number of errors on communication, learning and vigilance tasks after sleep deprivation. Wilkinson (1965) also found that the number of errors on the five choice reaction time test (tapping the wrong light), as a percentage of the total number of responses made, was also increased after sleep deprivation.

Task duration is important for uncovering decrements in performance due to sleep deprivation. Williams et al (1959) found that as the duration of the task increased so the number of errors increased. This interacted with the duration of sleep deprivation so that subjects made errors earlier on in the performance of these tasks as their duration of loss of sleep increased. Wilkinson (1965) showed that after sleep deprivation, in the first five minutes

of a reaction time test subjects' performance was similar to normal but it declined sharply as the duration of the test increased up to 30 minutes.

Reaction time and vigilance tests are relatively monotonous. Wilkinson (1964) made suggestions on the types of tasks which are susceptible to sleep deprivation by administering tasks of varying complexity and interest but of uniform duration. It appears that interesting, complex tasks are least susceptible to sleep deprivation, and that long, monotonous tasks that do not engage the subject are more likely to be impaired. This latter point was clearly demonstrated by Wilkinson (1961) by giving subjects feedback of their performance during the test. Their motivation to perform well was enhanced by feedback and they showed no deleterious effect of loss of sleep. Horne and Pettitt (1985) took this a step further and offered subjects cumulative amounts of money to maintain their performance up to baseline levels on a vigilance test over 72 hours of sleep deprivation. They found that subjects uprated their performance for 2 days but could not maintain this for the 3rd day of deprivation. In summary sleep deprivation impairs normal subjects' performance on tests that are monotonous, of little interest and of relatively long duration. However normal subjects can uprate their performance on these tests especially if they are given some incentive to do so.

2.11.2 Sleep Restriction

It can be argued that patients with sleep apnoea have reduced overall sleep. The Rechtschaffen and Kales (1968) criteria for sleep staging are based on averaged 30 second epochs which may not account for regular brief arousals from sleep caused by apnoeas or hypopnoeas. If the time spent in wakefulness was calculated on a second by second basis the SAHS patient may well have severely restricted sleep. Several studies have investigated the effects of partial sleep deprivation in order to find the

minimum amount of sleep necessary for maintenance of baseline performance.

Webb and Agnew (1965) allowed eight subjects 3 hours sleep a night for 8 consecutive days. They found that there was a significantly greater percentage of slow wave sleep on restricted nights than on the baseline nights largely at the expense of stage 2 and REM sleep. The authors however gave little data from the performance tests. Wilkinson (1969) restricted subjects sleep for 2 consecutive nights to 7.5, 5 , 3, 2, 1 or 0 hours. All subjects performed all conditions in randomised order. The days following sleep restriction subjects had a full day of performance tests simulating a day's work. Following one night of sleep restriction subjects' performance fell only if sleep was less than 3 hours, however after the second night of sleep restriction performance fell if sleep was less than 5 hours. Wilkinson attributed these findings to there being insufficient time on the second night of restriction to allow for a rebound of stage 4 sleep and thus on the 5 hour restriction regime there builds up a stage 4 sleep debt which only impacts on performance after the second night. There were no electrophysiological measurements of sleep made in this study and therefore the results should be interpreted with care.

The above results are somewhat borne out by those of Carskaddon and Dement (1981). They restricted sleep to 5 hours for 7 days. They found that there were progressive decreases in objective daytime sleepiness on the multiple sleep latency test (MSLT) from the second to the 7th day of sleep restriction. Although slow wave sleep was similar on all restriction nights compared with baseline there was a trend towards an increase in slow wave sleep on the first recovery night which indicates some slow wave sleep debt. This may have accounted for the gradual decline in mean sleep onset latency over the restriction period. Therefore it appears that performance following sleep restriction may be dependent in some part on slow wave sleep.

2.11.3 Sleep Disruption

In the preceding 2 sections the focus is on the quantity of sleep required for adequate functioning. The following 2 sections deal with the effect of sleep quality on daytime function.

There have been many studies on the effects of the sleep disruption suffered by junior doctors on their performance. Deary and Tait (1987) showed that a night spent on call (mean sleep time 5 hrs) did not impair their mood or cognitive function but that a night spent admitting emergency cases, (mean sleep time 1.5 hrs) impaired mood and short term memory. Deaconson et al (1988) found no effect of being on call (less than 4 hrs of continuous sleep in the previous 24 hrs) on cognitive function the following morning. The sleep data is self reported in both these studies and additionally the junior doctor's sleeping patterns are not a good model for sleep disruption, as their disruptions often involve long awakenings where they have to get out of bed and perform tasks.

Previous studies on sleep disruption have investigated the relationships between regular sleep disruption and daytime function in normal subjects. Bonnet (1985) looked at the effects of recurrent sleep disruption on daytime function. Healthy young subjects had their sleep disrupted every minute for 2 consecutive nights' sleep resulting in significantly reduced slow wave and REM sleep. Subjects had to respond behaviourally to each sleep disruption by subjectively rating their sleepiness on a scale of 1 to 7 or by pushing a button on awakening. On the day following disruption subjects were subjectively sleepier and had poorer performance on a reaction time test and the Wilkinson addition test than after a baseline night. These impairments were similar in nature to those suffered by normal subjects after sleep deprivation leading to the suggestion that these decrements could be due to slow wave sleep deprivation.

A subsequent study therefore looked at the effect of eliminating slow wave sleep by disrupting sleep whenever stage 3 or 4 appeared and

comparing performance during the day with that after a series of nights with a similar number of sleep disruptions but without the elimination of SWS (Bonnet 1986a). The difference in SWS between conditions did not have any impact on tests of performance, mood or objective daytime sleepiness measured on a single morning nap, implying that it is the frequency of sleep disruption which determines whether sleep is restorative and not the amount of slow wave sleep.

This leads to the question of how much sleep disruption affects performance and sleepiness. Badia et al (1985) investigated this by disrupting the sleep of normal subjects for 4 consecutive nights at an average rate of either 4 or 8 minutes. There was no difference between conditions in their relative effects on daytime sleepiness as measured by naps at 10 am and 2 pm the day after the disruption nights. In addition there was no difference in daytime sleepiness after sleep disruption of either frequency compared with a group of controls who had undisturbed sleep. These results suggest that sleep disruption at these frequencies is not sufficient to cause increased daytime sleepiness, although the lack of a full MSLT makes interpretation more difficult.

The same authors (Magee et al 1987) therefore increased the frequency of sleep disruption. Daytime sleepiness in 3 groups of normal subjects was compared following (1) an undisturbed night, (2) sleep disruption every minute, and (3) sleep disruption every 4 minutes. Daytime sleepiness this time was assessed with a full MSLT. They found that subjects whose sleep had been disrupted every 1 minute were significantly sleepier during the day than those whose sleep had been disrupted every 4 minutes or those subjects whose sleep had been undisturbed. There was no difference between daytime sleepiness in subjects who had had an undisturbed night's sleep or those whose sleep had been disrupted every 4 minutes. These results suggest that a sleep duration of about 4 minutes is critical for allowing sleep to be restorative.

Bonnet (1986b) also dealt with this idea by comparing daytime performance in normal subjects after 4 conditions of sleep disruption; awakening every minute, awakening every 10 minutes, 2.5 hours of sleep followed by awakening at each sleep onset, and sleep deprivation. Subjects performed best after the 2.5 hour condition closely followed by that seen after the 10 minute awakening condition. The worst performance was found after sleep deprivation. This was similar to that seen after the 1 minute awakening condition.

Levine et al (1987) used sleep deprivation as a baseline and disrupted recovery sleep to investigate at what level sleep could be restorative. Normal subjects were sleep deprived until 8.30am and then their 100 minutes of recovery sleep was fragmented at a rate of 1/minute, 1/3 minutes, or 1/5 minutes. There were 2 further conditions; 100 minutes of uninterrupted sleep, or further sleep deprivation for 100 minutes. Mean sleep onset latency on the MSLT was diminished after the fragmentation conditions compared with uninterrupted sleep in a dose dependent fashion. These studies (Badia et al 1985, Magee et al 1987, Bonnet 1986b, Levine et al 1987) suggest that there may be a critical minimum period of uninterrupted sleep necessary for sleep to be restorative. The data from these studies suggests that this period may be near 4 minutes.

2.11.4 Sleep Fragmentation

The studies described previously all require subjects to make behavioural responses to arousing stimuli thus major degrees of arousal occurred and this may have severely disrupted their sleep. If sleep disruption shortens total sleep time compared with an undisturbed night's sleep any decrements in daytime function may be attributed to this partial sleep deprivation, however slight. Patients with sleep apnoea most often have brief arousals (less than 15 seconds) at the end of their apnoeas and hypopnoeas of which they are unaware. They can have long total sleep times in an effort

to obtain recuperative sleep (Dement et al 1978). This, along with the above suggestion that there is minimum duration of sleep required for it to be restorative, suggests that in patients with sleep apnoea their lack of continuity of sleep due to brief arousals terminating apnoeas and hypopnoeas may cause their daytime sleepiness. Studies by Bonnet (1987), Philip et al (1994) and Roehrs et al (1994) have investigated this by modeling the effects of sleep fragmentation alone on daytime function.

Bonnet (1987) investigated the effects of more subtle forms of sleep disruption on morning sleepiness, performance tests and mood. Daytime function after a baseline night was compared with the impact on daytime function of 3 different responses to tones; (1) behavioural response to tones in a similar fashion to the previous study (Bonnet 1985), (2) by asking subjects to perform a 1/4 body turn in response to tones, (3) requiring an ongoing EEG change in response to tones. Acceptable EEG changes in response to tones included a sleep stage change, the appearance of alpha or any noticeable increase in EEG frequency. The first 2 conditions are again behavioural responses to arousing stimuli with the movement condition designed to mimic limb movements found in PLMS, which can cause daytime sleepiness, and the EEG condition to mimic the sleep fragmentation found in patients with sleep apnoea. Daytime function was measured in 11 young subjects using tests of daytime sleepiness; on one morning nap, performance; using a 30 minute addition test, a 30 minute vigilance test and 10 minutes of simple reaction time, and mood; using the Clyde mood scale. Sleep fragmentation (EEG condition) increased morning sleepiness, impaired vigilance and made subjects significantly sleepier and unhappier compared to a baseline night. Similar results were found for the first 2 disruption conditions. Although the EEG condition models sleep fragmentation there was no information given about duration criteria on the EEG for an optimum response to tones, and it appears that the total sleep time on the EEG condition is significantly shorter than on the baseline night which could perhaps account for the impairments seen in morning

sleepiness, mood and vigilance. In addition testing baseline daytime function is not built into the study design as a separate condition but is a night prior to each 2 night disruption paradigm.

Philip et al (1994) fragmented the sleep of 8 young adults for 1 night every minute and tested daytime sleepiness using the MSLT, and performance using tests which covered a range of functions including vigilance, attention and memory. Daytime function following fragmentation was compared with a randomised control night. Subjects had 5 training sessions with the performance tests to eliminate any potential learning effects. The fragmented study night was extended by the amount of wakefulness seen during the study night and therefore there was no difference in total sleep time between fragmentation and baseline nights. There was significantly more stage 1 sleep and significantly less slow wave sleep and REM sleep on the fragmented night. Fragmentation decreased mean sleep onset latency from 15.4 minutes to 8.8 minutes but did not affect performance tests. The authors found that SWS was significantly related to daytime sleepiness following study nights although REM and SWS were the only sleep variables entered into the regression equation. A threshold arousal response of 3 seconds was aimed for on the fragmentation night but there was no data on the number of brief arousals that were induced or how many of these were full awakenings. The percentage of wakefulness was over 18% indicating a high level of sleep disruption on the fragmentation night and there was no wake time given for the baseline night making true comparison of study nights difficult.

Roehrs et al (1994) induced sleep fragmentation with tones on average every 2 minutes in 36 young subjects for 2 nights. Daytime sleepiness was measured with the MSLT and performance using a divided attention test after each fragmentation night. Daytime function was compared with that following a screening night prior to the fragmentation nights. Total sleep time was similar on screening and fragmentation nights again due to extension of study time by the amounts of prior wakefulness on

fragmentation nights. Sleep onset latency decreased after one night of fragmentation (14.3 to 9.8 mins) but did not decrease any further after the second night of fragmentation (9.5 mins). There was no effect of sleep fragmentation on the one monotonous test of performance studied. There was a small rebound effect in sleep stages on the second fragmentation night towards screening night levels. This may either reflect adaptation to the laboratory or increased drive to sleep due to sleepiness caused by the previous night's sleep fragmentation. In either case it may account for the stabilising of daytime sleepiness after the second fragmentation night. The success rate of the fragmentation procedure was 78% on the first night and 68% on the second night but there were no comparisons of arousal indices between fragmentation and screening nights. A criticism of this study is that the control and fragmentation nights were not randomised. Performance tests are susceptible to learning effects and although subjects were trained on the divided attention test it is unclear how much practice subjects had. As the screening night came before the fragmentation nights any decrement in performance due to fragmentation may have been overcome by increased proficiency on this test.

These studies suggest that fragmentation affects daytime sleepiness but not performance on the tests used in these studies. On 2 out of these 3 studies there was no randomisation schedule (Bonnet 1987, Roehrs et al 1994) with Bonnet (1987) comparing daytime function after different total sleep times. Furthermore there was little information about how successful the sleep fragmentation protocol was in inducing arousals (Philip et al 1994, Bonnet 1987). All 3 studies used monotonous tests excluding short complex tests upon which SAHS patients also have poor performance.

2.12 Modelling Hypoxemia

Modelling nocturnal hypoxemia is the other approach to determine the cause of deficits in daytime function in SAHS patients. There has only been one study of this nature by Colt et al (1991). Patients with sleep apnea performed 2 experimental limbs in a randomised crossover design. Patients either spent 2 nights in the laboratory where they had sufficient CPAP pressure to eliminate their respiratory events, sleep fragmentation and hypoxemia or they spent 2 nights on CPAP sufficient to eliminate their respiratory events and sleep fragmentation with intermittent hypoxemia induced through the CPAP mask. Subjects had an MSLT before and after both experimental conditions. There was no difference between experimental conditions in the improvement in daytime sleepiness after CPAP. There were significantly more desaturations on the hypoxemia condition but there was no difference in any nocturnal sleep variable, including the number of arousals, apart from 8 minutes less stage 2 on the hypoxemia condition. These results suggest that intermittent hypoxemia alone does not cause daytime sleepiness in SAHS patients.

In conclusion patients with sleep apnoea have impairments of their daytime cognitive function which correlates with their severity of sleep apnoea, nocturnal hypoxemia and sleep fragmentation. It is difficult to separate out the relative contributions of hypoxemia and sleep fragmentation as they are highly interrelated themselves. Modelling studies have suggested that sleep fragmentation causes daytime sleepiness (Colt et al 1991, Philip et al 1994) but not cognitive dysfunction (Phillip et al 1994).

2.13 Improvements in Daytime Function after CPAP in SAHS Patients

Further evidence on the relationships between daytime function and nocturnal variables comes from studies on daytime function after CPAP therapy with the suggestion that daytime impairment in SAHS patients is somewhat reversible.

The effects of CPAP therapy on patients can be dramatic with some relief of daytime sleepiness occurring after one night (Lamphere et al 1989). Lamphere et al (1989) studied daytime sleepiness in three groups of patients with sleep apnoea before commencing on CPAP and again after either one, 14, or 42 nights on CPAP. They found that sleep architecture normalised during the first night of treatment and that daytime sleepiness improved significantly from 3 to 6 minutes after one night and from 3 to 10 minutes after 14 nights on CPAP. There was no further improvement after 42 nights. There was no difference between study groups for baseline severity of sleep apnoea or daytime sleepiness that could have explained these results, although there were no data on the age or weight of each group. Daytime sleepiness on the MSLT appeared to return to the normal range of greater than 10 minutes after 2 weeks on CPAP.

Although Bedard et al (1993) found a similar increase in MSLT from 5 to 9 minutes after CPAP there was residual sleepiness with post treatment MSLT significantly lower than that of age matched controls (14 minutes). Furthermore other studies have demonstrated even smaller, although significant, increases in the MSLT with CPAP therapy. Engleman et al (1993) found an increase of 2.1 minutes and 1.1 minutes (Engleman et al 1994a), and Kribbs et al (1993) an increase of 2.4 minutes with CPAP therapy.

Sangal et al (1992b) did not find any significant increase in MSLT after treatment however their sample was biased by the inclusion of patients who had had UPPP and whose severity of sleep apnoea had not subsequently decreased. They therefore divided their sample into patients treated with CPAP or UPPP and found a significant improvement from 18 to 32 minutes in sleep onset latency on the MWT after CPAP therapy.

Unfortunately results for changes in MSLT for the CPAP treated group alone were not reported. Sforza and Krieger (1992) asked patients with sleep apnoea to lie down in a dark room for 30 minutes without any instructions to fall asleep or to stay awake. Mean sleep onset latency for six naps every 2 hours improved from 17 minutes untreated, to 20 minutes after CPAP, but, similar to Bedard et al (1993), did not normalise remaining significantly shorter than in the control group (27 mins).

The failure of CPAP to normalise daytime sleepiness in some studies has been attributed to poor rates of compliance. Lamphere et al (1989), and Bedard et al (1993), who found the largest improvements in daytime sleepiness with CPAP, did not monitor objective compliance. Objective CPAP use in other studies were 3.7 hours (Engleman et al 1994a), 5.9 hours (Engleman et al 1993), 5.3 hours (Sforza and Krieger 1992) and 4.9 hours (Kribbs et al 1993). These rates are short of the ideal 8 hour per night. Correlation analysis to determine what drives the SAHS patient to use their machine shows that there is no relationship between CPAP compliance and severity of disease (Engleman et al 1994b, Kribbs et al 1994), baseline sleepiness, or improvement in daytime sleepiness with CPAP (Engleman et al 1994b).

An alternative explanation is that the MSLT tests how well subjects are able to fall asleep when they try to sleep. Patients with sleep apnoea may be well trained to fall asleep whenever the opportunity arises and this could persist some months into CPAP therapy. This problem may be circumvented by using the MWT. However even though the improvements in MWT with CPAP are impressive (14 minutes difference in mean sleep onset latency between MWT done before and after CPAP) there is no normal data to compare these changes with (Sangal et al 1992b).

Condos et al (1994) offered a further explanation of low CPAP compliance. They suggested that residual periods of increased UAR, which cause microarousals, after CPAP titration may account for the non-normalisation of the MSLT after CPAP therapy and thus the relatively low

compliance rates seen in studies of objective CPAP use (Kribbs et al 1993, Engleman et al 1994a, 1994b). This idea is supported by the recent findings of Engleman et al (1997) that mild SAHS patients who complied well with CPAP had significantly higher baseline AHI and microarousal indices. However this suggestion assumes that there is a relationship between CPAP use and patient benefit. Although subjective perception of benefit is associated with acceptance of CPAP, objective benefits do not appear to influence CPAP use. Patients who did not use CPAP had similar AHI on CPAP to those patients who did use CPAP (Rauscher et al 1991, Hoffstein et al 1992). In addition Engleman et al (1994b) demonstrated that there is no relationship between CPAP use and change in objective daytime sleepiness on the MSLT after CPAP.

Further evidence of the efficacy of CPAP therapy comes from testing cognitive function. Findley et al (1989), Bearpark et al (1987), Kribbs et al (1993), Bedard et al (1993) have all found significant improvements in performance and cognitive function after CPAP therapy. Results from these studies should be interpreted with care due their longitudinal nature which does not allow for the learning effects inherent in many cognitive tests with multiple adminstrations.

Although Bedard et al (1993) ran subjects through 3 practice runs on the four choice reaction time test subjects were not familiarised on the 11 other cognitive function tests. This makes it difficult to factor out true improvements in function caused by CPAP. Engleman et al (1993) found improvements in cognitive function with both CPAP and conservative therapy but they did not find any difference between treatments. They concluded that any improvements in cognitive function were due to learning effects and therefore controlled for this by comparing the effects of CPAP on cognitive function with an oral placebo in a randomised crossover design (Engleman et al 1994a). Subjects also performed a practice session with the cognitive tests prior to entry into the study to minmise the effects of learning. They found significant improvements in 4 out of 14 cognitive tests measuring vigilance,

general function, and mental flexibility. Improvements in vigilance, tested with Steer Clear for 30 minutes, may have been secondary to resolution of daytime sleepiness. However the improvements seen in complex tests of short duration, Digit Symbol substitution (90 secs) and Trailmaking B (mean time to completion on CPAP; 66 secs), suggests that at least some of the deficits in SAHS patients are reversible and are not due to irreversible hypoxic damage to cognitive centres in the brain as suggested by Berry et al (1986) and Bedard et al (1993).

Some studies have used auditory event related potentials (AERPs) as an index of brain function in patients with sleep apnoea, and to assess their response to CPAP (Wasleben et al 1989, Engleman et al 1995). These potentials consist of EEG waveforms within the first 800 msec of presentation of a higher pitched tone among a series of low tones. The latencies to particular waveforms reflect speed of cognitive processing, and waveform amplitudes reflect attention and motivation. Wasleben et al (1989) found that latencies to N2 and P3, were impaired in SAHS patients and P3 returned close to normal levels after 2 nights on CPAP. These results suggest that cognitive slowing that occurs with sleep apnoea may be reversible. Preliminary results from Engleman et al (1995) however are inconclusive.

2.14 Mood in Sleep Apnoea

As described previously (section 2.3) instantaneous mood has a biological basis and can be manipulated using physiological stressors such as acute hypoglycaemia (Gold et al 1995, Hepburn et al 1995, Hepburn et al 1996). The range of physiological changes occurring during apnoeas and the resulting disturbance of sleep architecture in the SAHS patient would be expected to have some impact on mood. Due to the chronicity of sleep apnoea these changes should not be instantaneous but may manifest themselves as an affective disorder.

In their original case series Guilleminault and Dement (1977) noted that SAHS patients can suffer from symptoms of depression. Kales et al (1985) measured this and demonstrated that SAHS patients had similar personality profiles to general medical outpatients, suffering from depression based on physical vulnerability. Millman et al (1989) found that 45% of SAHS patients had scores consistent with depression on the Zung self rating depression scale and although there was no relationship between these and severity of sleep apnoea the AHI was significantly greater in the depressed patients. Cheshire et al (1992) in addition to finding that a similar percentage of SAHS patients were in the clincally significant range for anxiety or depression (41%) on the Hospital Anxiety and Depression (HAD) (Zigmond and Snaith 1983) scale also found that scores on this scale correlated significantly with cognitive function; particularly Trailmaking A, testing processing speed, and the Auditory verbal learning test, testing memory.

These previous studies used patients who had moderate to severe sleep apnoea. A preliminary report by Gall and Kryger (1993) using 6 validated questionnaires, suggests that patients with mild sleep apnoea (mean AHI= 9/ hour slept) suffer from impairments in social functioning and alertness compared to normals. The authors point out that although SAHS patients scores were in the abnormal range they were not pathological. This appears to be a crucial point as studies by Lee (1990) and Cassel (1993) show no incidence of clinical depression in patients with sleep apnoea.

Cassel (1993) found no personality changes consistent with clinical depression in patients with sleep apnoea, and Lee (1990), out of 60 patients with sleep apnoea, did not find anyone who fulfilled the DSM-III-R criteria for depression. Cassel (1993) assessed patients prior to any diagnosis of sleep apnoea and therefore avoided patients' knowledge of their diagnosis having an influence on their scores. Furthermore Cassel suggests that the results of Kales et al (1985) may be due to patient concerns about undergoing a radical surgical procedure (tracheostomy) and the results of Millman et al (1989) may be due to their inclusion of questions that relate to sleepiness.

The latter would bias the sleepy patient towards scoring highly on a depression scale.

However, similar to other aspects of daytime function these measurements of mood can also improve with CPAP therapy. Derderian et al (1988), Kribbs et al (1993) and Engleman et al (1994a) found improvements in scores on a variety of well validated mood scales (McNair et al 1971, Matthews et al 1990, Zigmond and Snaith 1983, Goldberg and Hillier 1979, Hunt et al 1984) which incorporated questions about social functioning, depression/ anxiety, fatigue and alertness/ sleepiness.

In summary validated mood scales may be useful to look for improvements in SAHS patients with CPAP therapy but their baseline results should be interpreted with care.

2.15 Snoring and Daytime Function

Patients with mild sleep apnea (AHI 5 to 15) have improved daytime function with CPAP therapy (Engleman et al 1997). Snoring is an even milder form of sleep disordered breathing. It is very common in the general population and investigating whether it causes decrements in daytime function is important in determining whether it should be actively treated.

Snoring is a major symptom of sleep apnoea. Some patients are symptomatic for sleep apnoea but do not have apnoeas and hypopnoeas during sleep. Hillerdal et al (1991) demonstrated that heavy snorers and SAHS patients could not be separated on their symptoms alone. Nocturnal polysomnography does not reveal any difference in sleep architecture between snorers and non-snorers that may account for the proliferation of symptoms of SAHS in snorers (Hoffstein et al 1991). There was however no measure of sleep fragmentation used in this study, a parameter which some authors suggest may be raised in heavy snorers (Guilleminault et al 1991).

In that study Guilleminault et al (1991) investigated 15 male heavy snorers who all had AHI<5 and normal nocturnal oximetry. They found that

snoring in conjunction with large increases in inspiratory effort could be associated with microarousals. Inspiratory effort was measured using oesophageal balloons, a technique which can itself profoundly disturb sleep. Baseline daytime sleepiness was therefore measured with an MSLT after a 'normal' polysomnography night. Objective daytime sleepiness at baseline in these subjects was within the normal range, and it improved significantly after CPAP therapy. There was no difference in any polysomnographic variable between the 2 nights prior to the MSLTs except for a significant decrease in the arousal index on the CPAP night, suggesting that decreased arousals cause improvements in daytime sleepiness.

In a further study Guilleminault et al (1993) investigated a group of 15 patients who were originally diagnosed as having idiopathic hypersomnia with a mean sleep onset latency on the MSLT of 5.1 minutes. These subjects actually had large increases in inspiratory efforts prior to decreases in flow and subsequent microarousals. This increased upper airway resistance causing microarousals was suggested as the cause for these subjects' pathological daytime sleepiness as mean sleep onset latency on the MSLT increased to 13.5 minutes coincident with a decrease in microarousal frequency after a one month trial of CPAP therapy.

These 2 studies suggest that patients with mild SDB (snoring, increased UAR) may have daytime sleepiness which is mediated by microarousals. Two self report studies suggest further impairments in function due to snoring.

Stradling et al (1991b) found that questions relating to daytime sleepiness were correlated with self reported snoring independent of confounding variables for sleep apnoea, in particular 2 questions related to sleepiness while driving. This suggests that snorers may have impaired cognitive function.

In a epidemiological follow up study Jennum et al (1994) measured self reported snoring, daytime sleepiness, and cognitive complaints. In the

total population snoring did not relate to memory or concentration problems irrespective of different severities of hypersomnia. Hypersomnia itself was significantly associated with memory and concentration problems. In both studies data was self reported and therefore the incidence of snoring may have been underreported, and patients with sleep apnoea may have been included. The results suggest that any potential cognitive impairment in snorers may be secondary to the incidence of daytime sleepiness.

Telakivi et al (1988) performed cognitive function tests in middle aged self-reported habitual and occasional snorers, and non-snorers. They investigated various aspects of objective cognitive function including verbal and performance IQ, memory, psychomotor function and mental flexibility. Indices of severity of SDB were indicated by the periodic breathing index, from the Biomatt monitor, and the 4% desaturation index. Excessive daytime sleepiness was assessed subjectively from a questionnaire. There was no difference in age or cognitive function beween subject groups, however in habitual snorers excessive daytime sleepiness correlated with cognitive tests of memory, concentration, verbal fluency and psychomotor function. After adjusting for age and obesity in habitual snorers the number of 4% desaturations was associated with memory and spatial orientation tests. When subjects with oxygen desaturation indices greater than 10 per hour (subjects with sleep apnoea) were excluded from the analysis there were no significant relationships between hypoxemia and cognitive function tests. These results suggest that snoring itself does not cause cognitive impairment but that snorers' subjective perception of daytime sleepiness relates to their general performance. Although the authors suggest that daytime sleepiness is secondary to sleep fragmentation, there were no objective measures of sleep, sleep fragmentation, or daytime sleepiness used in this study to support this. The suggestion is however in agreement with objective results from Guilleminault et al (1991) and self report data from Jennum et al (1994) suggesting that snorers do suffer from daytime sleepiness.

Concluding Remarks

Previous research demonstrates that patients with SAHS have deficits in daytime function which are related to their nocturnal hypoxemia and sleep fragmentation. These are themselves interrelated making it difficult to distinguish which is the cause of daytime impairment. Current theory suggests that irreversible deficits in daytime function may be caused by hypoxemia and reversible deficits may be caused by sleep fragmentation. Previous modelling studies have focused on sleep disruption and have not answered this question fully. Part of the problem may be in the description of sleep fragmentation upon which there is poor agreement. The subsequent experiments describe sleep fragmentation more fully both manually and using computerised analyses. The main focus for this thesis remains the effects of various severities and distributions of sleep fragmentation alone on daytime function.

Chapter 3

METHODS OF MEASUREMENT

The studies presented in this thesis were all performed in the sleep laboratories in either the Rayne laboratory, City Hospital, Edinburgh, or ward 48, Royal Informary of Edinburgh. The methods used included overnight polysomnography and daytime function testing. Testing daytime function consisted of measurements of daytime sleepiness, mood and cognitive function. Studies were performed on both normal subjects and patients with SAHS.

3.1 Nocturnal Polysomnography

All studies were performed in sound proofed, electrically screened, air-conditioned bedrooms. In normal subjects we measured sleep, respiratory movement and electrocardiography (ECG), and in SAHS patients we measured sleep, leg electromyography (EMG), respiratory movement, oro-nasal flow and oxygen saturation. In addition in fragmentation protocol 2, beat to beat arterial blood pressure was measured using the Finapres device. Sleep was measured using electrooculography (EOG), electroencephalography (EEG), and submental electromyography (EMG).

Silver chloride electrodes were placed at the left and right outer canthi, international 10/20 EEG classification positions Fp1, Fp2, CZ and PZ (Cooper et al 1980). A subset of subjects had electrodes positioned at F3 and F4. All subjects had an earth electrode positioned at FpZ. Bipolar signals were derived from various combinations of these electrodes as follows.

Left EOG; right outer canthus/ Fp1.

Right EOG; left outer canthus/ Fp2.

Central EEG; CZ/ PZ.

Central EEG (backup); PZ/ CZ.

Left Frontal EEG; Fp1/ F3.

Right Frontal EEG; Fp2/F4.

Submental EMG was measured from 2 electrodes positioned under the chin on the belly of the genioglossus muscle.

Leg EMG was measured from 2 electrodes positioned on the belly of the anterior tibialis muscle.

All signals were subjected to high and low bandpass filtering to exclude any artefactual electrical signals. Notch filtering (50hz) was also applied to exclude any interference from electrical mains.

Thoraco-abdominal movement was measured with inductance plethysmography (Respitrace, Ambulatory Monitoring Inc) using bands attached to the subject's ribcage and abdomen. Oronasal airflow was monitored with thermocouples at the nose and mouth. Oxygen saturation was recorded with an Ohmeda 3700 oximeter using and ear probe positioned on the earlobe.

Polygraphic recordings were made onto paper, and 2 computerised polysomnography systems. Paper recordings were made with a multi channel polygraph (SLE 16b, Specialised Laboratory Equipment, Croydon, U.K) running at a paper speed of 15 mm/ second or 10 mm/ second giving epochs of 20 or 30 seconds respectively. In order to standardise these records for sleep scoring purposes the recordings made at 15 mm/ sec were renumbered into epochs of 30 seconds. Sleep studies were also recorded onto optical disk using either the Healthdyne Alice 3 computerised polysomnography system or Compumedics computerised polysomnography (Melbourne, Australia). Nine normal subjects had both their sleep fragmentation limbs studied on paper polysomnography, 14 had both fragmentation limbs on Healthdyne computerised polysomnography and 19 had both fragmentation limbs on Compumedics computerised polysomnography. Sixty SAHS patients had their overnight studies recorded

onto paper and the remaining 3 were recorded onto Healthdyne computerised polysomnography.

3.2 Measuring Arterial Blood pressure

Beat to beat arterial blood pressure was measured using digital infrared plethysmography with the Finapres (Ohmeda) device. The device functions according to the method described by Penaz (1973). A finger cuff is fitted onto the finger and inflated to a pressure equal to intra-arterial pressure, thus the pressure difference across the arterial wall, transmural pressure, equals zero. Arterial blood pressure is then determined indirectly from the cuff pressure. The finger cuff contains a plethysmograph which monitors blood volume underneath it and clamps it at a set point which is regularly adjusted by an electropneumatic servo controller to allow for shifts in arterial blood pressure. This is contained in a box, attached to the finger cuff, and strapped to the subject's hand. Parati et al (1989) successfully validated the Finapres with intra-arterial blood pressure monitoring in normals and hypertensive subjects, both at rest, and when performing a series of physiological manoeuvres known to produce fast and significant increases in blood pressure. The Finapres device does not measure absolute blood pressures accurately, however it does measure changes in blood pressure in response to stimuli with accuracy (Parati et al 1989).

In the studies presented in chapter 6, beat to beat systolic, diastolic and mean arterial blood pressure and heart rate were recorded in a digital data stream onto a PC. Due to the sensitivity of the Finapres device to finger or arm movements, during blood pressure recordings subjects were monitored with a video camera and any data obtained during periods of restless sleep were discarded.

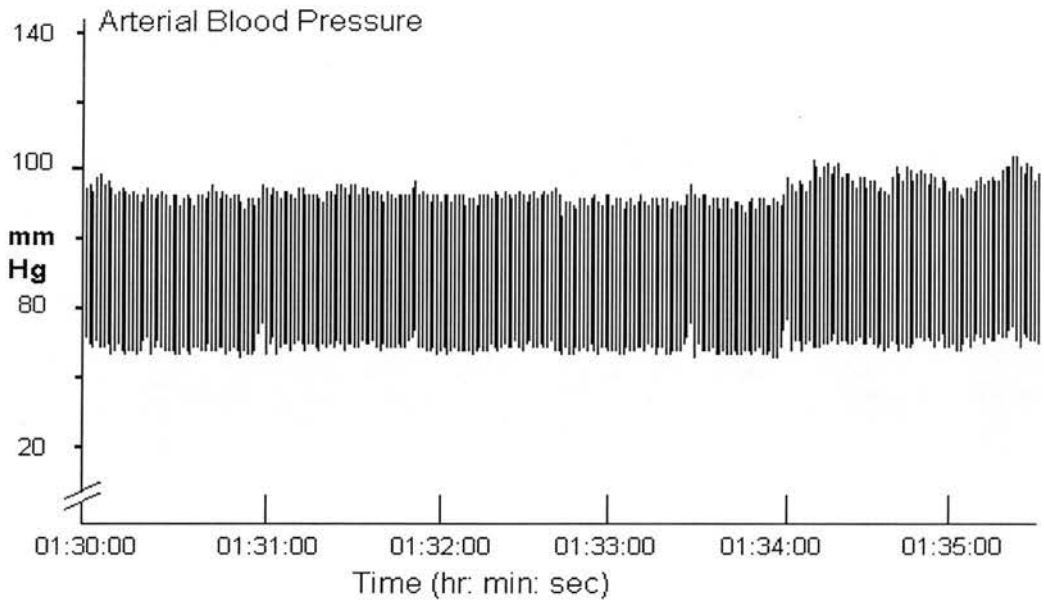


Figure 3.1; Sample of Finapres output available during sleep studies. The top of each vertical line is the systolic blood pressure and the bottom of each line is the diastolic blood pressure for each heartbeat. Millimetres of mercury (mmHg) is represented on the y axis and study time on the X-axis. Five minutes of data is shown here.

3.3 Sleep Scoring

Sleep was staged in 30 second epochs according to Rechtschaffen and Kales' (1968) guidelines. These consist of categorising sleep into 1 of 7 stages including wakefulness.

Stage WAKE is scored if more than 50% of that epoch consists of waking EEG frequencies, in the alpha (8 to 11 Hz (cycles per second)) or beta (greater than 16 Hz) range. In addition there may be eye blinks on the EOG and high EMG activity.

Stage 1 is scored if more than 50% of the epoch consists of theta EEG frequencies (4-7 Hz). EMG activity may be somewhat decreased and there

are usually slow rolling eye movements on the EOG channels (approximately 7 seconds in duration). Stage 1 is a transient sleep stage.

Stage 2 (figure 3.2) is characterised by more than 50% of the epoch consisting of EEG frequencies in the theta range (4 to 7 Hz). The epoch should include sleep spindles, which are short bursts (0.5 to 2 seconds) of sigma (12 to 15 Hz) EEG frequencies, and/ or K complexes, which consist of a rapid depolarisation followed by a rapid repolarisation (0.5 seconds in duration).

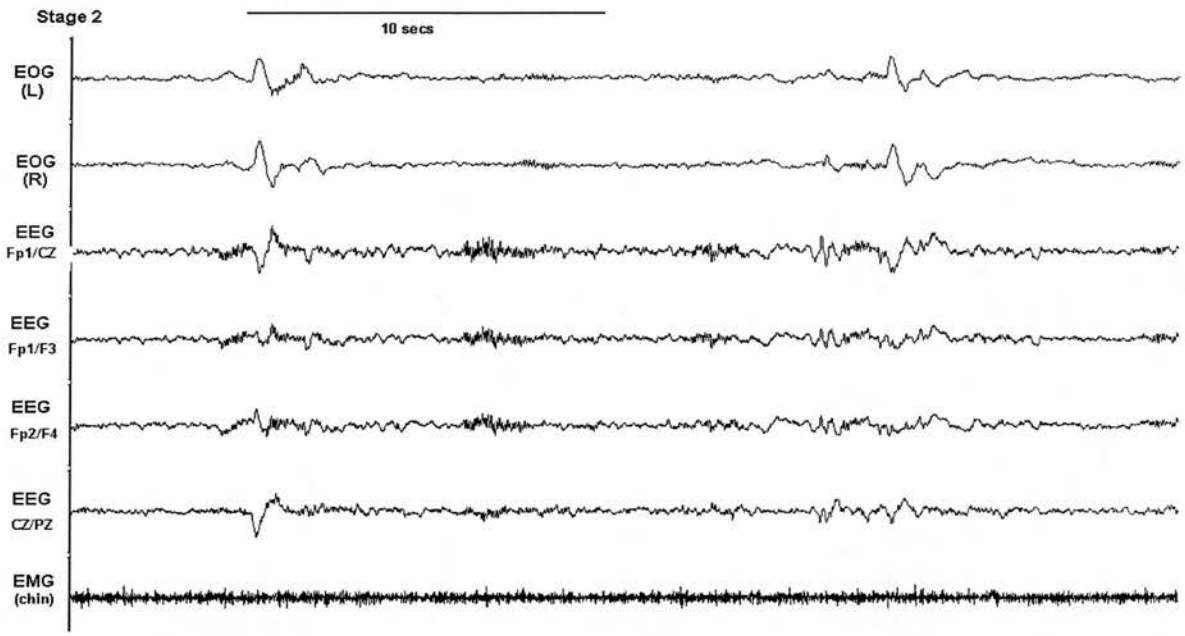


Figure 3.2; Example of a 30 second epoch of stage 2 sleep from a 25 year old male subject showing characteristic sleep spindles and a K complex.

Stage 3 is scored if between 20% and 50% of the epoch consists of delta or slow waves (0 to 3 Hz) of at least 75μv in amplitude. Slow waves can be mistaken for K complexes, however K complexes occur as isolated waveforms whereas slow waves occur in runs. This is another transient sleep stage.

Stage 4 (figure 3.3) is scored if more than 50% of the epoch consists of slow waves. Sleep spindles and K complexes have usually disappeared.

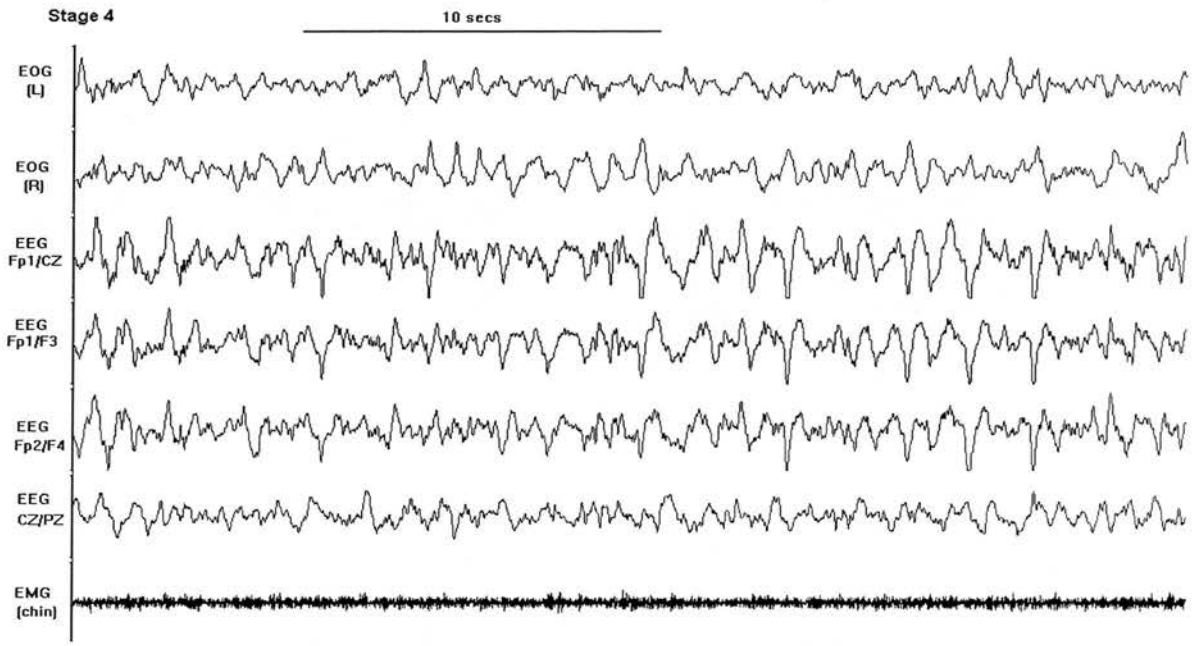


Figure 3.3; Example of a 30 second epoch of stage 4/ slow wave sleep (SWS) from a 25 year old male subject.

Stage REM (figure 3.4) is characterised by mixed frequency low voltage EEG frequencies similar to stage 1 and includes runs of sawtooth and vertex sharp waves. Rapid eye movements proliferate and EMG activity will be reduced to its overnight minimum apart from phasic twitches. In epochs where there are no rapid eye movements but the remainder of the record has the appearance of REM sleep, REM sleep should be scored provided 3 minutes has not passed since the last rapid eye movement. REM sleep always follows stage 2 or stage 4 sleep.

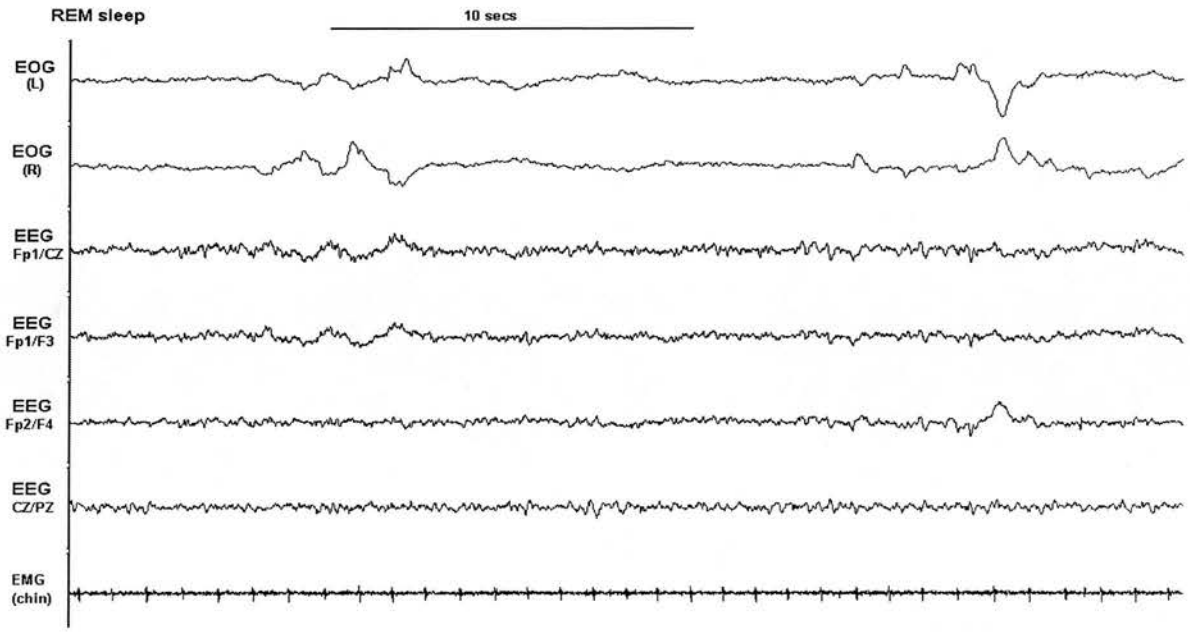


Figure 3.4; Example of a 30 second epoch of REM sleep from a 25 year old male subject showing eye movements and low chin EMG.

Movement Time; this is used when more than 50% of the epoch consists of movement artefact and the underlying sleep stage cannot be determined from any EEG or EOG channel.

The sleep of normal young adults who have good sleep hygiene and no sleep complaints may consist of; less than 5% of wake, 2-5% of stage 1, 45 to 50% stage 2, 3 to 8% stage 3, 10 to 15 % stage 4, and 20 to 25% stage REM (Carskaddon and Dement 1989).

Patients with severe sleep apnoea have disrupted sleep which often alternates between stage 2 (i.e. presence of sleep spindles and K complexes) and Wake. This presents a scoring difficulty due to Rechtschaffen and Kales' (1968) guidelines suggesting that stage 1 is scored prior to stage 2 after an awake epoch. I followed this laboratory's policy in these cases, which is to score these epochs as stage 2 if they can

be defined as such and thus in SAHS patient studies there are small amounts of stage 1.

3.4 Respiratory Events

These are classified into central, mixed and obstructive apnoeas, and hypopnoeas.

Obstructive; (figure 3.5) complete cessation of flow for a minimum of 10 seconds but with continued respiratory effort throughout the apnoea.
Central; complete cessation of flow and respiratory movement for a minimum of 10 seconds.
Mixed; complete cessation of flow for a minimum of 10 seconds. Respiratory effort is initially missing but returns mid way through the apnoea.
Hypopnoea; a minimum of 50% reduction in thoracoabdominal movement for a minimum of 10 seconds.

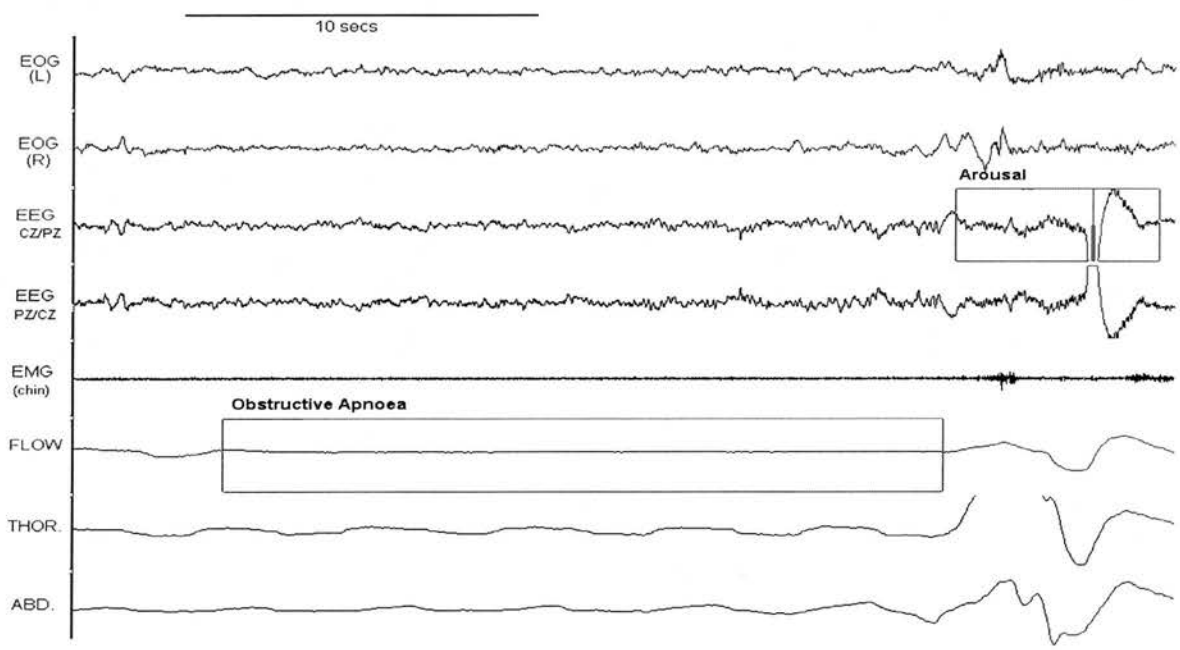


Figure 3.5; A 30 second epoch of stage 2 sleep with an example of an ***obstructive apnoea*** with continued respiratory effort while there is no oronasal airflow. The apnoea is terminated by a visible EEG arousal. Thor; thoracic movement, Abd; abdominal movement.

Definitions of hypopnoea vary between laboratories with some using a 50% reduction in flow as the guideline and other laboratories requiring an additional minimum 4% oxygen desaturation. The above definition has been validated in a series of patients with clinical features of sleep apnoea but who do not have apnoeas (Gould et al 1988).

3.5 Scoring Sleep Fragmentation (Arousals)

In this thesis 5 definitions of arousals were used.

1. The American Sleep Disorders Association (ASDA) has published a set of guidelines for arousal scoring (1992). These require a minimum of 3 seconds return to alpha or theta on the EEG channels during non-REM sleep with the additional criterion of a minimum concurrent 3 seconds increase in EMG tone during REM sleep. This is due to phasic muscle twitches being commonplace during REM sleep.

2. Modified ASDA (mASDA); This definition was modified in house to include the above criteria but for 1.5 seconds only.

3. Cheshire (1992); A minimum of 1.5 seconds return to alpha or theta on the EEG accompanied by any increase in EMG tone however brief.

4. Sleep fragmentation (figure 3.6); A return to alpha or theta EEG frequency for a minimum of 3 seconds regardless of sleep stage.

In the above 4 definitions 10 seconds of prior sleep was required as the minimum interval between arousal events.

5. Rechtschaffen and Kales awakenings (R&K); These were defined as a shift in sleep stage to stage Wake from any sleep stage. By definition they were longer than 15 seconds in duration.

During pilot studies of sleep fragmentation in normal subjects it was difficult to produce EMG increases during REM sleep without causing awakenings lasting longer than 15 seconds. Therefore we omitted any EMG

criterion for arousal scoring from this definition (no. 4). This approach was also used by Philip et al (1994) in their study modelling sleep fragmentation, although it was not specified that their arousal definition was modified for the above reason.

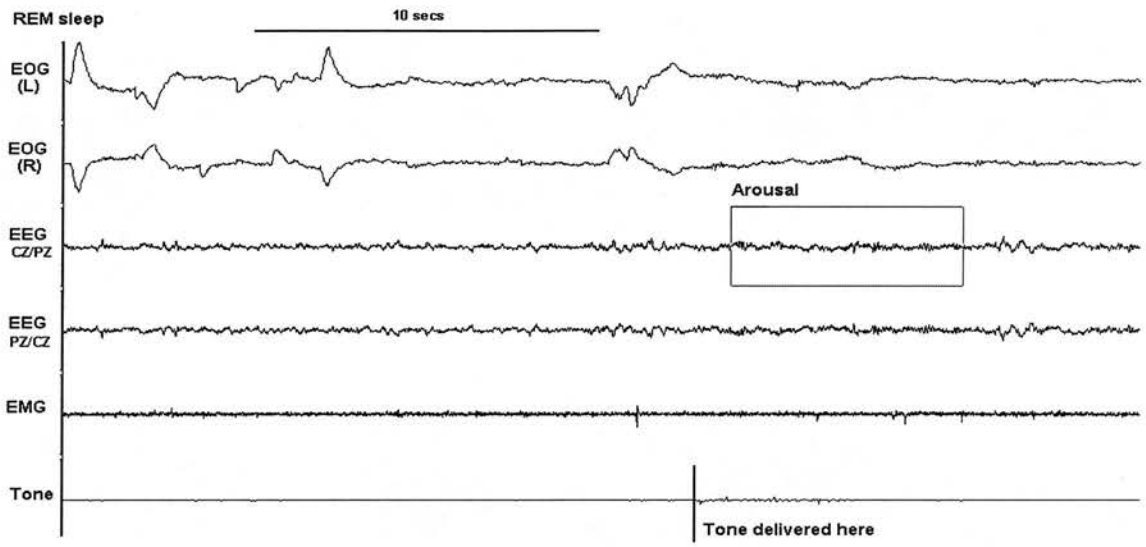


Figure 3.6: Sample trace of an arousal scored by the sleep fragmentation definition during REM sleep. A tone was delivered at the mark shown and produced alpha frequency on the EEG but there was no increase in EMG activity. 30 seconds of data is shown here.

3.6 Reliability of Arousal Scoring

This thesis is concerned specifically with sleep fragmentation and for this reason analysis of the reliability of arousal scoring was essential. Ten overnight sleep records from normal subjects and 10 from SAHS patients were selected for analysis. In the normal subjects arousals were rescored using the sleep fragmentation definition 6 months after their original score. In the SAHS patients arousals were rescored at least 18 months after their original score for the Cheshire (1992) definition only. All rescoring was carried out blind to patient information and previous results. Data from SAHS patients and normals was combined.

There were no significant differences between the first and second scores for arousals in normal subjects or SAHS patients.

	Score 1	**Score 2**	**p value**
Normal subjects	23.9 ± 6.3	23.4 ± 5.4	0.6
SAHS patients	53.4 ± 30.6	48.5 ± 21.9	0.3
Combined data	38.7 ± 26.2	36.0 ± 20.2	0.7

Table 3.1: Data for reliability of arousal scoring. All data are given as arousal frequencies per hour of sleep ± standard deviation.

Figure 3.7 (a) and (b) demonstrates the error between the 2 sets of arousal scores. Although figure 3.7a shows that the arousal scores are numerically close to each other, (b) shows that there are 2 data points which are more than 20 arousals per hour of sleep different to each other. Both of these are scores from SAHS patients.

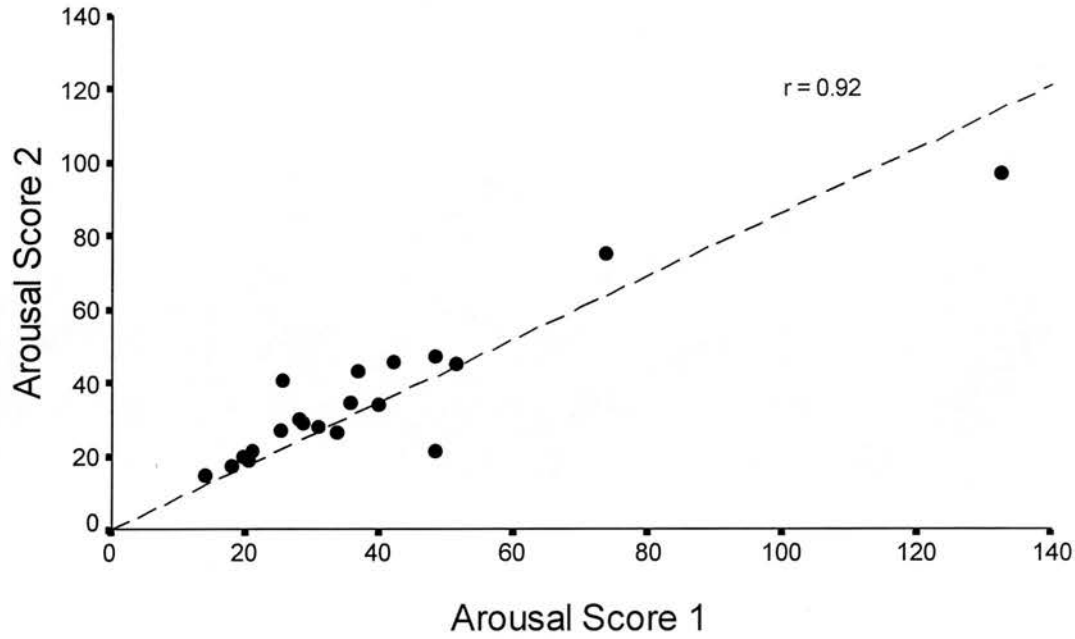


Figure 3.7; (a) Scatterplot showing the relationship between the first and second arousal score. Data points are arousal frequency/ hour of sleep. r= 0.92, p< 0.0001, ------ line of identity.

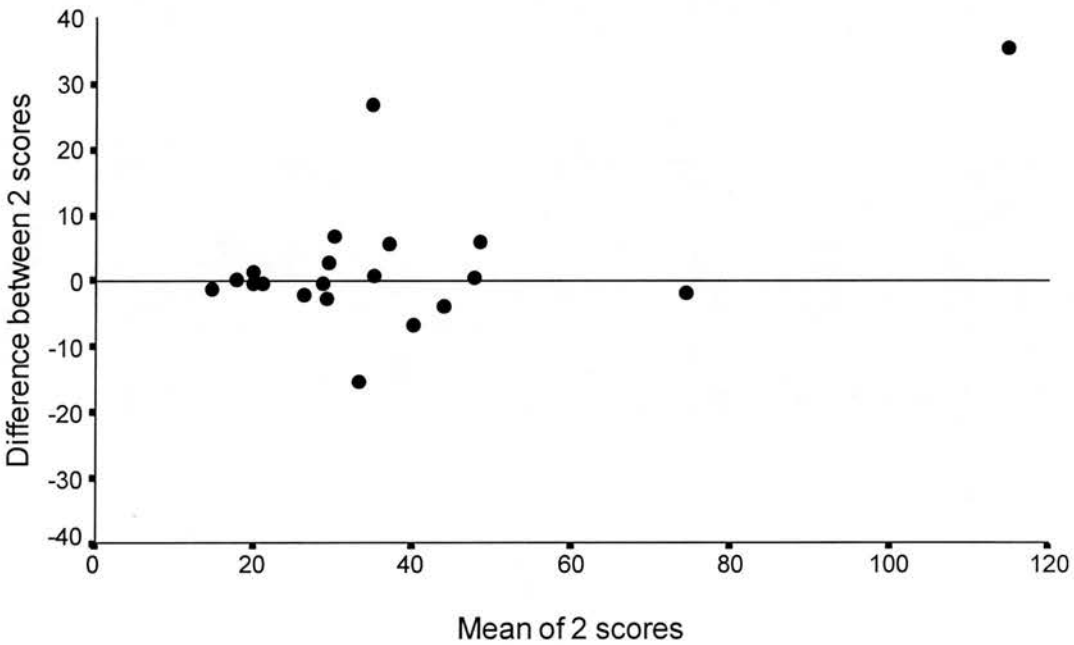


Figure 3.7; (b) Bland and Altman plot demonstrating the error between the 2 arousal scores. The difference between the 2 scores is score 1 - score 2. Data points are arousal frequencies per hour of sleep.

3.7 Fast Fourier Transformation

This technique works on the basis that physiological signals can be described as a series of sine waves of different frequencies. The underlying assumption is that EEG amplitude is inversely proportional to frequency, as EEG frequency (Hz) decreases EEG amplitude (μv) increases. Fast Fourier Transformation (FFT) calculates the power of the EEG which is equal to the square of the amplitude.

Raw data was downloaded from the overnight sleep studies using the facility on the Compumedics Replay version 5.25. The rawdata files were then entered into the FFT analysis programme and files of transformed data produced. This FFT analysis was developed by in house computing support (see acknowledgement) using moving windows of 2 seconds with a resolution of 1 second. Therefore there were FFT data points generated every second. Frequency bandwidths could be altered as required, for example; to investigate the changes in alpha frequency the bandwidth 8-11 Hz could be specified.

This FFT analysis is an improvement on that used by Rees et al (1995) and Drinnan et al (1996). Both studies performed FFT analysis on EEG data with windows of 4 seconds. The ability to select different EEG frequencies in this analysis is again an improvement on that of Rees et al (1995), who investigated changes in total EEG frequency.

Once the transformed data files were generated a further programme allowed for selection of peak EEG power within a specified number of seconds, after specified times. These times were taken from the raw data and were most likely to be the start times for arousals or the times at which tones were presented to normal subjects during the sleep fragmentation studies.

In conclusion there was a large amount of flexibility built into this FFT analysis of the EEG. FFT is used in chapters 6 and 8.

3.8 Daytime Sleepiness

Daytime sleepiness was measured objectively using the multiple sleep latency test (MSLT) (Carskaddon et al 1986, Thorpy 1992) and the Maintenance of Wakefulness Test (MWT) (Poceta et al 1992) as described in section 2.2. Subjective daytime sleepiness was measured in normal subjects using the Stanford Sleepiness Scale (SSS) and the Epworth Sleepiness Scale (ESS).

On the objective sleepiness tests sleep was monitored using EOG, EEG and EMG as previously described (section 3.1). For the MSLT normal subjects lay down in a dark room and were asked to try and sleep for 20 minutes at 10.00, 12.00, 14.00 and 16.00. For the MWT they were seated upright in bed in a dimly lit room and asked to try to stay awake for 40 minutes at 10.45, 12.45, 14.45, and 16.45. They were not allowed to read or exercise during the MWT. The naps were terminated as soon as one epoch of stage 1 sleep was seen during any nap on the MSLT or the MWT. If subjects did not fall asleep naps were terminated at 20 minutes on the MSLT or 40 minutes on the MWT. This was to prevent subjects obtaining any recuperative sleep which may have affected their subsequent daytime sleepiness. In practice caution was exercised in the termination of these tests to prevent terminating the test when sleep onset had not truly occurred, and many subjects may have had a second epoch of sleep prior to termination of the nap. As suggested in section 2.11.3, there may be a minimum duration of sleep that is critical for improvement in sleepiness. If this is as low as 4 minutes, combined with the fact that student subjects are a notoriously sleepy subject group (Levine et al 1988), then running naps on the MSLT for 20 minutes may allow these subjects to obtain recuperative sleep.

In SAHS patients the MSLT was administered at 10am, 12pm, 2pm, 4pm, and 6pm. The naps were terminated 15 minutes after sleep onset, determined as the time to the first epoch of any sleep stage, or after 20 minutes whichever occurred first (Thorpy 1992). Although it is possible that

SAHS patients may have obtained recuperative sleep using this protocol, SAHS patients by definition would have had fragmented sleep, and therefore any sleep they may have had on the MSLT naps would not have been restorative.

Subjective daytime sleepiness was measured using the Stanford Sleepiness Scale (SSS). This is 7 point scale from alert (1) to excessively sleepy (7) upon which subjects have to assess their instantaneous sleepiness. This scale was administered at 7am and, in the sleep fragmentation studies presented in chapters 6 and 7, prior to each nap on the MSLT. Thus circadian variations in subjective sleepiness were assessed.

3.9 Reliability of MSLT and MWT Scoring

The reproducibility of sleep onset recognition was assessed by rescoring 48 daytime sleepiness (24 MSLT and 24 MWT) records from normal subjects at least 3 months after their initial score. Half of the studies were recorded after an undisturbed night's sleep and the other half came after a fragmented night. Data from the MSLT and MWT were combined. Mean sleep onset latency did not change significantly between scores (score 1; 17.2 ± 12.4 (SD), score 2; 17.4 ± 12.4 mins, $p=0.2$).

The differences between the first and second scores of sleep onset latency are best demonstrated in figure 3.8 (a) and (b). In (a) all the data points lie on or close to the line of identity whereas in (b) there are 2 occasions when there are 3 minutes difference between the 2 scores. All these rescores were inserted as alternative data points in the sleep fragmentation studies from which they were taken but they had no significant effect on any of the daytime sleepiness results presented in this thesis.

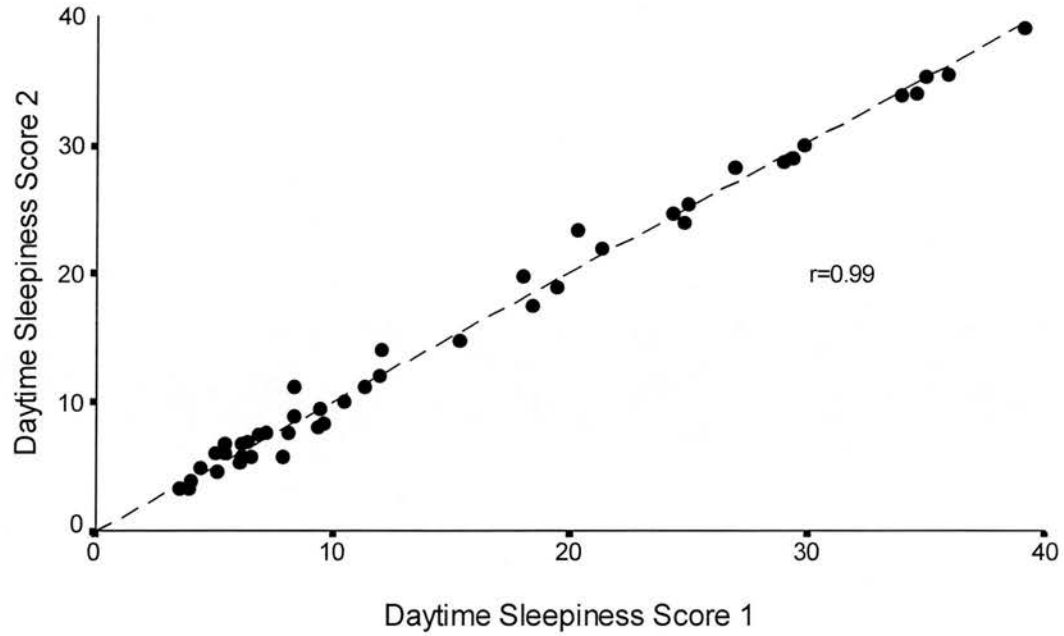


Figure 3.8; (a) Scatterplot showing the relationship between the 2 daytime sleepiness scores, ---- line of identity.

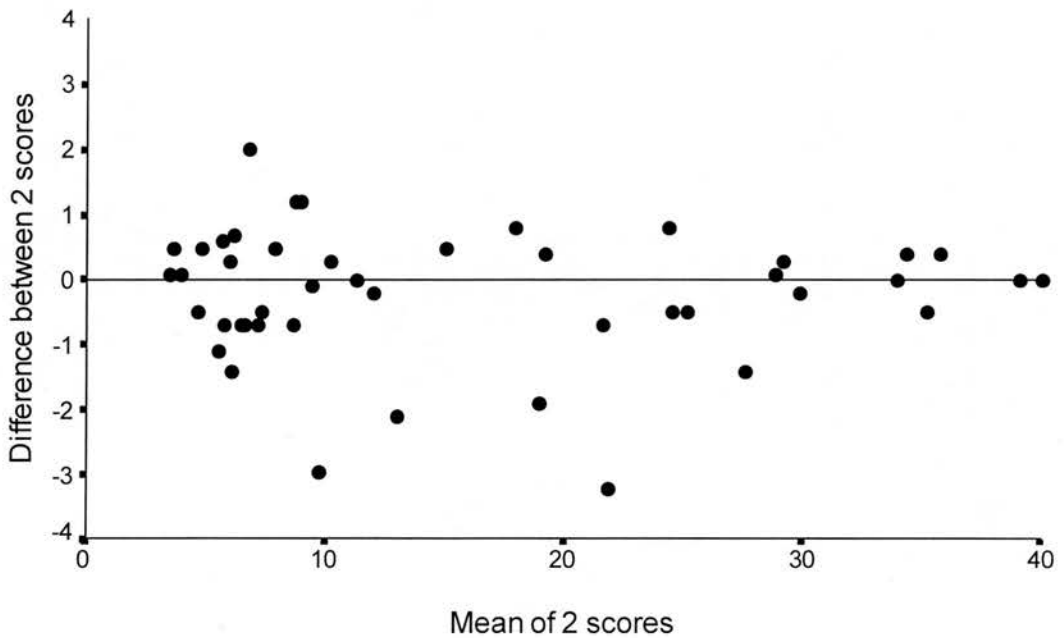


Figure 3.8 contd.; (b) Bland and Altman plot showing the error between the 2 scores for mean sleep onset latency on the MSLT and MWT.

3.10 Mood

Mood was tested using the University of Wales Institute of Science and Technology (UWIST) mood adjective checklist (Matthews et al 1990), the General Health Questionnaire (Goldberg and Hillier 1979), the Hospital Anxiety and Depression scale (Zigmond and Snaith 1983) and part 2 of the Nottingham Health Profile (Hunt et al 1984).

UWIST mood adjective checklist (UMACL)

This scale consists of 24 adjectives testing three dimensions of mood, energetic arousal, tense arousal, and hedonic tone. Each dimension consists of 8 adjectives (table 3.2). Subjects are asked to read the adjectives and rate whether they are definitely, slightly, slightly not, or definitely not, e.g.sluggish, at the time. Subjects have to do this for each adjective.

Energetic Arousal	Tense Arousal	Hedonic Tone
Sluggish	Anxious	Depressed
Tired	Jittery	Dissatisfied
Unenterprising	Tense	Sad
Passive	Nervous	Sorry
Vigorous	Relaxed	Cheerful
Alert	Calm	Happy
Active	Restful	Contented
Energetic	Composed	Satisfied

Table 3.2; The adjectives used in each mood dimension on the UWIST mood adjective checklist.

Subjects score 1 to 4 points according to the adjective, for example scoring 'definitely' sluggish gives 1 point and 'definitely not', 4. High scores are positive for energetic arousal and hedonic tone, and negative for tense arousal.

General Health Questionnaire (GHQ)

This is a 28 question scale which is divided into 4 subscales; somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. Subjects are asked to relate their answers to how they have been feeling over the last few weeks. They are asked to answer the questions according to one of four choices, 2 of which constitute no change from usual, and 2 of which suggest that subjects feel worse than usual.

Hospital Anxiety and Depression scale (HAD)

This is a 14 item scale which is divided into two seven item subscales; anxiety and depression. Subjects are asked to read each item and agree with one of 4 statements, whichever comes closest to how they have been feeling in the last week. Scores for answers range from 0 to 3 therefore scores for both subscales range from 0 to 21. Scores of 11 or above for either subscale were considered clinically significant.

Nottingham Health Profile part 2 (NHP)

Subjects are asked 20 questions relating to 6 areas of their daily lives, work, jobs around the house, home, social, sex, and hobbies and interests. These are chosen as they are areas of daily living which may be affected by health problems. Subjects can answer 'yes' or 'no' to the questions in this scale.

3.11 Cognitive Function.

Cognitive function was tested in normal subjects and in SAHS patients. The selected tests reflected a wide range of function and included tests that we have previously found were sensitive to one month on CPAP therapy in SAHS patients (Engleman et al 1994a).

Digit Symbol (Weschler 1981)

This is a Performance subtest of the Weschler Adult Intelligence Scale-Revised battery of tests. The test consists of 93 single digit numbers which have spaces below them for subjects to complete with pencil drawn symbols according to a code. The code of symbols corresponding to the numbers is displayed above the test. The subject has 90 seconds to fill in as many of the symbols as possible beneath the numbers. The score is the number of correctly drawn symbols. This tests subjects' coding speed.

Block Design (Weschler 1981)

This is another Performance subtest in the WAIS-R IQ battery. Subjects are given cubic blocks with which to construct 2 dimensional images displayed to them. The blocks have 2 sides which are all white, 2 sides all red, and 2 sides diagonally divided into half red and half white. The images displayed to subjects require either 4 or 9 blocks to construct, and scores are based on how quickly subjects complete the picture with a time limit on each. There are 9 images to construct in total. This tests the subject's visuo-spatial ability.

Estimated Performance IQ

This is calculated using scores from the digit symbol and block design tests. Scores from these tests are scaled as instructed (Weschler 1981). Scaled scores are then added and the total multiplied by 2.5 to give an approximate scaled score. This is then translated into a Performance IQ dependent on age using published tables (Weschler 1981).

Steer Clear (Findley et al 1988).

This is a vigilance task which lasts for 30 minutes. Subjects sit down in front of a computer screen upon which there is a bird's eye view of a 2 lane road. There is a car travelling up the road at a predetermined speed. The subject has to avoid obstacles which pop up in front of the car, at irregular intervals - on average 40/ minute - by changing lanes, using the space bar. This test is monotonous and further tests subjects' ability to remain vigilant by including periods when no obstacles appear in front of the car.

Trailmaking A and B (Lezak 1983)

This test is part of the Halstead-Reitan neuropsychological test battery. In part A subjects are shown a page with numbers 1 to 25 displayed on it. They are then required to join up the numbers in ascending order with a pencil as quickly as possible. In part B subjects are shown a page with numbers 1 to 13 and letters A to L displayed on it. They are required to join up alternate increasing numbers and later letters of the alphabet 1-A-2-B etc (figure 3.9, page 80). Both parts test subjects' tracking speed and psychomotor ability with part B testing mental flexibility also.

Rapid Visual Information Processing (RVIP) (Petrie and Deary 1989).

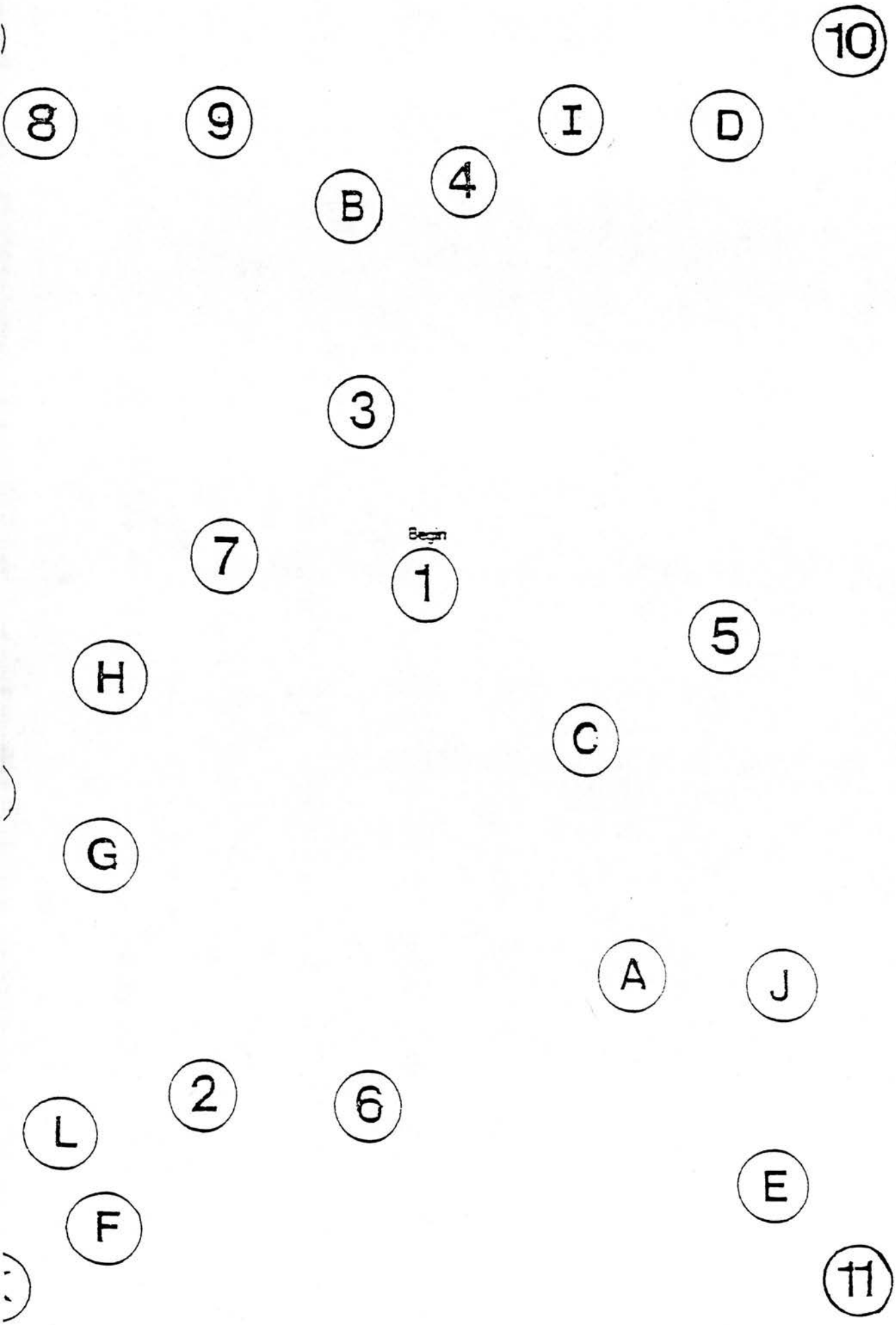
Subjects are seated in front of a computer screen in a darkened room. Single digit numbers from 1 to 8 inclusive flash up in the centre of the screen at the rate of 1 per 0.6 seconds (100 per minute). Embedded in these random numbers are sequences of 3 odd or 3 even numbers which subjects have to recognise by pressing the space bar ('hits'). 'False alarms' are noted if subjects press the space bar when there was no triplet sequence. There are 8 sequences to be recognised in any minute. The test usually lasts for 10 minutes. RVIP tests stimulus encoding speed and response caution mechanisms.

Paced Auditory Serial Addition Test (PASAT) (Lezak 1983)

Subjects listen to a tape of a person calling out single digit numbers either every 4 or 2 seconds. They are required to add up the last two numbers that the person calls out and give the answer to the experimenter. There are 61 numbers and, therefore, the subjects can score a maximum of 60. We used both 4 and 2 seconds parts of the test. This tests subject's attention and concentration.

Over page for figure 3.9

Figure 3.9; Sample of the Trailmaking B test with numbers and letters spread over the page.


10
8
9
I
D
4
B
3
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Begin
1
5
H
C
G
A
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6
L
E
F
11

3.12 Tone Generation

In all the sleep fragmentation studies described in this thesis sleep was fragmented with tones. These were generated using an in-house noise generator which consisted of a control box attached to a loudspeaker. The loudspeaker was positioned on the headboard of the bed directly above the subject's head. Arbitrary units were drawn along the volume control position and these were calibrated against a sound level meter in the Audiology department of this hospital. The minimum sound generated was 38dB and the maximum was 101dB. Tone administration in each sleep fragmentation protocol is described in greater detail in subsequent chapters 5, 6 and 7.

3.13 Pilot Studies

In order to test whether sleep could be fragmented adequately with sound according to the different sleep fragmentation paradigms pilot studies were performed in normal volunteers. In these pilot studies various methods of measuring autonomic activity during sleep were tested, including normal subject's ability to tolerate the Finapres device for whole or part night studies. Pilot studies were conducted in 6 (4 men, 2 women) volunteer subjects recruited from the employees within the Respiratory Medicine Unit and student population. They were aged 21 (M), 21 (M), 24 (F), 24 (F), 26 (M), and 34 (M).They slept in the laboratory for one night each only. In addition to the standard electrode placement, 2 subjects wore the Finapres device, one subject wore an ear oximeter to measure heart rate, and another subject wore 3 ECG leads and a finger pulse oximeter to measure pulse transit time.

In two pilot subjects I aimed to fragment their sleep to produce changes in EEG frequency on the EEG channels. Tones were delivered from the noise generator described above. For half of each night sleep was fragmented in a regular fashion every 2 minutes of sleep and for the remaining half of each night sleep was fragmented in a clustered fashion, allowing the subject to sleep for an hour and then administering tones every

30 seconds for half an hour. It was clear that the sleep of both subjects could be cortically fragmented with tones, with sleep stage and time of night as factors for determining tone volume and duration as previously described (Williams et al. 1964). There were however differences between the 2 subjects in the volumes and durations of tones required to produce visible EEG arousals during the same sleep stages at similar times of night. Therefore due to subject variability the process of inducing sleep fragmentation with tones could not be automated.

In the 2 pilot studies where the subjects wore the Finapres the aims were twofold, to investigate whether normal subjects could tolerate the Finapres device for whole night studies and to investigate the possibility of fragmenting sleep using blood pressure changes, without any visible change on the EEG, as a marker of arousal. During one pilot study night the subject could not tolerate the Finapres device which was removed after 2 hours of intermittent sleep. During the second pilot study the subject slept well with the device switched on for the first sleep cycle, approximately 90 minutes, but subsequent to this, switching on the device woke the subject easily. In the first pilot study any tones that I administered to the subject while they were wearing the Finapres device caused cortical arousals or awakenings. In the second study sleep was fragmented to induce transient increases in arterial blood pressure, without any visible cortical arousals, during the first sleep cycle only. In subsequent sleep cycles sleep was intermittent and if the subject did stay asleep tones caused cortical arousals or R&K awakenings.

Due to the problems with toleration of the Finapres device, the possibility of using PTT (as described in section 2.5.2) and heart rate as markers of autonomic sleep fragmentation was also investigated. The RM50 (Parametric Recorders), a prototype portable sleep study device, which has PTT as one of its measurements, was tried out as a method of measuring autonomic activity. PTT can be calculated in real time from the ECG signal and the pulse oximeter on the finger, provided the device is linked to a PC. We studied on line PTT during a night of cortical sleep fragmentation and

found that it was not sensitive enough to indicate transient changes in PTT, and consequently blood pressure, within the range required.

Heart rate was investigated with an ear oximeter attached to a chart recorder during a night of cortical sleep fragmentation. There were changes in heart rate in response to tones that produced cortical arousals, however this response was too variable to be used alone as a reliable indicator of visible EEG arousal. Therefore it would not be suitable as an autonomic marker of arousal in response to tones that did not produce visible EEG arousals. Parallel processing of the heart rate signal to obtain beat to beat rather than averaged heart rates may have been of use, however this is not available on our computerised polysomnography system.

Due to the above problems with monitoring autonomic markers of arousal from sleep it was decided to use the Finapres device for part of the sleep study in combination with heart rate as a guideline for the remainder of the night. The actual fragmentation paradigm for this fragmentation study is described in further detail in chapter 6.

3.14 Study Design

There were 3 sleep fragmentation protocols which were all based on a randomised, within subject comparison design.

1. Fragmentation to induce visible EEG arousals.
2. Fragmentation to induce autonomic responses to tones without inducing visible EEG arousals that could be scored as microarousals by current definitions.
3. Fragmentation to induce visible EEG arousals in either a regular fashion or a clustered fashion.

Each study required subjects to spend 2 pairs of 2 nights in the sleep laboratory. Prior to the first night in the laboratory subjects received

instructions on the tests of mood and cognitive function that were used in these studies and had one practice session. The nights were divided into 2 pairs of 2 nights a week apart. The first night of each pair was for acclimatisation to the laboratory to avoid any "first night effect", and without which subjects may have had abnormally disrupted sleep. On the second night of each pair subjects were randomly assigned to having one or other of the study nights depending on the protocol (figure 3.10).

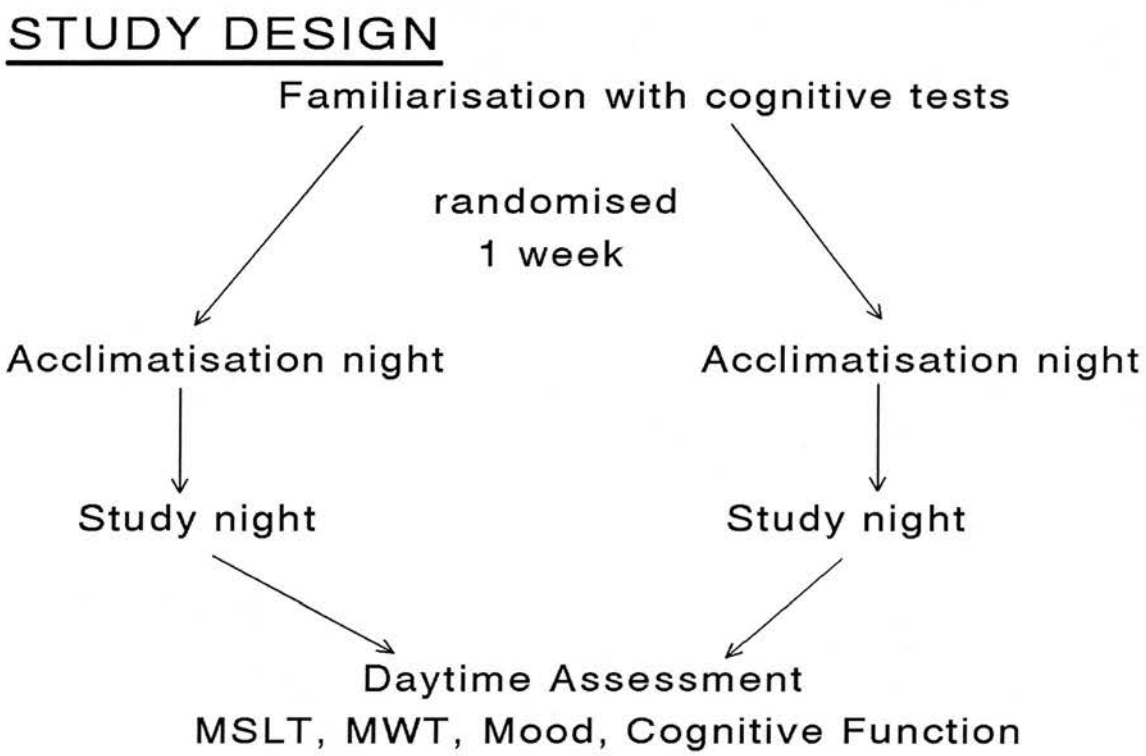


Figure 3.10; Schematic diagram of the randomised study design used in the sleep fragmentation studies.

Subjects spent the day following each pair of nights undergoing testing of daytime sleepiness, mood and cognitive function. Subjects had their tests of daytime function tested at similar times on both study limbs to avoid any circadian variation between assessments.

3.15 Normal Subject Recruitment

Normal subjects for the sleep fragmentation studies were recruited from the local student population using advertisements that did not refer to sleep. Subjects who responded were sent a questionnaire without any information about the study. This was our in house sleep/ wake questionnaire which is used to assess patients prior to their attendance at this sleep laboratory. Subjects with possible sleep disorders were excuded if they had abnormal sleep hygiene or if their answers on the questionnaire were symptomatic for SAHS, narcolepsy or PLMS. In addition the questionnaire includes the Epworth Sleepiness Scale. Subjects were also excluded if they had Epworth Sleepiness Scores greater than 9, 10 being the upper limit for normal daytime sleepiness (Johns 1991). The full questionnaire is given in Appendix 1. Subjects were paid an inconvenience fee of £90 if they completed all assessments within any one sleep fragmentation study. They were not allowed to participate in more than one protocol. Ethical permission was obtained for this study from the Lothian Health Research Ethics Committee and from The University of Edinburgh Ethics committee.

Chapter 4

Comparison and validation of different microarousal definitions in patients with Sleep Apnoea/ Hypopnoea Syndrome (SAHS).

4.1 INTRODUCTION

Scoring microarousals has recently become more common in clinical sleep studies particularly when the patient's daytime sleepiness can not be attributed to sleep apnoea or narcolepsy. The raised microarousal frequencies seen in some patients who do not have sleep apnoea may be due to heavy snoring (Guilleminault et al 1991) or increases in upper airway resistance (Guilleminault et al 1993). The conclusion is that microarousals cause daytime sleepiness. This is largely due to the finding that upon application of CPAP therapy, there is a decrease in microarousal frequencies seen coincident with an improvement in daytime sleepiness, as measured by the MSLT.

In heavy snorers Guilleminault et al (1991) defined short EEG arousals as increases in EEG frequency, or EMG tone, or changes in R-R interval, that did not lead to full awakenings. There was however no indication of a minimum timescale required for scoring microarousals. In patients with increased upper airway resistance syndrome Guilleminault et al (1993) used a stricter definition of microarousal, which was a burst of alpha lasting for at least 3 seconds.

The original description of sleep apnoea by Gastaut et al (1965, 1966) includes descriptions of arousals from sleep of different durations that terminated apnoeas. It is possible to extract indices of sleep fragmentation from the sleep staging guidelines of Rechtschaffen and Kales (1968) by scoring the number of stage shifts to wakefulness (section 3.5), or stage shifts to a lighter sleep stage. This does not allow for the recurrent brief arousals (less than 15 secs) that are seen in patients with sleep apnoea.

Phillipson and Sullivan (1978) drew the attention of researchers to arousals as responses to respiratory events in sleep apnoea. This was an editorial encouraging researchers in the field to study the mechanisms of arousal responses and did not give any guidelines as to how to score them. Roth et al (1980) suggested a more sensitive measure of arousals using an increase in EMG (leg or chin) for longer than 3 seconds associated with respiratory events.

Although sleep fragmentation should be measured in as sensitive a manner as possible it is unclear whether duration of arousals is critical in contributing to daytime sleepiness. Stepanski et al (1984) approached this by using a four level arousal scoring system in normal subjects and patients with sleep apnoea, insomnia and periodic leg movements. Arousals were scored as: 1. an increase in EEG frequency and EMG amplitude; 2. alpha burst on the EEG for (a) 0-5 seconds, or (b) 6-29 secs, with accompanying EMG amplitude increase during REM sleep; 3. stage shift to a lighter sleep stage; 4. awakening from (a) stage 1 or REM, or (b) stage 2, 3, or 4. They found that patients with sleep apnoea had more short arousals than awakenings and that total number of arousals explained 23% of the variance in objective daytime sleepiness in all subjects. In individual subject groups there were no significant relationships between arousals and daytime sleepiness, a fact that the authors attribute to the small amount of variability in daytime sleepiness within each subject group. Alternatively this may have been due to the small number of subjects in each group. In answer to the question of arousal duration there were no significant relationships between arousals of different durations and daytime sleepiness. There were however trends for positive relationships between daytime sleepiness and arousals in patients with sleep apnoea and patients with periodic leg movements, who suffered from EDS, and for negative relationships in patients with insomnia, who did not.

Gould et al (1988), in the definition of the sleep hypopnoea syndrome, defined arousal as an episode lasting at least 1.5 seconds in which there

was a return to alpha or theta on the EEG associated with an increase in EMG activity. Cheshire et al (1992) subsequently used this definition to correlate arousals with daytime sleepiness and cognitive function. In this same study the arousal definition was re-evaluated to a return to alpha or theta for at least 1.5 seconds accompanied by any increase in EMG activity, which showed a better correlation with AHI (r=0.88) than the previous definition (r=0.63). There was a larger number of significant correlations between this definition of arousal and cognitive function, and these relationships were more significant than with the previous definition.

Also in 1992 the Altas Task force of the American Sleep Disorders Association published guidelines for the scoring of arousals; a return to alpha or theta frequency on the EEG for at least 3 seconds with an associated 3 second increase in EMG activity during REM sleep. These guidelines are based on research findings such as Roehrs et al (1991), Guilleminault et al (1991), Roth et al (1980), and Stepanski et al (1984) that some variance in daytime sleepiness can be attributed to sleep fragmentation.

The increases in EMG are vital for scoring arousals during REM sleep. Alpha bursts are common during REM and are generally accepted as part of the normal pattern of REM sleep and not as arousal phenomena. Therefore adding a criterion of increases in EMG activity during REM sleep would guard against erroneous scoring of microarousals. For a similar reason bursts of EMG activity in the form of muscle twitches are also accepted as part of normal REM sleep and therefore the EMG cannot be used on its own as a method of scoring arousals. It can be argued that during REM sleep alpha bursts could occur accompanied by muscle twitches by coincidence and result in the erroneous scoring of arousals. This is a problem regardless of the definition of microarousal.

The bulk of data on microarousal scoring comes from patients with sleep apnoea and sleep disordered breathing. It is unclear what constitutes a normal arousal frequency using any of these definitions. Mathur and Douglas (1995b) compared 3 definitions of microarousal (ASDA, mASDA, and

Cheshire), and stage shifts to wakefulness for their relative frequencies in a group of control subjects ranging in age from 16 to 74. This group of subjects had 21 ASDA arousals and 14 Cheshire arousals per hour of sleep. Although this may seem high, the upper 95% confidence interval of 56 ASDA and 55 Cheshire arousals per hour of sleep was more surprising. These figures were not altered by the exclusion of those subjects who were over 60 years of age, had snoring, daytime sleepiness, or witnessed apnoeas, or who had less than 4 hours of sleep on their polysomnography night. The authors attributed these results in part to the invasive nature of polysomnography which would bias subjects towards having poor quality sleep, however it remains that normal subjects can have profoundly fragmented sleep on the first night of polysomnography.

Scoring microarousals is a more sensitive estimate of sleep fragmentation in SAHS patients than conventional sleep staging (Stepanski et al 1984). There is however no agreement on which microarousal definition is the definition of choice for use in routine clinical sleep studies as different definitions correlate significantly with daytime function (Roth et al 1980, Roehrs et al 1989, Cheshire et al 1992). Although high microarousal indices may cause daytime sleepiness results from single night polysomnography studies in normal subjects suggest that the upper limit of normal is surprisingly high.

Therefore 3 definitions of microarousal and 1 of arousal (> 15 secs) were compared for their frequencies in SAHS patients, their presence at the termination of apnoeas and hypopnoeas and for their relative abilities to predict daytime sleepiness, mood and cognitive function.

4.2 METHODS

Subjects

Subjects were recruited from patients referred to the sleep laboratory with suspected sleep apnoea who lived within 50 miles. They had to have 2 or more symptoms of sleep apnoea and an AHI $\geq$ 5 per hour of sleep on an overnight polysomnography prior to being invited to take part in this study. A consecutive series of 63 patients (55 men) were recruited. Group mean data shows that they were relatively obese and most had some degree of daytime sleepiness as shown by their Epworth sleepiness scores (Johns 1993) (table 4.1).

n	63 (55 men, 8 women)
Age (years)	49 SD 10
BMI (kg/m^2)	31 SD 8
AHI per hour of sleep	36 SD 31
ESS (0 to 24)	12 (range 5 to 19)

Table 4.1; Descriptive data for the study sample. BMI; body mass index. AHI; apnea/ hypopnea index. ESS; Epworth Sleepiness Score.

Protocol

Subjects had full overnight polysomnography according to our standard procedures (Douglas et al 1992). EEG, EOG, submental EMG, anterior tibialis EMG, thoracoabdominal movement, oro-nasal airflow and oxygen saturation were recorded as described in section 3.1 onto a 16 channel polygraph (SLE) at 10 mm/ second paper speed giving epochs of 30 seconds. Sleep and respiratory events were scored according to standard criteria (see sections 3.3 and 3.4). A single polysomnographer scored sleep

fragmentation with 3 microarousal definitions and 1 definition of awakening. Separate passes through each overnight study were made for each definition. Data for test-retest reliability of microarousal scoring for this experimenter are presented in section 3.6. Subjects had assessment of subjective and objective daytime sleepiness, mood and cognitive function within 6 months of the original polysomnography night. Subjects did not have CPAP therapy in the intervening period between polysomnography and daytime function testing.

Arousal Definitions

There were 3 definitions of microarousal employed in this study: ASDA, mASDA, Cheshire; and 1 definition of awakening; R&K awakening. They are described in greater detail in section 3.5. It was also noted whether microarousals were associated with apnoeas or hypopnoeas. A microarousal was defined as being associated with an apnoea or hypopnoea if it occurred within 10 seconds of the termination of the respiratory event. Total microarousal frequencies could therefore be divided into microarousals occurring spontaneously and microarousals occurring in association with respiratory events.

Daytime Function

Objective daytime sleepiness was assessed using the MSLT performed as described in section 3.8. Subjective daytime sleepiness was assessed in a subgroup of 30 subjects using the Epworth Sleepiness Scale (Johns 1991). Mood and psychosocial function was assessed using the HAD scale (Zigmond and Snaith 1983), the NHP part 2 (Hunt et al 1984), and the GHQ-28 (Goldberg and Hillier 1979) (section 3.10). Instantaneous mood was assessed using the UWIST mood adjective checklist (Matthews et al 1990) as described in section 3.10. Cognitive function was assessed using Digit

Symbol, Steer Clear, and Trailmaking B as described in section 3.11. Engleman et al (1994b) previously found that these mood scales and cognitive function tests showed significant improvements in SAHS patients after one month on CPAP therapy.

Statistical Analysis

Frequency tables for all variables were drawn up and examined for normality. The nocturnal variables; AHI and arousal frequencies, were skewed and therefore non-parametric statistical tests were used to analyse these data. Comparisons of arousal frequencies were made using the Wilcoxon matched pairs test with Bonferroni corrections for multiple comparisons where appropriate. Relationships between nocturnal variables and daytime sleepiness were investigated using Spearman correlation coefficients. Interrelationships between microarousal frequencies were investigated using Pearson correlation coefficients.

There were a large number of daytime function variables to enter into a correlation matrix with nocturnal variables. This could lead to problems with multiple comparisons and increases the likelihood of finding significant relationships between nocturnal and daytime variables by chance. In a set of measurements where there is redundancy among the measured variables, principal components analysis (PCA) is a useful technique to reduce the number of outcome measures. There were significant interrelationships between outcome measures on the mood scales and therefore PCA (Child 1990) was used to reduce the number of mood variables. In a similar fashion there were significant interrelationships between outcome measures on the cognitive function tests and PCA was applied to them also.

4.3 RESULTS

Microarousal Frequencies

There were significantly more total microarousals per hour of sleep by any definition than R&K awakenings. There were significantly more mASDA and Cheshire microarousals than ASDA microarousals (both $p<0.001$) but there was no significant difference between the number of either 1.5 second definitions-Cheshire and mASDA ($p>0.7$). There were significantly more spontaneous microarousals by any definition than R&K awakenings. There were significantly less spontaneous ASDA microarousals than Cheshire microarousals (table 4.2).

Definition	spontaneous arousals	arousal associated with A or H	total
ASDA	12 ± 1* (40 ± 3%)	27 ± 3**	39 ± 3**
mASDA	14 ± 1 (41 ± 3%)	29 ± 3	43 ± 3
Cheshire	14 ± 1 (41 ± 3%)	29 ± 3	43 ± 3
R&K	4 ± 1** (44 ± 4%)	6 ± 1**	10 ± 1**

Table 4.2; Mean ± SEM (with percentages where appropriate) number of spontaneous arousals, arousals associated with respiratory events and total arousals per hour of sleep scored by each definition. A+H; apneas+hypopneas, ** $p<0.0001$ significantly different to all other definitions. * $p<0.01$ ASDA significantly different to Cheshire.

Significantly more respiratory events were terminated by microarousals than by R&K awakenings (all $p<0.001$) (table 4.2). More apneas and hypopneas were terminated by 1.5 second microarousals than by ASDA microarousals (both $p<0.001$) but there was no significant

difference between either 1.5 second definition ($p>0.7$) (table 4.2). The percentage of respiratory events that were terminated by arousals of different definitions is shown in table 4.3.

ASDA	mASDA	Cheshire	R&K
75 ± 4	83 ± 4	81 ± 4	18 ± 1

Table 4.3; The mean ± SEM percentage of apnoeas and hypopnoeas that terminated in the various different arousals.

Microarousal frequencies were all significantly correlated with AHI and with each other although the r values for relationships between ASDA, mASDA and Cheshire arousals were higher than with R&K awakenings.

	ASDA	mASDA	Cheshire	R&K
AHI	0.84	0.83	0.82	0.59
ASDA		0.97	0.94	0.79
mASDA			0.98	0.78
Cheshire				0.77

Table 4.4: Interrelationships between AHI and arousals scored by the different definitions. All $p<0.0001$.

The relationships between AHI and microarousals are similar to that found by Cheshire et al (1992) (figure 4.1). It is interesting to note that in patients with AHI < 20 per hour of sleep, all the microarousal frequencies are higher than the AHI.

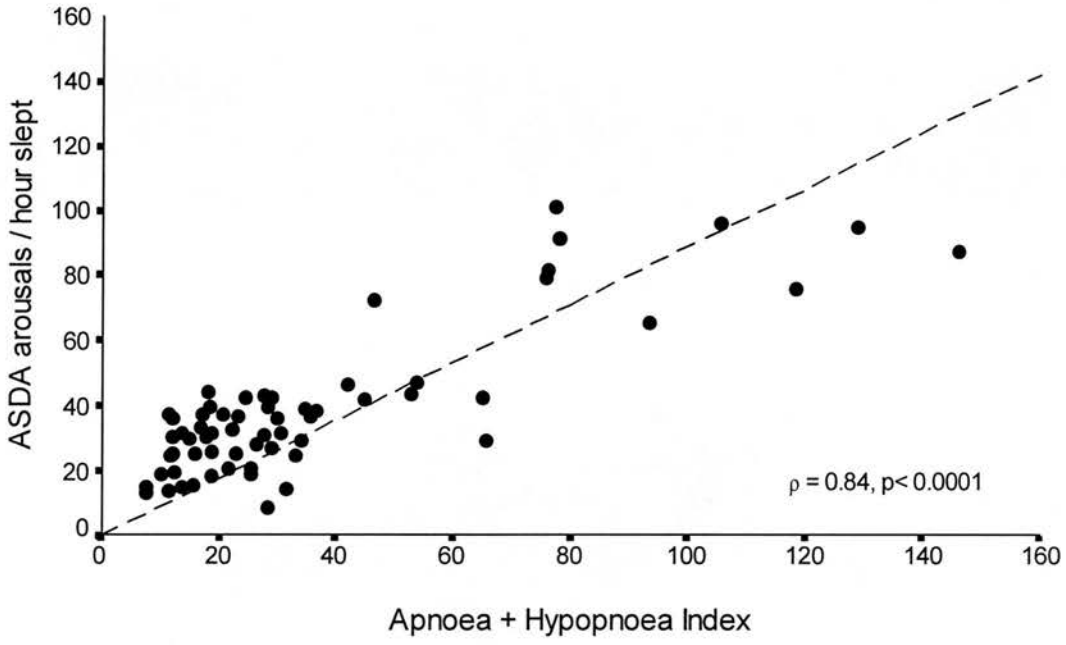


Figure 4.1: Scatterplot demonstrating the relationship between AHI and ASDA microarousal frequencies. - - - - Line of Identity.

Correlation with Daytime Function

There was no significant relationship between objective daytime sleepiness on the MSLT and subjective daytime sleepiness on the ESS.

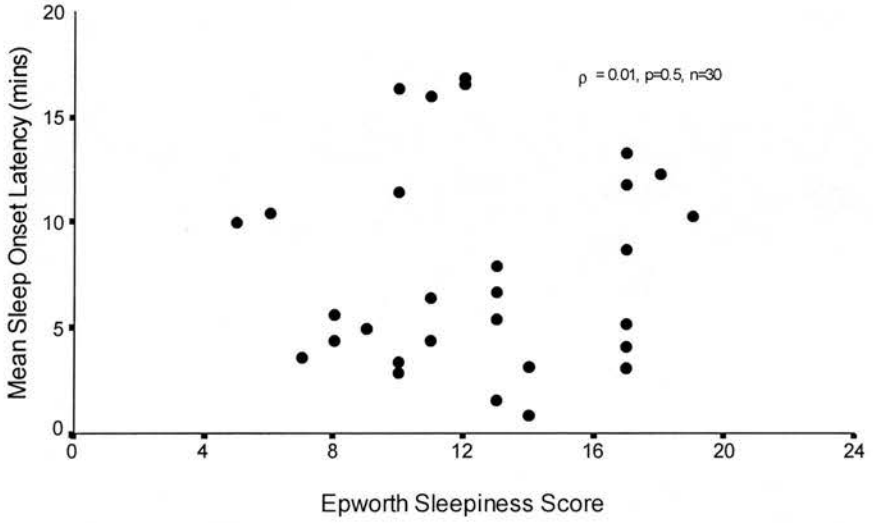


Figure 4.2; Scatterplot showing the relationship between objective (MSLT) and subjective (ESS) daytime sleepiness.

Apneas and hypopnea frequency correlated significantly with mean sleep onset latency on the MSLT (figure 4.3).

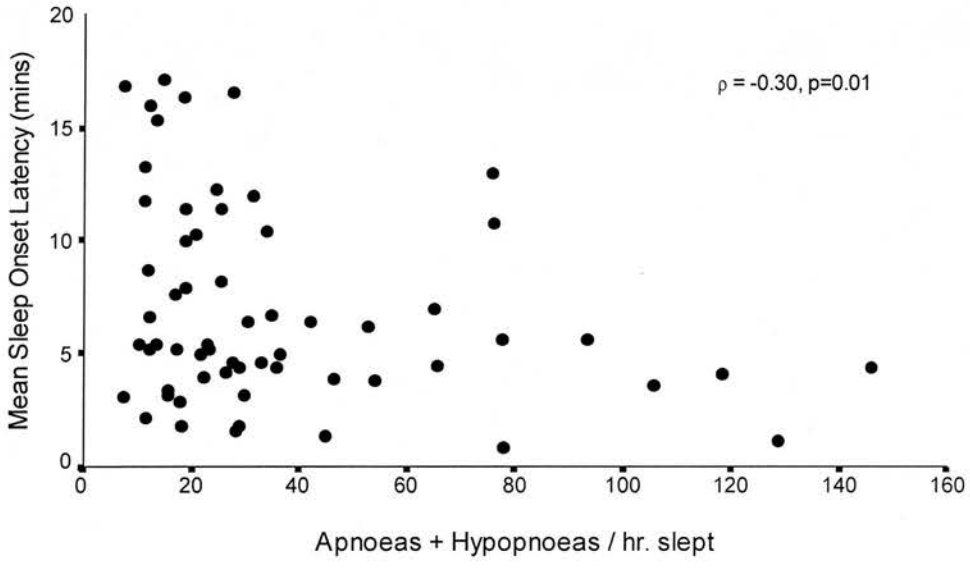
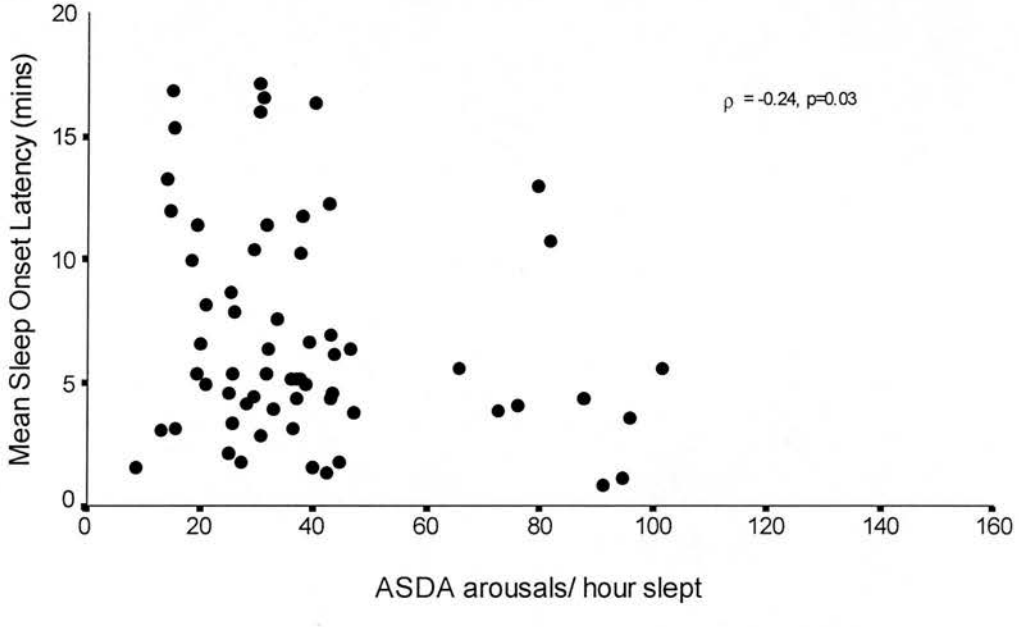
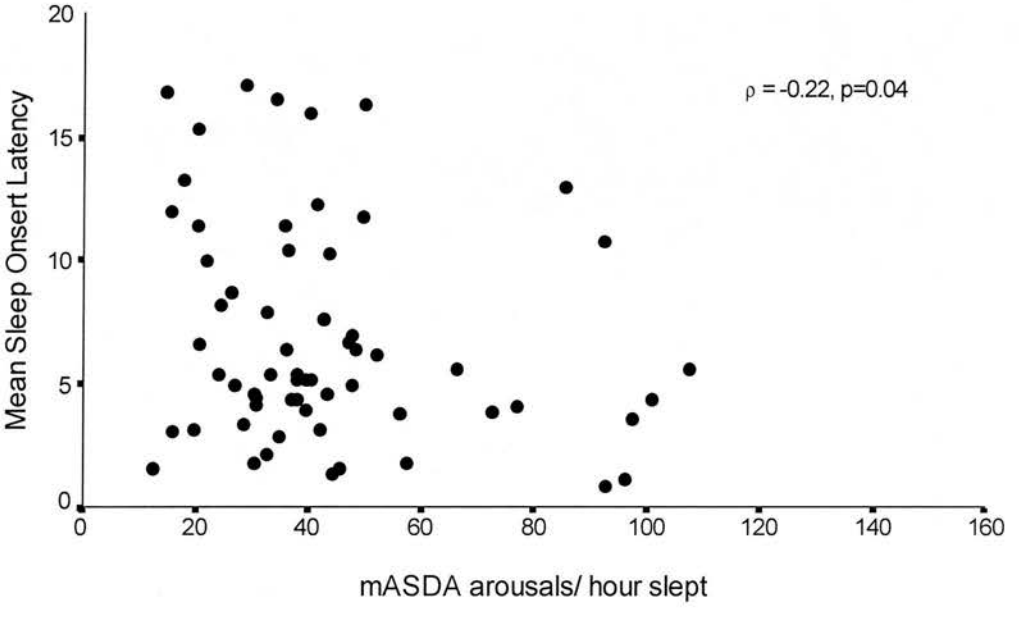


Figure 4.3; Scatterplot showing the relationship between daytime sleepiness on the MSLT and AHI.

There was a significant but weak relationship between microarousals scored by any definition and mean sleep onset latency (all $\rho \geq -0.22$, all $p \leq 0.04$) (figure 4.4). There was no significant relationship between R&K awakenings and mean sleep onset latency ($\rho = -0.04$, $p=0.4$). Stepwise multiple linear regression found that the best predictor of objective daytime sleepiness was AHI.

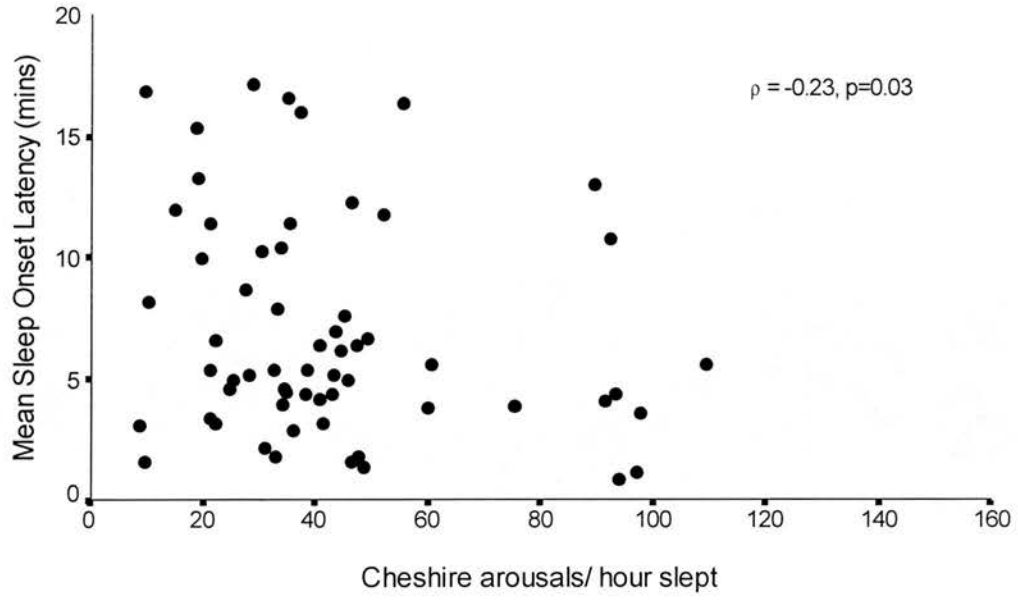


(a)

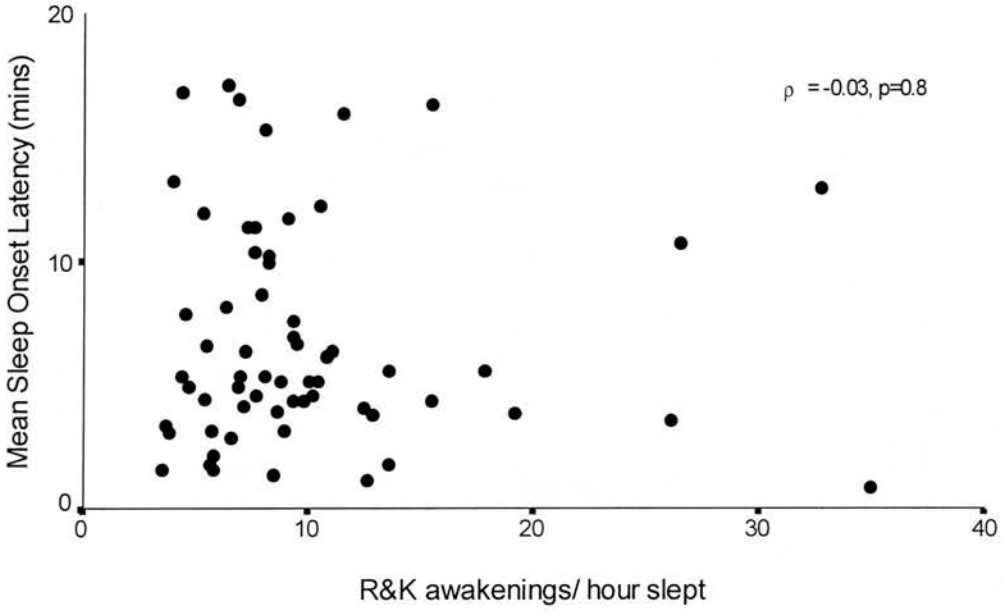


(b)

Figure 4.4; Scatterplot showing the relationships between ASDA (a) and mASDA (b) microarousal frequencies and daytime sleepiness on the MSLT.



(c)



(d)

Figure 4.4 contd.; Scatterplots showing relationships between Cheshire (c) microarousal frequency and R&K awakenings (d), and daytime sleepiness on the MSLT.

There were no significant relationships between arousals scored by any microarousal definition and subjective daytime sleepiness (all ρ <0.1, p >0.2). There was no significant relationship between AHI and subjective daytime sleepiness.

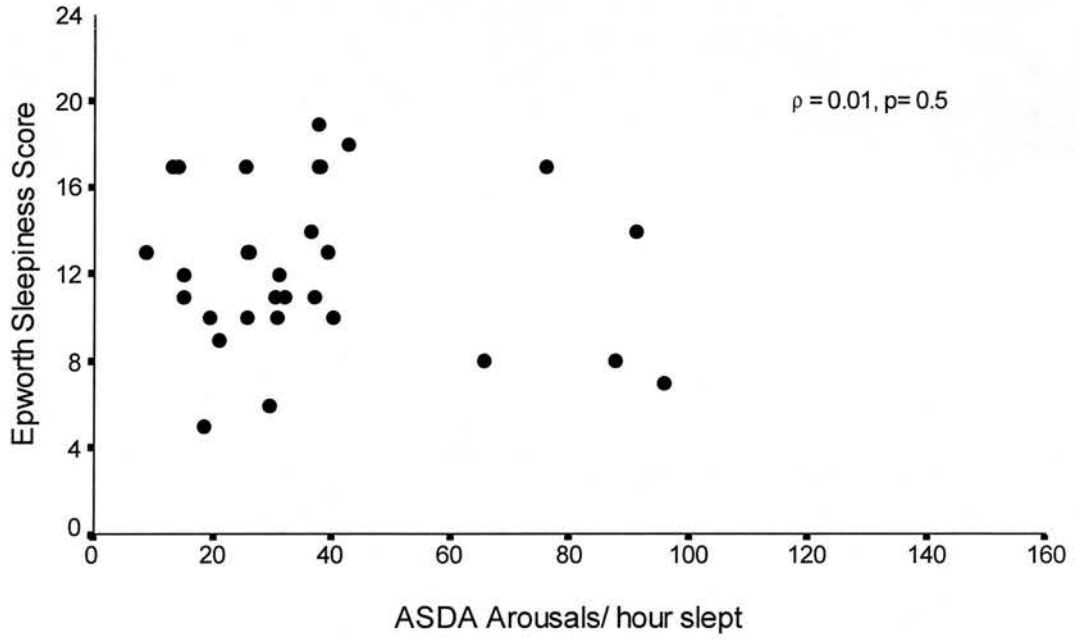


Figure 4.5; Scatterplot showing the relationship between ESS and ASDA microarousal frequency. Relationships between other arousal definitions and ESS were similar.

Outcome measures from GHQ-28, HAD; anxiety and depression, NHP pt 2, and UMACL; energetic arousal dimension, were entered into principal components analysis. One factor with an eigenvalue greater than 1 was extracted which accounted for 71% of the total variance of all these mood scales. Scores for each subject on this factor were saved as an extra variable and correlation analysis performed between it and the arousal definitions. There were no significant relationships between mood factor scores and arousal frequencies scored by any definition (figure 4.6).

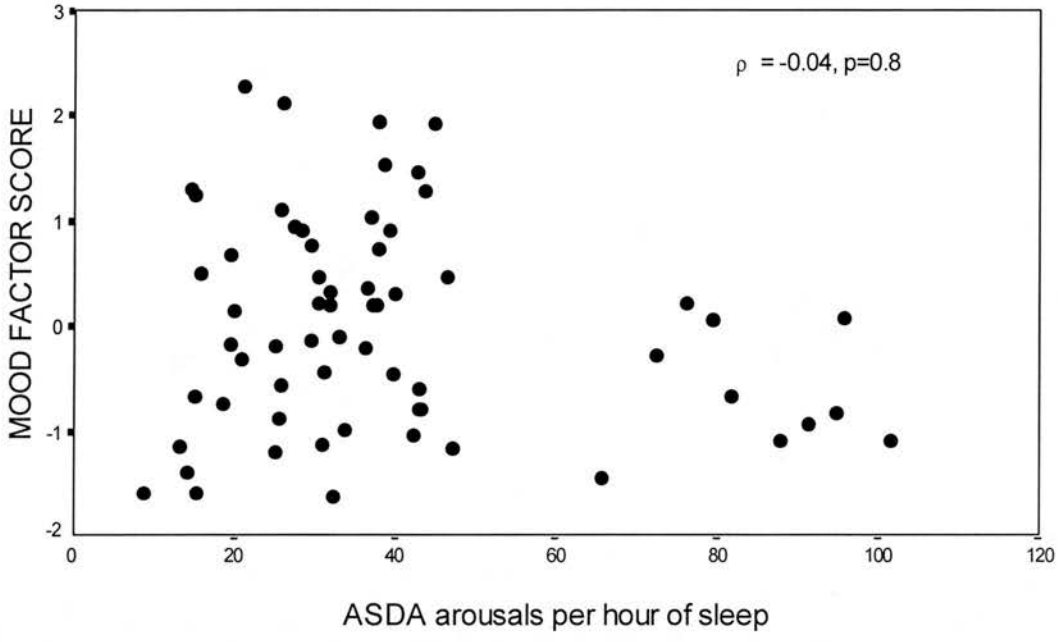


Figure 4.6; Scatterplot showing the relationship between ASDA microarousals and the mood factor score. Relationships were similar for all other microarousal definitions.

Baseline scores from the Digit Symbol substitution, Trailmaking B, and Steer Clear performance tests were entered into principal components analysis. One factor was extracted which accounted for 75% of the total variance of these test scores. These factor scores were then correlated with arousal frequencies scored by the different definitions. There were no significant relationships between arousal frequencies and the cognitive function factor score (figure 4.7).

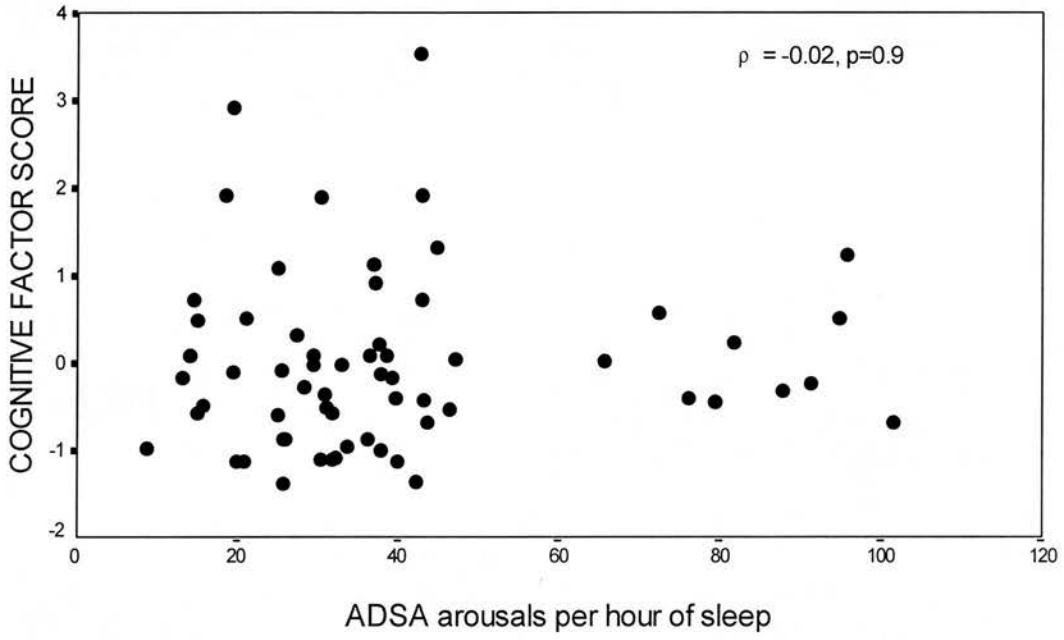


Figure 4.7; Scatterplot showing the relationship between ASDA microarousal frequency and cognitive factor scores.

4.4 DISCUSSION

This study confirms the finding of Rees et al (1995) that not all apneas and hypopneas are terminated by visible microarousals. In addition more respiratory events are terminated by 1.5 second microarousals than by 3 second microarousals. In contrast to Cheshire et al (1992) but similar to Roehrs et al (1989) there were significant but weak relationships between AHI and objective daytime sleepiness, and microarousals and objective daytime sleepiness. In contrast to Johns (1993) there was no relationship between severity of sleep apnea and subjective sleepiness. Furthermore this study has confirmed the finding of Kingshott et al (1995) that there is no relationship between Epworth sleepiness scores and microarousal frequency.

The interrelationships between microarousal definitions are all greater than r=0.94 indicating that the differences between individual definitions are stable across all 3 microarousal definitions. Refinement of the ASDA guidelines to a shorter duration of 1.5 seconds significantly increased the number of respiratory events terminated by microarousals from 75% to 83%. Mathur and Douglas (1995) have previously tried to manually score microarousals by shortening the duration criteria to less than 1.5 seconds but found that this introduced methodological difficulties in the confusion of sleep spindles for increases in EEG frequency. Rees et al (1995) had a shorter duration for microarousal scoring of 1 second. It is unlikely that this slightly shorter duration increased the likelihood of scoring arousals as a greater percentage of respiratory events were not terminated by arousals in their study (30%) compared with this study (25 to 17%). Rees et al (1995) only used data from stage 2 sleep which may have had some effect on their results. The slightly increased percentage of respiratory events terminated by 1.5 second ASDA arousals suggests that this maybe the most clinically relevant definition to use.

All three microarousal frequencies correlated significantly with AHI with ρ values similar to each other and to that of Cheshire et al (1992).

Although the 3 second ASDA definition had a slightly stronger association with AHI than either 1.5 second definition, the nature of the relationship was similar in each case. The scatter of data points in Figure 4.1 is towards mild SAHS patients having more spontaneous arousals that are not associated with respiratory events, and those more severe cases of sleep apnoea having less arousals than respiratory events. The finding of Rees et al of 30% of respiratory events not terminated by arousal may have been due to their subject sample including more severe SAHS patients.

Seventeen percent of apneas and hypopneas were not terminated by visible microarousals suggesting that more sophisticated analyses of the EEG signal are required to truly assess sleep fragmentation in patients referred to sleep laboratories complaining of daytime sleepiness. Rees et al (1995) used Fast Fourier Transformation of EEG signals and found that median EEG frequency increased significantly from the first half of an apnea to the second half of an apnea even if that event did not terminate in a visible cortical arousal. Davies et al (1993) using an artificial neural network, found EEG changes in normal subjects in response to auditory/ vibratory stimuli that were not visible to the human eye.

Alternatively non-EEG techniques may be more useful in determining fragmented sleep. Rees et al (1995) found that the chemical and mechanical stimuli to terminate an apnoea are similar regardless of whether the event is terminated by a visible EEG arousal or not. In addition respiratory events are terminated by transient increases in blood pressure whether or not there are coincident cortical arousals (Rees et al 1995, Shepard 1986). Recording blood pressure by digital infrared plethysmography (Finapres 2300, Ohmeda) is the current method of choice for measurement of sub-cortical arousals however it is cumbersome and poorly tolerated. Recently Pitson et al (1994) have investigated pulse transit time (PTT), which is inversely proportional to blood pressure, as a marker of arousal in normals, and of inspiratory effort in patients with sleep apnea (Pitson et al 1995). In the 1994 study Pitson et al

found that there were significant changes in PTT in response to tones that did not cause "any discernible change" on the EEG.

The concept of measuring arousals by a technique not dependent on EEG is attractive however it is uncertain whether arousals such as those (0a) described by Davies et al (1993) and Pitson et al (1994) have an impact on daytime function. Although respiratory events that do not terminate in visible EEG arousals, do terminate in blood pressure rises and increases in EEG frequency preliminary results from Sahloul et al (1995) suggest that arousals detectable by blood pressure rises alone may not have any impact on daytime sleepiness. This question is addressed further in chapter 6 of this thesis.

Patients with increased upper airway resistance (Guilleminault et al 1993) and heavy snoring (Guilleminault et al 1991) associated with cortical arousals are less sleepy during the day after one night on CPAP. These patients had been identified by their high cortical arousal indices which were significantly reduced with CPAP therapy. Although the 1.5 second definitions score more microarousals that the 3 second definition neither 1.5 second definition has a markedly more significant relationship with daytime sleepiness. This is as anticipated as all 3 microarousal definitions are scoring similar numbers of events. Furthermore neither mood nor cognitive function correlated with any microarousal definition. This is in contrast to the results of Cheshire et al (1992) who found in a smaller study that 3 measures of cognitive function were significantly correlated with microarousal frequency. It should be added however that these were not the same cognitive function tests that were used in this study. The disparity of results between these two studies may be due to the inclusion of mild sleep apnoea patients (AHI< 15) in this study although Engleman et al (1997) has shown that mild SAHS patients show objective benefit in mood and cognitive function after 1 month on CPAP therapy. In particular the mild SAHS patients who complied well with CPAP (more than 3 hours per night) had twice as many microarousals

per hour of sleep on their diagnostic polysomnography than those who did not comply well with CPAP.

The lack of routine measurement of Davies et al (1993) and Pitson et al's (1994) 0a arousals may account for the consistently poor relationships, found in this and other studies (Guilleminault et al 1988, Roehrs et al 1989, Cheshire et al 1992), between daytime sleepiness and severity of sleep fragmentation. A further source of error may be in the site of EEG measurement. Sleep studies usually measure EEG from central sites on the scalp (Rechtschaffen and Kales 1968). Preliminary evidence from O'Malley et al (1996) suggests that more respiratory events may be associated with microarousals scored from frontal EEG scalp sites. They found that 96% of respiratory events were terminated by EEG arousals scored from frontal EEG channels compared with 73% of respiratory events terminated by arousals scored at the central sites. In order to further investigate this question frontal EEG was measured in normal subjects undergoing sleep fragmentation in chapter 6 of this thesis.

In conclusion 1.5 second microarousal definitions provide the best visual measure of the sleep disruption resulting from respiratory events and the 1.5 second ASDA definition may be clinically most useful. This should be qualified however by suggesting that none of these definitions are adequate in predicting deficits in daytime function in patients with SAHS.

Chapter 5

The Effect of Cortical Sleep Fragmentation on Daytime Function.

5.1 INTRODUCTION

Patients with the sleep apnea/ hypopnoea syndrome (SAHS) suffer from impaired daytime function (Roth et al 1980, Greenberg et al 1987, Cheshire et al 1992, Naegale et al 1995). They are severely sleepy during the day as measured by the MSLT (Dement et al 1978, Roth et al 1980) and they suffer from impaired cognitive function compared to age and educationally matched controls (Greenberg et al 1987, Neagale et al 1995). Cheshire et al (1992) and Millman et al (1989) previously found that SAHS patients had scores in the clinically significant range for anxiety and depression on the HAD scale and the Zung self rating depression scale respectively. Furthermore Kribbs et al (1993) found that both mood and daytime sleepiness, which had improved after CPAP therapy, had returned to pretreatment levels during the day after one night off CPAP.

The nocturnal sequelae of apneas and hypopnoeas in SAHS patients are recurrent drops in oxygen saturation and frequent sleep fragmentation in the form of short (<15 seconds) microarousals (Cheshire et al 1992, ASDA 1992). There is controversy (Roth et al 1980, Greenberg et al 1987, Guilleminault et al 1988, Roehrs et al 1989, Bedard et al 1991a, Cheshire et al 1992) as to which of these is the cause of the daytime sleepiness and cognitive dysfunction seen in patients with SAHS.

Excessive daytime sleepiness in SAHS patients was best predicted by the level of nocturnal sleep disturbance (Guilleminault et al 1988) and sleep fragmentation (Roth et al 1980, Roehrs et al 1989). However Bedard et al (1991a) found that daytime sleepiness was predicted by severity of nocturnal hypoxemia whereas Cheshire et al (1992) found no relationship between daytime sleepiness and nocturnal hypoxemia or sleep fragmentation. In a similar fashion cognitive dysfunction in SAHS patients has been related to both their nocturnal hypoxemia (Greenberg et al 1987, Bedard et al 1991b,

Cheshire et al 1992, Neagale et al 1995) and their sleep disruption/ fragmentation (Bedard et al 1991b, Cheshire et al 1992).

Unfortunately the magnitude of sleep disruption and the extent of oxygen desaturation in SAHS patients are interrelated (Cheshire et al 1992) confounding attempts to determine in SAHS patients what specifically causes daytime dysfunction. Sleep disturbance in normal subjects causes increased daytime sleepiness (Bonnet 1985), and impaired mood and altered cognitive function (Bonnet 1987). However these studies had decreased total sleep time on the disruption nights compared with baseline, and they did not all mimic the short repetitive microarousals found in SAHS patients. Therefore the hypothesis tested in this study is that sleep fragmentation causing repetitive visible EEG microarousals may lead to the increased sleepiness and impaired mood and cognitive function found in patients with SAHS.

5.2 METHODS

Subjects

Eighteen subjects started the study, and 2 subjects dropped out midway, one man due to his inability to sleep in the laboratory environment, and one woman for personal reasons. Sixteen subjects completed the study. They had a mean age of 24 (SD 3) years, were all non-obese (BMI; 23 SD 3 kg/m^2) and had Epworth sleepiness scores (Johns 1991) within the normal range (median 4, range 0 to 9).

Protocol

The study was designed as described in section 3.14. In this sleep fragmentation protocol the second night of each pair of nights was either an undisturbed night's sleep or subjects had their sleep fragmented with tones to cause visible EEG arousals that could be scored by the sleep

fragmentation definition described in section 3.5. The order of conditions was randomised with 8 subjects having the fragmented limb first and 8 having the undisturbed limb first.

Subjects were allowed to reach stage 2 sleep, every 2 minutes after which the duration and volume of tones was varied to try to produce a similar microarousal response after each tone; i.e. a return to alpha or theta rhythm for longer than 3 seconds but, where possible, not longer than 15 seconds on the EEG channels. If this response was achieved, the 2 minute intertone interval began from the reappearance of stage 2 sleep defined as the first occurrence of a well defined K complex or sleep spindle. If a microarousal response did not occur on the first tone 10 seconds were allowed to elapse before repeating with a louder and/ or longer tone. Minimum tone volume was 38dB, and minimum tone duration was 0.28 seconds.

Lights out on all nights was standardized to 11pm and the study time finished at 6.30 am on all nights except on the fragmented study night when study time was extended by 20 minutes in all subjects regardless of previous sleep quality to allow for any possible sleep loss due to the fragmentation. Fragmentation continued throughout this extra 20 minutes.

The arousal frequency consisted of, the number of microarousals scored according to the Sleep Fragmentation definition plus the number of R&K awakenings (section 3.5) per hour of time slept. Arousals were further divided into durations of 3-5 seconds, 5-10 secs, 10-15 secs and 15+ secs (if not scored as a stage shift to wakefulness).

Daytime Assessment

The daytime function testing schedule was as follows;

7am to 9am; Stanford Sleepiness Scale (Hoddes et al 1973).

UWIST mood adjective checklist (Matthews et al 1990)

WAIS-R subtests- Digit Symbol substitution, Block Design Trailmaking A and B

Steer Clear

RVIP

PASAT at 4 and 2 seconds.

10am, 12pm, 2pm, 4pm; UWIST mood adjective checklist + MSLT

10.45am, 12.45am, 2.45pm, 4.45pm; MWT

Statistical Analysis

Paired data were analysed using a mixed two-way analysis of variance (SPSS-PC+) for repeated measures with study night as a within subjects effect and order of conditions as a between subjects effect. The only test with a significant order effect was the Stanford Sleepiness Scale. This variable was therefore analyzed as suggested by Hills and Armitage (1979) using an unpaired t-test on first limb data only.

5.3 RESULTS

Sleep Architecture

There was no significant difference in total sleep time (TST) between the undisturbed and fragmented study nights, however, there was a trend towards a greater percentage of time awake on the fragmented night ($p=0.06$) (table 5.1). There was a significant general shift towards lighter sleep on the fragmented night, with significantly more stage 1 ($p<0.02$) and stage 2 ($p<0.001$) sleep and significantly less SWS ($p<0.001$) and REM ($p<0.02$) sleep (table 5.1).

	Undisturbed	**Fragmented**	**p value**
TST (mins)	400 ± 20	396 ± 24	0.6
Wake (SPT) %	8.0 ± 3.9	11.2 ± 5.8	0.06
Stage 1 %	3.2 ± 2.0	5.4 ± 2.5	0.02
Stage 2 %	42.9 ± 7.1	59.3 ± 6.7	0.0001
SWS %	29.1 ± 11.2	15.4 ± 9.1	0.0001
Stage REM %	23.0 ± 5.0	19.1 ± 3.3	0.02

Table 5.1; Comparison of sleep architecture between study nights. Values are mean ± SD. TST; total sleep time, SPT; sleep period time, all sleep stages are %TST.

Arousals

There was a mean of 183 SD 20 tones presented to subjects during the fragmented night of which a mean of 82 ± 8% resulted in arousals. While 18% of tones failed to produce arousals between 3 and 15 seconds in duration, 10 ± 4% of tones caused R&K awakenings. The maximum tone volume used to produce a visible EEG arousal in any subject was 100dB and the maximum duration was 13 seconds.

Fragmentation more than doubled the arousal frequency (p=0.0001) (table 5.2). There were significantly more R&K awakenings per hour of sleep on the fragmented night than on the undisturbed night. There were significantly more arousals per hour slept of any duration on the fragmented night (all p<0.01) (table 5.2). On the fragmented night 31% of arousals were less than 5 seconds in duration compared to 25% on the undisturbed night. Furthermore 68% of arousals were less than 10 seconds in duration on the fragmented night compared to 55% on the undisturbed night.

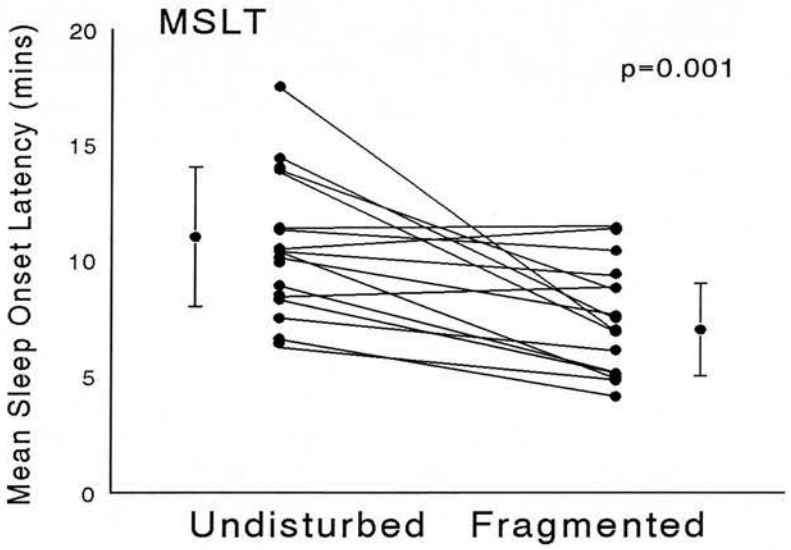
Duration (secs)	**Undisturbed**	**Fragmented**	**p value**
3-5	3.8 ± 2.6	10.9 ± 3.8	0.0001
5-10	4.7 ± 1.7	12.3 ± 2.2	0.0001
10-15	1.9 ± 1.7	3.5 ± 1.7	0.002
15+	1.0 ± 0.6	1.9 ± 1.2	0.0001
R&K	4.1 ± 1.1	5.7 ± 1.9	0.01
Total arousal frequency	15.5 ± 3.7	34.3 ± 5.0	0.0001

Table 5.2; Comparisons of arousal frequencies/ hour slept of different durations between study nights. Values are mean ± SD.

Daytime Sleepiness

There were significant decreases in mean sleep onset latencies on the MSLT (undisturbed; 11 ± 3, fragmented; 7 ± 2 mins) (figure 5.1a) and the MWT (undisturbed; 34 ± 8, fragmented; 24 ± 10 mins) (figure 5.1b) after fragmentation.

(a)



(b)

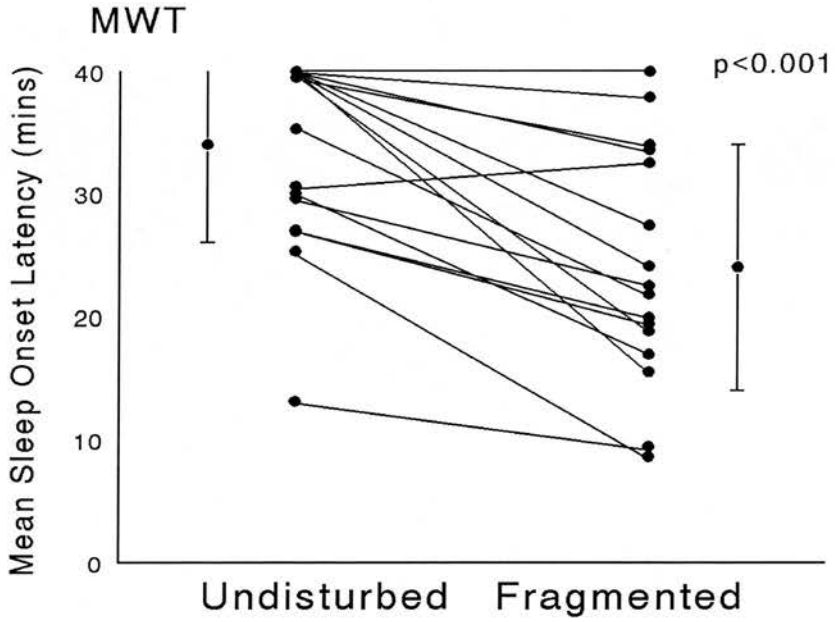
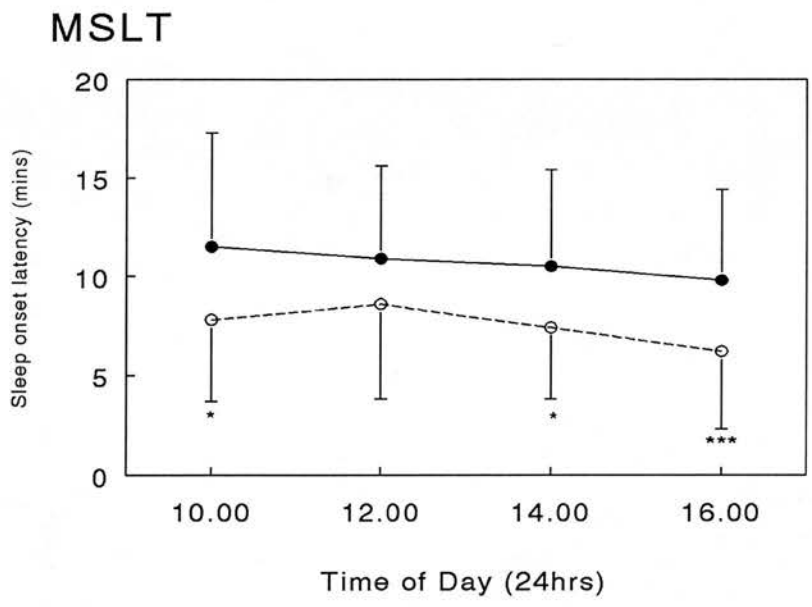
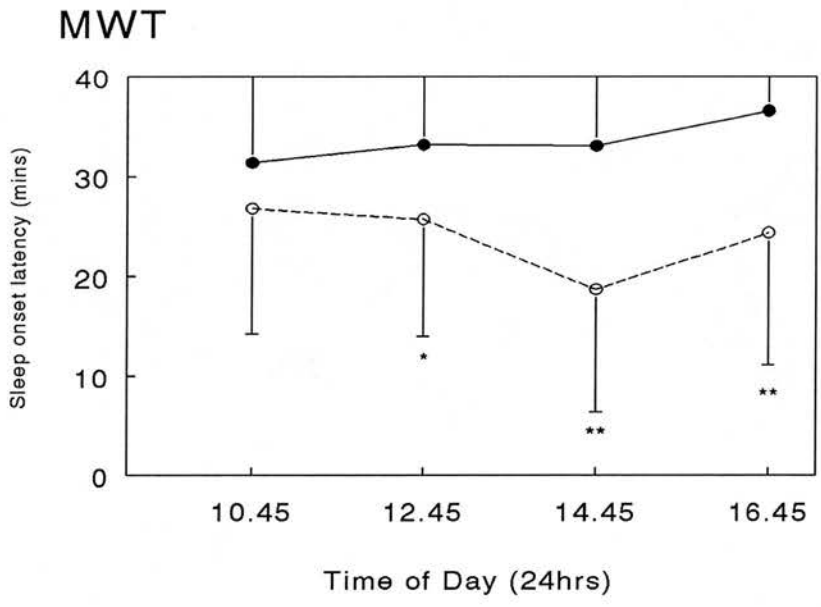


Figure 5.1; Individual paired point graphs for mean sleep onset latencies on MSLT (a) and MWT (b) for both study nights. Single points are mean ± SD for all subjects.

On the MSLT there were significant decreases in individual naps at 10.00, 12.00 and 16.00 after fragmentation (figure 5.2a). On the MWT there were significant decreases in naps at 12.45, 14.45 and 16.45 after fragmentation (figure 5.2b).



(a)



(b)

Figure 5.2; Sleep onset latencies for individual naps on the MSLT and MWT. Values are expressed as mean ± SD for each time of day. * $p<0.05$, ** $p<0.01$, ***$p<0.001$. ---●--- undisturbed, - - - ❍- - -; fragmented.

There was no change in subjective sleepiness on the SSS after fragmentation (p=0.8).

Mood

In addition to individual scores on the UMACL the mean of the 5 assessments was calculated for each dimension. The mean energetic arousal score (undisturbed; 22 SD 4, fragmented; 19 ± 4, score range 8 to 32; p<0.001) and the mean hedonic tone score (undisturbed; 29 ± 4, fragmented; 27 ± 4; p=0.05), were significantly lower after fragmentation. Fragmentation did not affect mean tense arousal scores (undisturbed 11 ± 3, fragmented 11 ± 3, p=0.3). The individual energetic arousal scores were significantly lower after fragmentation at all times except 12pm (figure 5.3a). Individual hedonic tone scores were significantly lower after fragmentation at 10am (undisturbed; 30 SD 3, fragmented; 27 ± 4, p=0.005) only (figure 5.3b). The individual tense arousal scores were increased after the fragmentation night at 8am (undisturbed; 11 SD 3, fragmented; 13 ± 3; p=0.01) and 10am (undisturbed; 10 ± 2, fragmented; 12 ± 2; p=0.05) only (figure 5.3c).

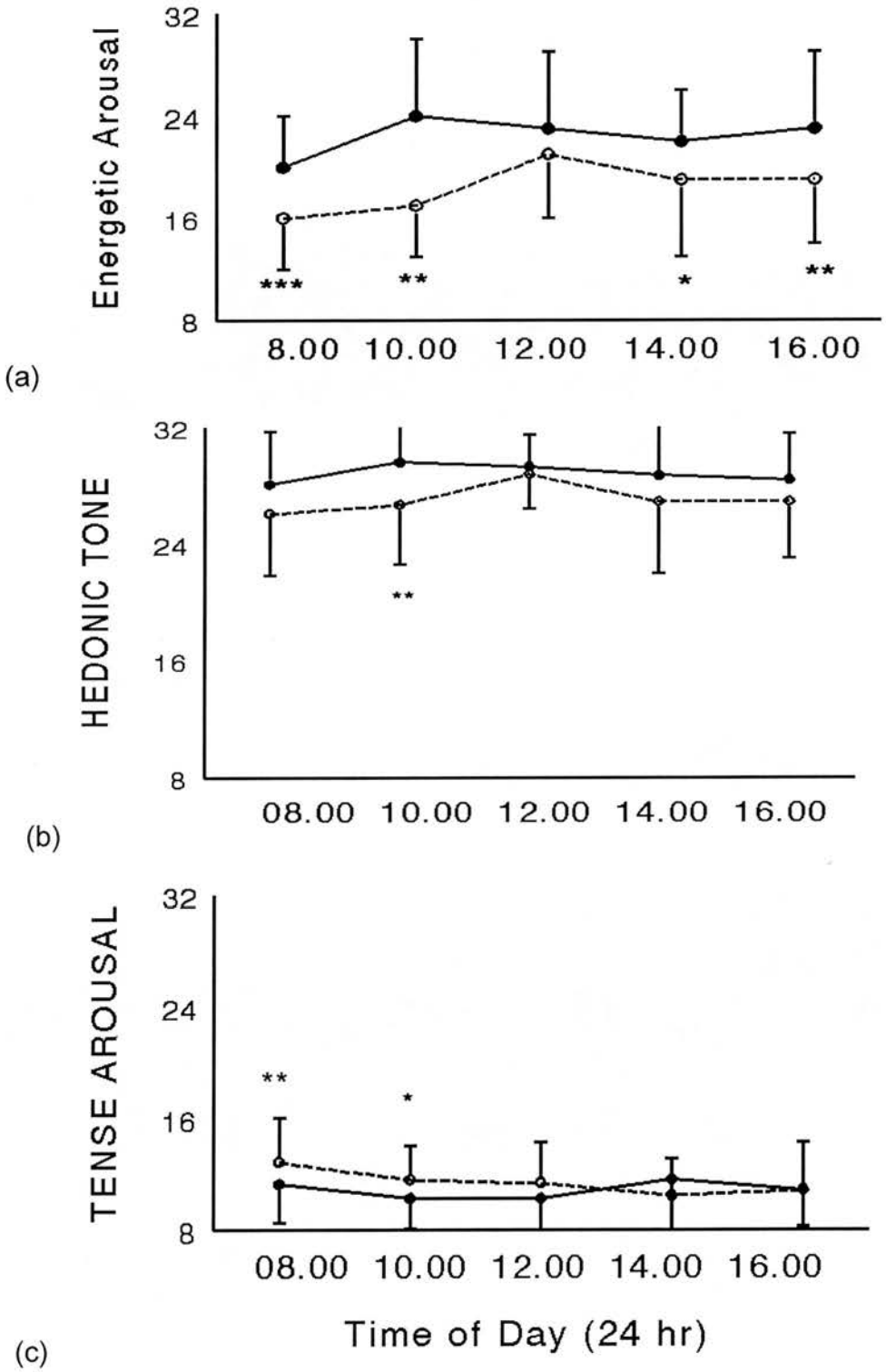


Figure 5.3; (a) Individual Energetic Arousal, (b) Hedonic Tone and (c) Tense Arousal scores for both test days. Values are mean + SD.

---●--- undisturbed, - - -○- - - fragmented. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Cognitive Function

Subjects had a significantly slower time to complete the Trailmaking B task ($p=0.05$) (figure 5.4) and scored significantly fewer correct additions on the PASAT 4 second test ($p<0.03$) after the fragmented night (table 5.3). No other cognitive variables were altered significantly by sleep fragmentation (table 5.3).

COGNITIVE TEST	Undisturbed	Fragmented	p value
Digit Symbol	76 ± 11	76 ± 11	0.5
Block Design	45 ± 6	45 ± 6	1.0
Est. PIQ	132 ± 16	131 ± 15	0.9
Steer Clear hits	31 ± 16	36 ± 19	0.3
RVIP hits	47 ± 7	46 ± 10	0.8
RVIP misses	6 ± 13	2 ± 2	0.2
Trailmaking A (secs)	20 ± 6	19 ± 4	0.5
Trailmaking B (secs)	40 ± 14	43 ± 10	0.05
PASAT 4 sec	59 ± 2	58 ± 3	0.03
PASAT 2 sec	48 ± 9	49 ± 8	0.8

Table 5.3; Mean ± SD for cognitive outcome measures after both study nights. Est PIQ; estimated performance IQ, RVIP; rapid visual information processing, PASAT; paced auditory serial addition test.

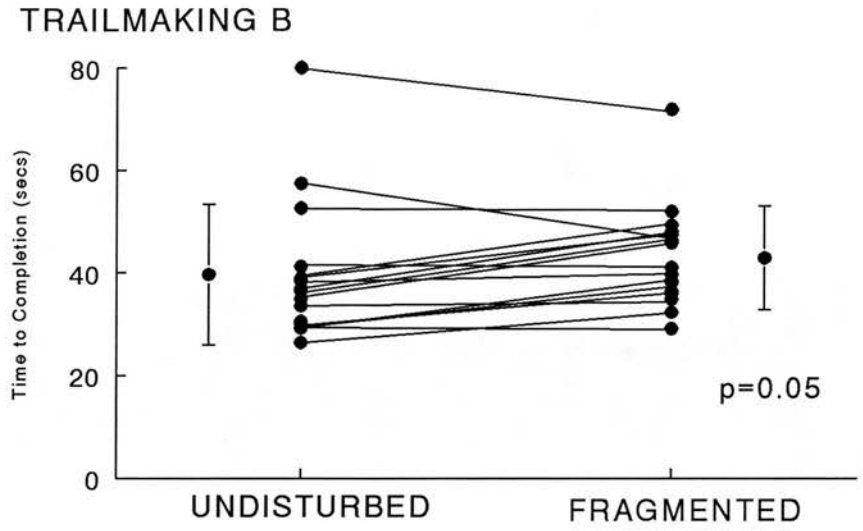


Figure 5.4; Paired point graph showing individual data points for scores on the Trailmaking B test after the undisturbed and fragmented study nights. Single points are mean ± SD for all subjects.

5.4 DISCUSSION

This study confirms recent findings by Philip et al (1994) and Roehrs et al (1994) that one night of sleep fragmentation with short arousals causes increased objective daytime sleepiness. In addition this study demonstrates that sleep fragmentation causes decrements in the mood and cognitive performance of normal subjects. This sleep fragmentation design improves on previous studies, which did not include an acclimatization night to the laboratory (Philip et al 1994, Roehrs et al 1994), or a randomised control undisturbed night (Bonnet 1987, Roehrs et al 1994). Previous studies by Bonnet (1985, 1986b, 1987) have induced longer and more marked arousals than often occur in SAHS, with a subsequent decrease in total sleep time. This study also improved on the daytime assessments of the aforementioned studies as Bonnet (1985, 1986b, 1987) investigated daytime sleepiness with one morning nap only whereas the full MSLT was used in this study, none of the above studies assessed daytime sleepiness with the MWT, and the

studies by Roehrs et al (1994) and Philip et al (1994) did not look at the effects of fragmentation on mood.

Subjects in this study became sleepier after fragmentation than in previous studies (Roehrs et al 1994, Philip et al 1994) and in this study subjects' ability to stay awake was also impaired. The instruction to "stay awake" without stimulation mimics more closely daytime situations in which the excessively sleepy patient may find themselves, trying to keep themselves awake, and thus the MWT may give more relevant clinical information than how quickly the patient falls asleep. These results show that after a single night of sleep fragmentation normal subjects have similar difficulty in staying awake as untreated SAHS patients (Poceta et al 1992, Sangal et al 1992a). Clearly SAHS patients may clinically respond differently to normal subjects with a similar degree of objective daytime sleepiness. For example their ability to alert themselves may be affected by years of experience of sleepiness.

Sleep fragmentation impaired performance in 2 tests; Trailmaking B, testing mental flexibility and attentional capacity, and PASAT 4 sec, a sustained attention task. Thus sleep fragmentation is probably affecting attention. A previous study from this laboratory found both these measures to be improved by treatment in SAHS patients (Engleman et al 1994a). Bonnet (1985) found that 2 nights of sleep disruption (not fragmentation) decreased performance on a simple reaction time task, the Wilkinson addition task and digit symbol substitution. However total sleep time was significantly reduced by an hour which may have accounted for the changes in daytime function found in this study. In further studies Bonnet (1986b, 1987) found that the Wilkinson addition task only was impaired after sleep disruption.

In contrast to results in this study however, the studies of Roehrs et al (1994) and Philip et al (1994) which induced short arousals similar to those seen in SAHS patients found no change in performance after fragmentation. They did not use either Trailmaking B or PASAT but had selected tests for

their monotonous quality. Steer Clear (30 minutes) was used in this study to assess vigilance and there was no change in performance. It appears that normal subjects can overcome the effects of sleep fragmentation on such monotonous tasks. Wilkinson (1965) demonstrated that performance after sleep deprivation is most likely to be impaired on monotonous tasks and that normal subjects can upregulate their function to baseline on short complex tasks. In particular Wilkinson (1965) demonstrated that performance over the first five minutes of a simple reaction time test remains similar to baseline even after 60 hours of sleep deprivation. The daytime function tests in this study which were altered after sleep fragmentation are short complex tasks. Trailmaking B is subject paced, and the mean duration to completion was less than 45 seconds after either study night. The PASAT 4 second test is experimenter paced and lasts for 4 minutes. These results suggest that sleep fragmentation may impair cognitive function in a different manner to sleep deprivation. These decrements, similar to those found in SAHS patients, may not be a result of increased daytime sleepiness after sleep fragmentation but may be due to functional impairment of cognitive processing pathways. This is in contrast to the suggestion by Bedard et al (1991b) that sleep fragmentation causes daytime sleepiness and that it is this increased sleepiness that explains some of the variance in decrements of cognitive function in SAHS patients.

Alternatively these decrements in cognitive function tests may be due to a type 1 statistical error, due to the number of comparisons that were made. Although there may be some redundancy within the cognitive function measures used in this study the aim of this study was to model the sleep fragmentation found in SAHS patients. Studies of daytime function in SAHS patients (Greenberg et al 1987, Naegale et al 1995, Engleman et al 1994a) used individual cognitive tests to describe deficits and therefore individual analyses were used in this study in order to make them comparable.

In this study one night of fragmentation resulted in energetic arousal scores in normal subjects similar to those of untreated SAHS patients (Engleman et al 1994a). Decrements in energetic arousal after fragmentation mirror the decreases seen on the individual MSLT and MWT naps suggesting that the energetic arousal dimension of mood maybe a subjective indicator of objective daytime sleepiness. Totterdell et al (1994) found that self reported sleep quality and number of awakenings correlated significantly with scores on the energetic arousal dimension of mood. Mood is most susceptible to an external stress in the early part of the day as demonstrated by the global changes in mood at 10am after fragmentation. Sleep deprivation has similar global effects on mood (Matthews et al 1990). These results suggest that sleep fragmentation is as detrimental to mood as sleep deprivation. These mood results also agree with the theory of Thayer (1989) that arousal has its basis in biological systems and can therefore be manipulated using sleep fragmentation (see section 2.3).

In this study the arousal frequency during the fragmented night was similar to that seen in untreated SAHS patients (Greenberg et al 1987, Gould et al 1988). The arousal frequency, even when altered for spontaneously occurring arousals from sleep was still greater than that of Roehrs et al (1994) whereas Philip et al (1994) refer to the number of stimulations during the fragmented night but do not give data as to the number of arousals.

The decrements in daytime function found in this study may be due to the small, but significant changes in sleep architecture on the fragmented night. Philip et al (1994) found a significant relationship between nocturnal slow wave sleep (SWS) and mean sleep latency on the MSLT but did not examine the relationship with arousal frequency. Furthermore there were 2 data points for each subject which artefactually increases the power of the regression analysis. Bonnet (1986a) found that daytime sleepiness on a single (MSLT like) morning nap was similar after 2 limbs of equal amounts of

sleep disruption but with one limb manipulated to eliminate SWS. Thus presence or absence of SWS did not impact on daytime sleepiness given equal amounts of sleep disruption. This should however be interpreted with caution due to the lack of a full MSLT.

These results have implications for the diagnosis and treatment of patients with sleep disordered breathing especially those with low AHI (AHI < 15) and no nocturnal hypoxemia. Results from chapter 4 show that for patients with and AHI less than 20 per hour of sleep the arousal frequency is higher than the AHI. Further to this an elevated microarousal index may be the only indicator of a milder form of sleep disordered breathing which may be mis-diagnosed as idiopathic hypersomnolence (Guilleminault et al 1993). These results show that an elevated microarousal index alone may lead to impairments of daytime function.

This study shows that a single night of sleep fragmentation to induce visible EEG arousals can cause increased objective daytime sleepiness and altered mood and psychometric function similar to that found in SAHS patients.

Chapter 6

The effect of non-visible (autonomic) sleep fragmentation on daytime function.

6.1 INTRODUCTION

Apnoeas and hypopnoeas can be terminated by intermittent dips in nocturnal oxygen saturation and arousals from sleep both of which correlate with daytime function (section 2.7, 2.10). Although previous studies show that daytime sleepiness in SAHS patients is best predicted by sleep fragmentation the variance in daytime sleepiness due to arousals is at best 13% (Roehrs et al 1989). In the previous study in this thesis, sleep fragmentation that caused visible EEG arousals produced similar deficits in daytime function as those found in SAHS patients. This suggests that elevated microarousal frequencies alone can cause deficits in daytime function.

Brief EEG arousals from sleep are accompanied by transient increases in blood pressure. Results from chapter 4 of this thesis demonstrate that not all sleep related apneas and hypopneas are terminated by visible EEG arousals, a finding similar to that of Rees et al (1995). Rees et al (1995) demonstrated that although these apnoeas and hypopnoeas were not terminated by visible EEG arousals they were terminated by the blood pressure rise of arousals. Davies et al (1993) demonstrated that this autonomic response can be induced in normal sleeping subjects with tones, without causing any discernible change on the EEG. Rees et al (1995) also found increases in computer detectable EEG frequency whether or not there was a visible EEG arousal at the end of the apnoea or hypopnoea.

Given the low amount of variance in daytime sleepiness described by visible EEG arousals the hypothesis for this study is that sleep fragmenting events may occur which are unaccompanied by visible EEG change and that these events may contribute towards impairments in daytime function found in SAHS patients. In this study the sleep of normal subjects was fragmented

and its effects on subsequent daytime function investigated. Sleep was fragmented to induce recurrent arousals as detected by transient blood pressure and/ or heart rate increases alone, without any change in EEG frequency that could be scored as an arousal, by current definitions (section 3.5).

6.2 METHODS

Subjects

Subjects were recruited as described in section 3.15. Fourteen subjects entered this study; 8 men and 6 women. One woman dropped out of the study due to technical and lab scheduling problems and one man was dropped after the first night due to his inability to sleep in the laboratory. Twelve subjects were studied (7 men, 5 women) with a mean age of 25 ± 6 years. They were all non-obese (body mass index, 22 ± 2 kg/m^2) and had Epworth sleepiness scores within the normal range (median 5, range 2 to 8) (Johns 1991).

Protocol

On the second night of each pair of nights subjects were randomly assigned to having either an undisturbed night's sleep or having their sleep fragmented with tones. Sleep was recorded and scored as described in section 3.3. All study nights were recorded on computerised polysomnography (Compumedics, Melbourne, Australia). In addition in 8 subjects 2 frontal EEG channels were recorded from 10/20 standard EEG recording sites Fp1/ F3 and Fp2 / F4.

Sleep was fragmented with tones to produce what was termed **a non-visible arousal** response. This was defined as an increase in arterial blood pressure or heart rate without any visible change on the EEG that could be

scored by the sleep fragmentation definition of arousal (section 3.5) (figure 6.2 (a) and (b)).

Beat to beat blood pressure was recorded with the Finapres device (Ohmeda) (see figure 3.1 for example of online output). Recorded data can be examined offline from a beat to beat output as follows;

Time (hr min sec)	Systolic	Diastolic	Mean BP	Pulse rate
12 58 13	93	58	72	48
12 58 14	84	53	72	48
12 58 15	87	54	65	48
12 58 17	88	54	67	48
12 58 18	87	54	68	51
12 58 19	89	57	68	53

Table 6.1; Sample of beat to beat recording of output from the Finapres. Six individual beats of data are shown; from subject no. 1, undisturbed study night.

Due to the Finapres device causing disrupted sleep as ascertained from pilot studies in 2 subjects (section 3.13), blood pressure was recorded continuously for the first one and a half hours of sleep from the onset of slow wave sleep. If subjects had a full awakening the device was switched off and subjects were allowed to go back to stage 2 sleep before switching the device on again. During blood pressure recording heart rate responses to tones that produced non-visible arousal responses as defined were closely monitored and used as a guideline for non-visible responses to tones during the remainder of the study night after the Finapres had been removed from the subjects' hand. The volume and duration of tones was increased during

the night in accordance with data showing that normal subjects acclimatise to arousing stimuli (Williams et al 1964, Bonnet 1985, Bonnet 1987). By doing this it is assumed that the autonomic response to arousing stimuli acclimatises to repetitive stimuli in a similar fashion to the visible EEG arousal response to repetitive stimuli. Subjects were monitored by video camera to check for any movement which may have affected blood pressure recording.

Every 1 minute from the onset of slow wave sleep (SWS) the duration and volume of tones was varied to produce, not a visible EEG change but an autonomic response, i.e. a minimum increase in systolic blood pressure of 4 mm Hg or, when the subject was not wearing the Finapres, an increase in heart rate of at least 4 beats per minute without any visible cortical arousal response on the EEG channels. The response should occur within 15 seconds of the tone, and because blood pressure varies with the respiratory cycle, should be sustained over at least 3 beats compared to blood pressure over the 15 seconds prior to the tone. Blood pressure responses were assessed by the experimenter from a real time display on a PC situated next to the Compumedics polysomnography computer.

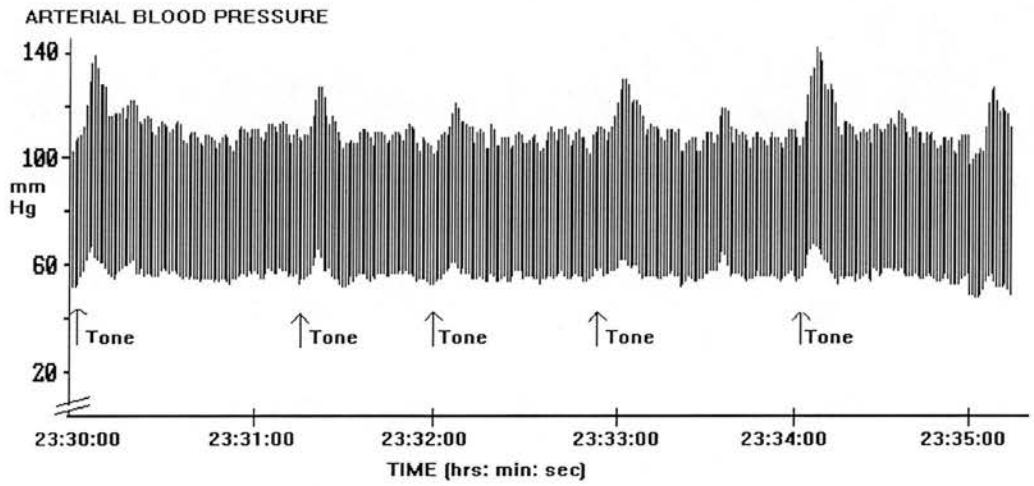


Figure 6.1; Sample of online beat to beat blood pressure output from the Finapres device that is available in real time during an overnight sleep study. Time is displayed on the X axis, with blood pressure on the Y axis (mmHg). Five minutes of data is displayed with tones delivered at the arrows shown.

Beat to beat heart rate was also assessed from a real time display on a cardiac rate monitor. If this required arousal response was achieved, the next tone came 1 minute after the previous tone. If tones produced cortical arousals I waited until the reappearance of the first sleep spindle or K-complex and then waited 1 minute before applying the next tone. If this non-visible arousal response was not achieved on the first tone 30 seconds was allowed to elapse before repeating with a louder or longer tone.

Sample visible and non-visible EEG responses to tones are depicted in Figure 6.2 (a) and (b). Tones of 1000Hz were presented to subjects via a loudspeaker positioned above the subjects' head.

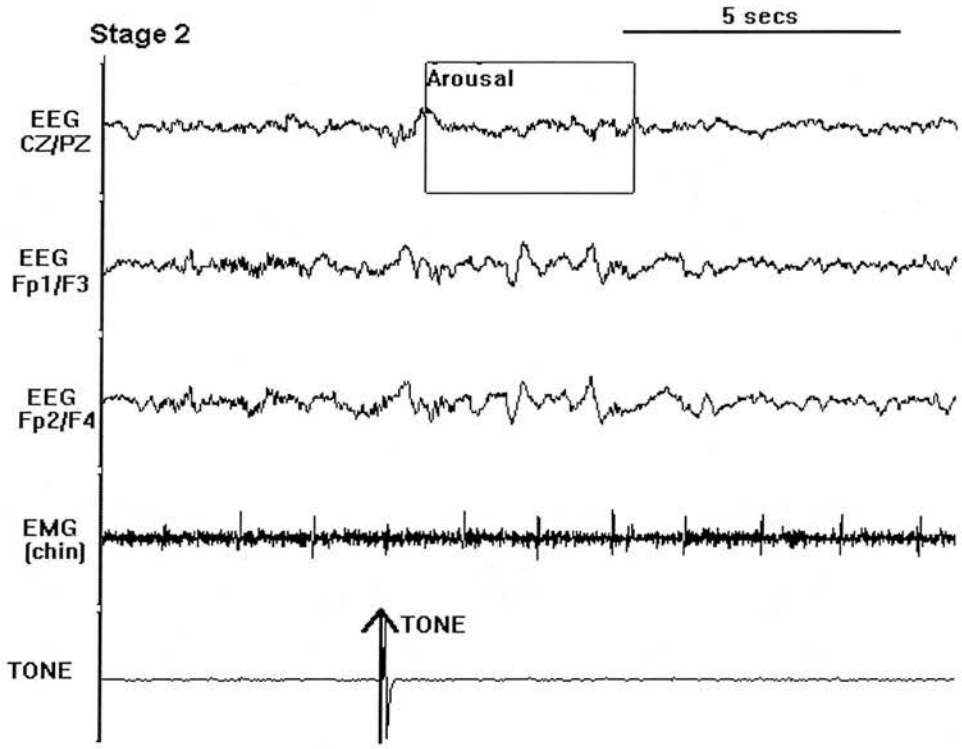


Figure 6.2 (a); Sample visible EEG responses to tones. The channels depicted are central EEG; CZ/ PZ, Frontal EEG; Fp1/ F3, Fp2/ F4, Chin EMG and tone marker channel. A tone was administered at the mark shown. Peak EEG power, in the range 8-11 Hz, within 5 seconds of the tone was 3.3 Hz and maximim blood pressure increase within 15 seconds of the tone was 16 mmHg. 15 seconds of data is shown.

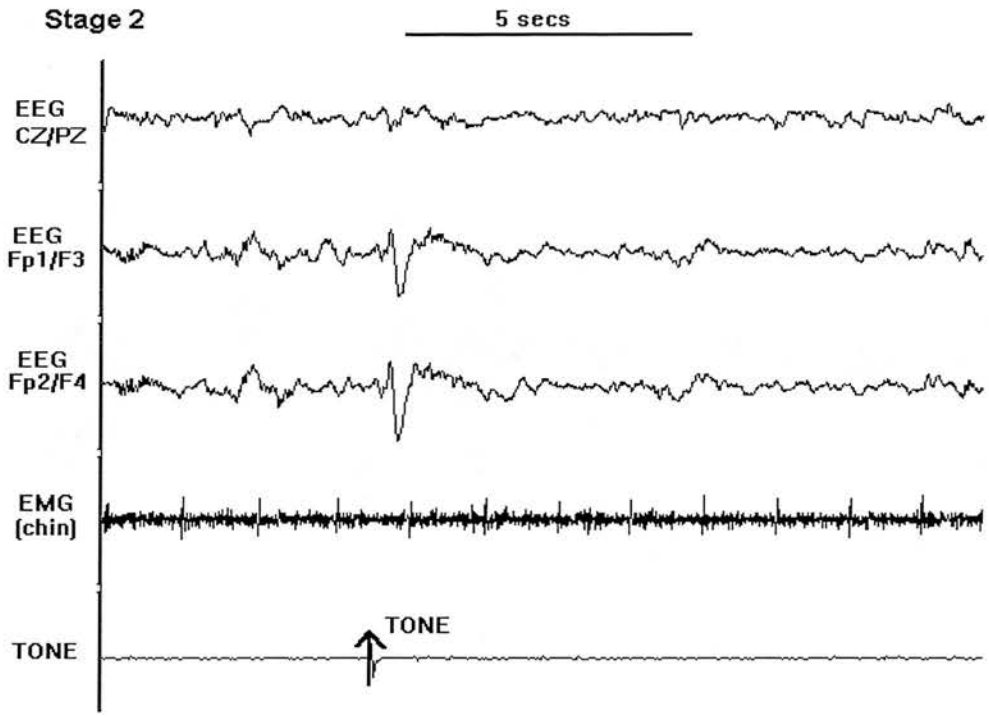


Figure 6.2 (b); Sample non-visible EEG response to a tone. A tone was administered at the mark shown. Peak alpha EEG power within 5 seconds of the tone was 2.6 Hz and maximum BP increase after the tone was 5 mmHz.

Lights out on all nights was at 11 pm, with study time finishing at 6.30 am on all nights except for the fragmented night when study time was extended by 15 minutes to allow for any sleep loss due to fragmentation regardless of prior sleep quality. Fragmentation of sleep continued throughout this extended study time.

On the fragmented study night the change in systolic blood pressure in response to tones was calculated for 10 seconds around the maximum blood pressure response and, as a control, for 10 seconds prior to each tone. The mean delay to maximum BP response was noted for each subject. In order to compare blood pressure responses to tones between study nights the blood pressure records from the undisturbed study night were randomly marked with an equal number of sham tones to the fragmented study night.

The "maximum" blood pressure response to the sham tone was taken as the blood pressure X seconds after each tone, X being the mean delay to maximum blood pressure within 15 seconds of a tone from that subject's fragmented study night. The mean systolic blood pressure was then calculated for the 10 seconds prior to each "tone" and for the 10 second period 5 seconds before and after the "maximum" blood pressure response.

Subject ID no.	**Mean delay to Max BP after tone (secs)**	**Mean rise in systolic BP after tones (mm Hg)**	**Mean rise in systolic BP after "sham" tones (mm Hg)**
201	8	8.7	0.4
202	8	10.4	0.6
203	7	4.7	-0.2
204	11	6.8	-1.6
205	14	9.5	0.4
206	8	10.5	-1.5
207	9	5.4	0.7
208	8	15.0	0.2
209	12	7.0	-1.6
210	9	6.5	-0.3
211	8	12.1	0.1
212	7	6.7	0.6
Mean ± SD	9 ± 2	8.0 ± 2.2	-0.2 ± 0.8

Table 6.2; Individual mean data for the delay to maximum blood pressure after tones on the fragmented night, and blood pressure increases after tones on the fragmented night and after "sham" tones on the undisturbed night.

Arousals were defined according to the sleep fragmentation definition (section 3.5). This definition was used regardless of sleep stage and whether arousals were induced by tones or not. The arousal frequency consisted of the number of spontaneous + induced arousals and the number of Rechtschaffen and Kales awakenings per hour of sleep. Frontal (Fp1/ F3, Fp2/ F4) and occipital (CZ/ PZ) arousal frequencies were scored separately. One hour sections of stage 2 sleep were also scored for 1.5 second arousals from the frontal leads.

Fast Fourier Transformation

Using in-house computing support (see acknowledgement) the frontal EEG raw data signal from stage 2 sleep were analysed using Fast Fourier transformation (section 3.7). Raw data was taken from all the stage 2 sleep in the fragmentation study nights of all 12 subjects. In selection of frequency bands for this analysis we were guided by the instructions in arousal definitions which are to look for a return to alpha or theta on the EEG for a given duration (section 3.5). I selected the alpha frequency range; 8-11 Hz, as stage 2 sleep consists largely of EEG in the theta frequency range and arousals are usually scored as a return to alpha EEG frequency. Time point data files corresponding to the times at which tones were administered to subjects were generated along with control time point files either 30 seconds before or after the tones. These were used to allow selection of peak alpha EEG power, within 5 seconds of tones and control time points. Five seconds was chosen as the time window within which any change in EEG in response to tones should be apparrent, due to the finding in the previous chapter, that if an arousal stimulus was sufficiently strong to induce a visible EEG arousal, then it would do so within a few seconds of applying the stimulus.

Daytime Assessment

The daytime assessment schedule was as follows;

7am to 9am; UMACL (UWIST mood adjective checklist) + SSS

Digit Symbol substitution

Block Design,

Trailmaking A and B

Steer Clear

PASAT (4 and 2 secs).

10.00 to 17.25; MSLT + MWT.

UMACL + SSS prior to each nap on the MSLT.

The RVIP test was dropped from the test battery as previous studies from this laboratory had found that it was not sensitive to changes in cognitive function after one month of CPAP therapy (Engleman et al 1994a) or after one night of cortical sleep fragmentation (chapter 5). Subjects were asked to stay awake during the day between the cognitive function tests and the daytime naps and were encouraged to sit in an area of the laboratory different to their bedroom in order to facilitate this.

Statistical Analysis

All outcome measures, both nocturnal and daytime variables, were analysed using a mixed 2 way analysis of variance (SPSS-PC+) for repeated measures on 2 study limbs, with order of conditions as a between subjects effect. The outcome measures were examined for non-normal distributions and ceiling effects found on all individual naps on the MWT and all measures of Hedonic Tone. These can occur because subjects who score the

maximum on the fragmented limb are unable to show an improvement in function during the undisturbed limb, assuming that it is present. These variables were analysed using the Wilcoxon matched pairs test.

Peak alpha EEG power was selected within 5 seconds after control times and after time points at which tones were administered. These values were then compared using paired t-tests. Tones were divided into those that induced arousals and those that did not. This was selected as a factor which may have contributed to any significant differences found between peak EEG power after control and tone time points. Differences between individual subjects may also have contributed to any significant differences found in peak EEG power after control and tone time points. Therefore Multivariate Analysis of Variance (MANOVA) was performed on the difference between peak EEG power after control and tone time points with outcome (whether tones caused arousals or not) and between subject variability as factors.

6.3 RESULTS

Sleep Architecture

There were no significant differences between study nights in total sleep time (TST), amounts of wakefulness, stage 1, stage 2, or REM sleep. However there was significantly less slow wave sleep (SWS) on the fragmented study night (p=0.007).

	UNDISTURBED	FRAGMENTED	p Value
TST (mins)	419.0 ± 27.4	414.0 ± 32.2	0.5
Wake (% SPT)	7.4 ± 4.2	8.3 ± 4.4	0.5
Stage 1 (% TST)	3.3 ± 1.9	3.7 ± 1.8	0.5
Stage 2 (% TST)	49.8 ± 4.8	53.8 ± 6.2	0.1
SWS (% TST)	23.9 ± 5.0	19.5 ± 4.3	0.007
Stage REM (% TST)	23.0 ± 4.2	23.1 ± 4.2	0.9

Table 6.3; Comparison of sleep architecture between undisturbed and fragmented study nights. TST; total sleep time, SPT; sleep period time, SWS; slow wave sleep. Values are expressed as mean ± SD.

Arousals

The minimum tone volume and duration used was 38dB for 0.25 seconds. The maximum volume and duration of tones required to produce a non-visible arousal response in any subject was 65dB, and all tones were applied for less than 4 seconds.

Subjects had a mean of 253 (SD 23) tones presented to them during the fragmented study night, 21 ± (SD) 7% of which caused central arousals and 23 ± 9% of which caused frontal arousals. There was no significant

difference between these; p=0.3. The central arousal frequency on the fragmented night was divided into arousals induced by tones and spontaneous arousals. The arousal frequency on the fragmented night consisted of the induced arousal frequency (7.8 ± 2.2 per hour of sleep) and the spontaneous arousal frequency (16.7 ± 4.4 per hour of sleep). The spontaneous arousal frequency from the fragmented night was significantly smaller than the arousal frequency on the undisturbed night (22.4 ± 4.3 per hour of sleep; p=0.001). The spontaneous and induced arousal frequencies from the fragmented night were not significantly different to the arousal frequency from the undisturbed night (table 6.4). There were no significant differences in either frontal or 1.5 second arousal frequencies between study nights (table 6.4).

	UNDISTURBED	**FRAGMENTED**	**p value**
Central arousals/ hr.	22.4 ± 4.3	24.5 ± 5.7	0.4
Frontal arousals/ hr.	22.8 ± 6.0	26.3 ± 5.0	0.1
1.5 sec arousals/ hr.	26 ± 12	27 ± 12	0.7
R&K awakenings/ hr.	3.7 ± 1.6	3.8 ± 1.2	0.8

Table 6.4; Arousal frequencies per hour of sleep. Values are expressed as mean ± SD. Central; CZ/PZ, Frontal; Fp1/F3 and Fp2/F4, 1.5 sec arousals scored from frontal leads.

Fast Fourier Transformation

Events were divided into tones that produced visible EEG arousals (n=191) and those that did not (n=575). Peak α EEG power was significantly greater after tones compared to controls both when tones induced visible EEG arousals (control 4.9 ± (SD) 2.2, tone 10.6 ± 4.9 μv; $p<0.0001$) and when tones did not (control 5.3 ± 2.7, tone 7.4 ± 3.3 μv; $p<0.0001$). There was a significantly greater increase in peak EEG power after tones that caused arousals than those that did not (Figure 6.3) ($p=0.008$) with no significant contribution from between subject variability.

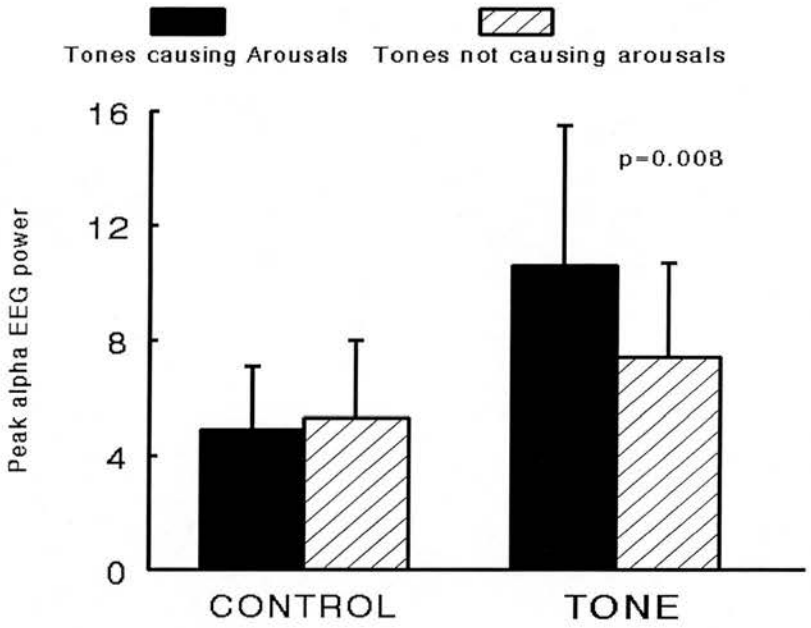
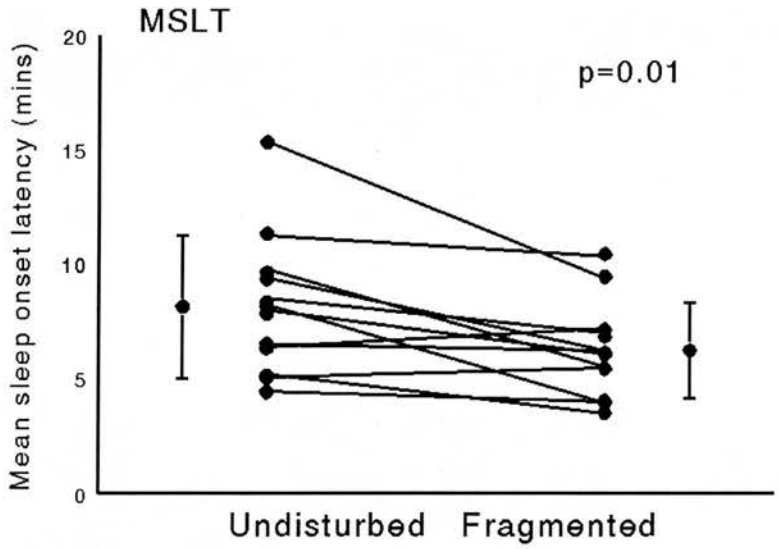


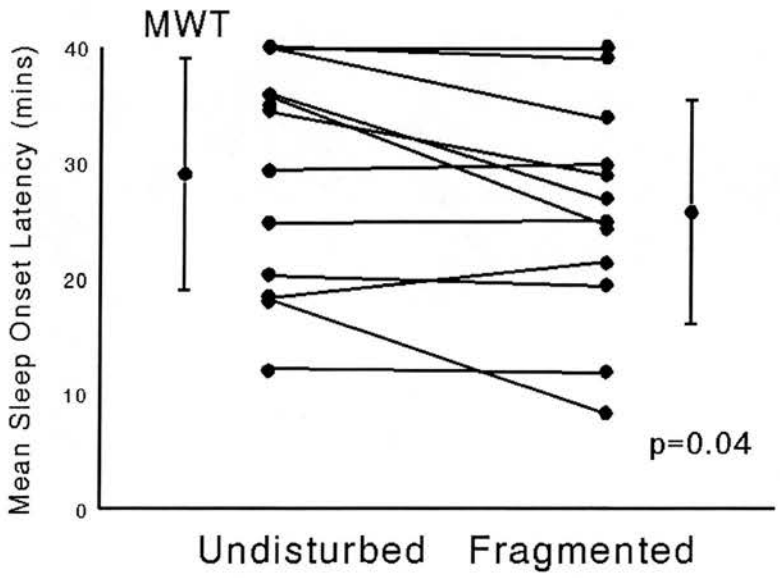
Figure 6.3; Peak alpha EEG power (μv) within 5 seconds of a control time point compared to that within 5 seconds of a tone for tones that cause arousals (filled bars) and for those that do not (hatched bars).

Daytime Sleepiness

There were significantly shorter mean sleep onset latencies on the MSLT (undisturbed; 8.0 ± SD 3.1, fragmented; 6.2 ± 2.1 mins; p=0.01) (Figure 6.4a) and the MWT (undisturbed; 29.0 ± 10.0, fragmented; 25.7 ± 9.7 mins; p=0.04) (Figure 6.4b) after non-visible sleep fragmentation.



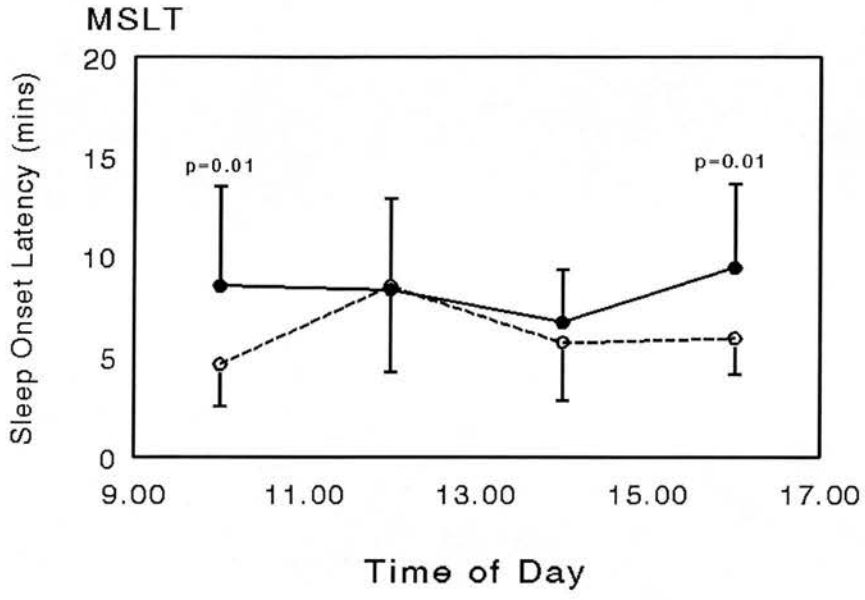
(a)



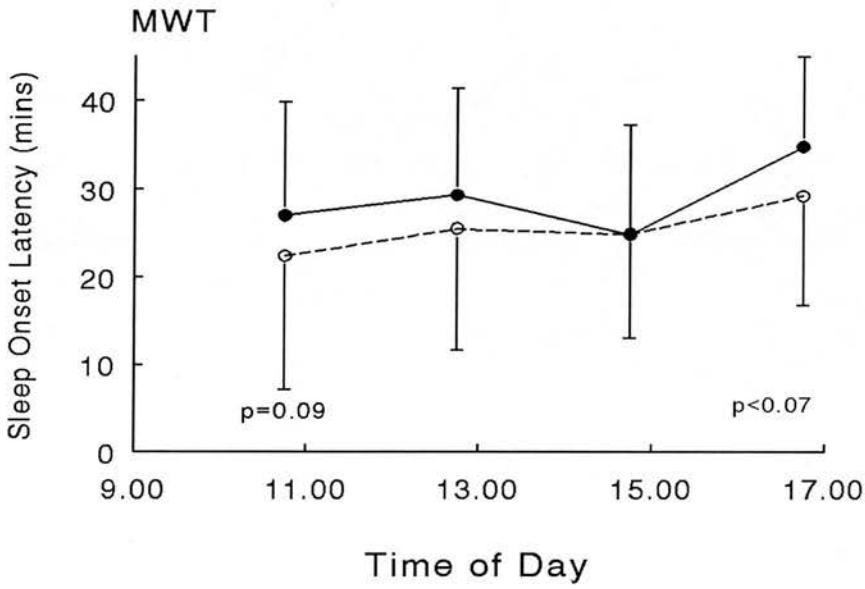
(b)

Figure 6.4; Paired points for individual subjects' mean sleep onset latencies on the MSLT (a) and the MWT (b) after undisturbed and fragmented study nights. Single points are mean ± SD for all subjects.

On the MSLT there were significantly shorter sleep onset latencies on individual naps at 10.00 (p=0.01) and at 16.00 (p=0.01) after fragmentation (figure 6.5a). On the MWT there were trends towards significant differences in sleep onset latencies on individual naps at 10.45 (p=0.09) and at 16.45 (p=0.07) after non-visible fragmentation (figure 6.5b).



(a)



(b)

Figure 6.5; Sleep onset latencies for individual naps during the day on the (a) MSLT and (b) MWT. Values are mean ± SD; ---●--- undisturbed, - - -○- - - fragmented.

There was no difference in subjective daytime sleepiness as measured by the Stanford sleepiness scale (SSS) (mean SSS; undisturbed 3 ± 1, fragmented 3 ± 1; p=0.7) after either study night.

Mood

There was a significant decrease in Hedonic tone at 7am (p=0.03) and there was trend towards a significant increase in tense arousal at 7am (p<0.09) after fragmentation. (Figure 6.6a and b). There was no change in energetic arousal at any time of the day after fragmentation.

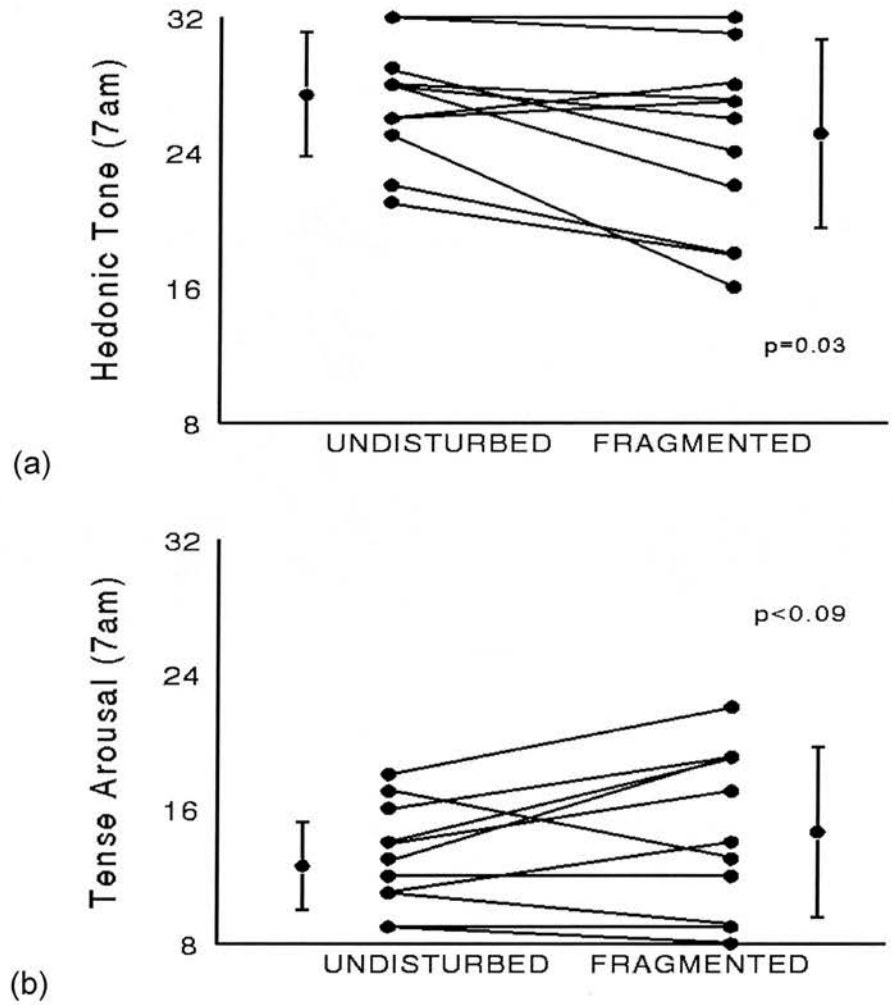


Figure 6.6; Individual paired data points for mood dimensions of (a) Hedonic Tone and (b) Tense Arousal at 7am after undisturbed and fragmented study nights. Single points are mean ± SD for all subjects.

Cognitive Function

Fragmentation did not have any adverse effects on cognitive function in the performance tests that were used in this study. Performance on the Trailmaking B test was affected by fragmentation but in a counterintuitive direction (table 6.5).

	UNDISTURBED	FRAGMENTED	p value
Digit Symbol	74 ± 10	72 ± 13	0.3
Block Design	42 ± 7	43 ± 8	0.4
Est. PIQ	127 ± 16	126 ± 18	0.8
Steer Clear	47 ± 27	45 ± 28	0.7
Trailmaking A	19 ± 4	20 ± 5	0.6
Trailmaking B	46 ± 15	39 ± 11	0.03
PASAT 4 sec	58 ± 2	58 ± 2	0.8
PASAT 2 sec	47 ± 10	45 ± 12	0.1

Table 6.5; Mean ± SD for cognitive outcome measures after both study nights. Est. PIQ: estimated performance IQ. PASAT; paced auditory serial addition test.

6.4 DISCUSSION

This study shows that non-visible sleep fragmentation affects sleep architecture, daytime sleepiness, as measured by the MSLT and the MWT, and mood upon awakening. There was no coincident significant increase in the number of visible cortical arousals on the EEG, however this study demonstrates that small but significant increases in EEG power do occur in response to tones that do not cause visible EEG arousals that can be scored according to current criteria.

In the previous study (chapter 5) inducing visible EEG arousals every 2 mins decreased the MSLT from 11 to 7 mins and the MWT from 34 to 24 mins, impaired all mood dimensions in the morning and energetic arousal for the rest of the day as well, and caused decrements in cognitive function. Non-visibly detected arousals decreased the MSLT from 8 to 6 mins and the MWT from 29 to 26 mins. In addition induced non-visible arousals caused impairment of hedonic tone and a trend towards impairment of tense arousal mood dimensions on awakening only, but they had no deleterious effect on cognitive function. These results contrast with preliminary results from Sahloul et al (1995) who found, in 4 subjects, that there was no difference in sleep onset latency on the MSLT after non-visible sleep fragmentation during 3 hours of recovery sleep compared with 3 hours of undisturbed recovery sleep. The differences between this current study and that of Sahloul et al (1995) may be due to a number of reasons; this study included more subjects, whole night studies were used here compared to 3 hour study durations in the study of Sahloul et al 1995, and this study design incorporated acclimization nights on both study limbs. In addition mood and cognitive function were tested, and daytime sleepiness was tested with the maintenance of wakefulness test as well as the multiple sleep latency test.

In this study there were small but significant changes in daytime sleepiness in response to non-visible sleep fragmentation. Despite the changes in MSLT and MWT there was no difference in subjective sleepiness after fragmentation. This is not suprising as there was no change in SSS

after cortical sleep fragmentation which is more disruptive to sleep than this protocol. In addition previous studies have shown that these Stanford Sleepiness scores and objective sleepiness do not always move in parallel (Dement et al 1978). Thirty four tones per hour were presented to subjects to induce non-visible arousals compared to 30 tones per hour to induce visible EEG arousals in the previous study (chapter 5). Although there were slightly more tones per hour presented presented to subjects to induce non-visible arousals they were of shorter duration and lower volume and the more subtle changes in daytime sleepiness between the 2 studies reflect this difference. The maximum volume and duration of tones required to produce a non-visible arousal response was 65dB for less than 4 seconds which is much less than that required to induce visible cortical arousal in the previous fragmentation study; 100dB for up to 12 seconds.

On the MSLT this 2 minute change in daytime sleepiness after non-visible sleep fragmentation is similar in magnitude to that seen in patients with sleep apnea after they have been established on CPAP therapy (Engleman et al 1993, Kribbs et al 1993). Sangal et al (1992b) found that sleepiness on the MWT improves with CPAP therapy by a magnitude (8 min) in between the size of the decrease seen in normal subjects after induced visible EEG arousals (10 min), as seen in the previous study (chapter 5), but by a greater magnitude than the decrease after non-visible arousals (4 min) seen in this study.

These subjects appeared to be sleepier after the undisturbed night than those in the previous fragmentation study. Therefore subjects' working habits were inspected closely. Three of our student subjects had evening jobs at weekends which ran into the early morning. Each was studied at the same time in the week on both limbs and always after at least 2 nights of normal sleep at home plus the acclimization night before the study night. These 3 subjects may have increased the overall sleepiness of the study sample.

Blood pressure was monitored for the first sleep cycle only, because during pilot studies normal subjects were not sleepy enough to tolerate blood pressure monitoring for the whole night without sleep disruption (section 3.13). The Finapres device may have increased arousal frequency on study nights as the arousal frequency on the undisturbed night in this study was 22 per hour compared to 15 per hour on the undisturbed night in our previous fragmentation study. Bonnet (1985, 1987) found that mood, cognitive function and daytime sleepiness in normal subjects are impaired by sleep disruption and thus monitoring blood pressure over the whole night may have compromised this study.

There was no significant difference between study nights in arousal frequencies measured centrally or frontally. Nor was there a difference between study nights when the arousal duration criterion was shortened to 1.5 seconds. There was no significant difference between cortical areas in the number of tones that caused arousals. Frontal EEG monitoring was included in the study montage because O'Malley et al (1996), in a provisional report using topographic brain mapping, found that in patients with mild sleep apnea frontal arousals were seen at the termination of 95% of respiratory events, whereas only 73% were detected at occipital sites. In contrast in this study visual scoring of the frontal EEG did not increase the detection of visible EEG arousals in response to tones in normal subjects.

Frontal EEG from stage 2 sleep was subjected to Fast Fourier transformation (FFT). There were significant increases in EEG frequency in response to tones that did not cause visible EEG arousals. Davies et al (1993) tracked changes in EEG in normals in response to auditory stimuli using a computerised artificial neural network without seeing visible cortical arousals. These changes were always accompanied by transient increases in arterial blood pressure. Rees et al (1995) Fast Fourier Transformed the EEG of SAHS patients and found increases in EEG frequency coincident with increases in blood pressure at the end of respiratory events whether or not they terminated in cortical arousals. This evidence taken together with

the induced decreases in daytime sleepiness that we have demonstrated in this study suggests that perhaps a more sophisticated analysis of the EEG or, a non-visible marker of arousal such as Pulse Transit Time (PTT) (Brock et al 1993) should be included in routine sleep studies to assess the true extent of sleep fragmentation suffered by patients being assessed for sleep disorders.

The results from this study and the previous study (chapter 5) may also suggest that there is a gradient of cortical arousal from sleep. Although the arousals induced in this study could not be scored according to conventional criteria the fact that computer detectable increases in alpha frequency on the cortical EEG were found after tones suggests that they are also cortical arousals of some kind. This could be represented as milder tones inducing less obvious arousals on the EEG which had a milder effect upon daytime function.

There was a significant decrease in hedonic tone and a trend towards an increase in tense arousal on awakening after non-visible fragmentation. This is consistent with findings in studies using acute hypoglycaemia as a physiological stressor (Hepburn et al 1995, Hepburn et al 1996). Normal subjects had decreased hedonic tone and increased tense arousal maximal with the onset of autonomic reactions to acute hypoglycaemia (Hepburn et al 1995) whereas adrenalectomised subjects, who do not have the normal adrenaline response to hypoglycaemia, did not show these changes (Hepburn et al 1996). Together these results suggest that changes in hedonic tone and tense arousal could be autonomically mediated, while changes in energetic arousal are due to cortical stimulation. This hypothesis is supported by the findings here of transient changes in mood due to repetitive non-visible arousal from sleep, and in the previous sleep fragmentation study, more longer lasting impairment of energetic arousal due to cortical sleep fragmentation.

Although there was no adverse impact of fragmentation on cognitive function there was an improvement in performance on the Trailmaking B test

after fragmentation. This test is a well validated test of general cognition and is widely used to assess cognitive impairment in a range of illnesses (Lezak 1983). In SAHS patients, Cheshire et al (1992) found that scores on this test correlate with mood impairment, and Engleman et al (1994) have found improvements in performance on this test after one month of CPAP therapy. In normals subjects it shows decrements in cognition after sleep fragmentation (chapter 5) and in patients with nocturnal asthma it is sensitive to cognitive impairment (Fitzpatrick et al 1991). Yesavage et al (1985) found that it correlates with respiratory disturbances in the elderly and Findley et al (1986) found that it distinguishes between hypoxemic and non-hypoxemic patients with sleep apnoea. The widespread use of this test in studies measuring cognitive function suggest that this counterintuitive change in performance after non-visible sleep fragmentation may be a spurious result.

In this study one night of induced non-visible sleep fragmentation causes increased daytime sleepiness and impaired mood upon awakening. The importance of sleep fragmentation with non-visible EEG arousals in patients with sleep disorders needs to be assessed.

Chapter 7

The Effect of Clustered Versus Regular Sleep Fragmentation on Daytime Function.

7.1 INTRODUCTION

As outlined in the introduction to this thesis (chapter 2) SAHS patients suffer from impaired daytime function. There is debate as to whether the cause of these deficits is the nocturnal hypoxemia or sleep fragmentation suffered by these patients. Roehrs et al (1994) and Philip et al (1994) found that one night of cortical sleep fragmentation makes normal subjects sleepier during the day. Further to these studies an earlier study in this thesis (chapter 5) found that one night of acoustically induced sleep fragmentation, causing regular visible EEG arousals, impairs daytime sleepiness, mood and cognitive function in normal subjects. These decrements in function demnonstrate that fragmentation can induce reversible deficits in daytime function similar to those found in SAHS patients.

Sleep fragmentation in association with apnoeas and hypopnoeas occurs in a clustered fashion in 2 subsets of patients with sleep apnea; those with REM sleep related apnea and those with supine/ postural related apnea. In the description of disease progression from snoring to severe sleep apnoea by Lugaresi et al (1983) they dismissed REM related respiratory events as non-pathological citing the inherent respiratory instability of REM sleep (Douglas 1994). As REM sleep occurs approximately every 90 minutes during a night's sleep any sleep fragmentation resulting from REM specific respiratory events therefore occurs in a clustered fashion during sleep. These clusters of sleep fragmentation are interspersed with periods of uninterrupted sleep, in particular slow wave sleep, the duration of which correlates with objective daytime sleepiness on the MSLT (Philip et al 1994) and is thought to be vital for cerebral restitution (Horne 1988) and efficient cognitive functioning.

In addition patients that suffer from PLMS have periods of uninterrupted sleep (Montplaisir et al 1994). This disorder is characterised by repetitive limb movements during sleep which may or may not induce visible EEG arousals. These limb movements are only found during NREM sleep, as motor inhibition during REM sleep ensures that they do not occur in this sleep stage, and they are often clustered to either the beginning or the end of the night. Daytime sleepiness is a common symptom of this disorder.

It is uncertain whether these periods of uninterrupted sleep are sufficiently restorative for these patients to overcome the effects of fragmentation on daytime function. Therefore this study investigated the relative effects of similar frequencies of fragmentation, but dispersed in either a clustered or regular fashion, on daytime sleepiness, mood and cognitive function.

7.2 METHODS

Subjects

Eleven subjects (6 men, 5 women) entered this study but one woman dropped out after the first limb due to sickness. Ten subjects completed the study. They were 23 SD 3 years old, were all non-obese (body mass index, 21 ± 3 kg/m^2) and had Epworth sleepiness scores (Johns 1991) in the normal range (mean 5; range 0 to 8).

Protocol

This study consisted of 2 limbs of sleep fragmentation with subjects spending 2 nights in the sleep laboratory on each limb. On the second night of each pair of nights subjects were randomly assigned to having either of 2 fragmentation paradigms: **Regular**- sleep fragmentation every 90 seconds from the onset of stage 2 sleep; or **Clustered**- sleep fragmentation every 30 seconds, for 30 minutes every 90 minutes thus allowing subjects to obtain 60

minute long periods of uninterrupted sleep. On the clustered paradigm fragmentation starts one hour after the onset of stage 2 sleep. Five subjects had the clustered fragmentation limb first and 5 had the regular fragmentation limb first. These 2 paradigms are designed to increase arousal frequencies by a similar number on both study nights while allowing for periods of uninterrupted sleep on the clustered study night. Seven out of the ten subjects had both study limbs recorded onto the Compumedics computerised polysomnography system, and the remaining 3 subjects were recorded on the Healthdyne system.

During fragmentation the duration and volume of tones of 1000 hz was varied to try to produce a standard microarousal response; i.e. a return to alpha or theta rhythm for longer than 3 seconds but, where possible, not longer than 15 seconds on the EEG channels. If an arousal or awakening was achieved, the next intertone interval began from the reappearance of stage 2 sleep defined as the first occurrence of a well defined K complex or sleep spindle. If an arousal response was not achieved on the first tone 10 seconds was allowed to elapse before repeating with a louder and/or longer tone. Lights out on all nights including acclimisation nights was standardized to 11pm and the study time finished at 6.45 am on all nights.

On study nights arousals were scored according to the sleep fragmentation definition of arousal (section 3.5). The arousal frequency consisted of the number of microarousals plus the number of Rechtschaffen and Kales awakenings per hour of total sleep time (TST).

Daytime Assessment

At 7am after study nights subjects began the battery of mood and cognitive function tests. They filled out the UWIST mood adjective checklist and Stanford sleepiness scale. They then completed Digit Symbol, Block Design, Steer Clear, Trailmaking A and B, Rapid Visual Information Processing (RVIP) and Paced Auditory Serial Addition Test (PASAT) at 4 and 2 seconds. In order to make the RVIP more searching than in the previous cortical sleep fragmentation study (chapter 5) three consecutive 10 minute tests were employed and the results from the three summed. The remainder of the day was taken up with testing mood and daytime sleepiness (MSLT, MWT) as previously described (chapter 6).

Statistical Analysis

Data were analysed using a mixed two-way analysis of variance (SPSS-PC+) with study condition (regular or clustered study night) as a repeated measure and order of conditions as a between subjects effect. All outcome measures were examined for non-normal distribution. This was done by checking through the rawdata to see if subjects had scored the maximum or minimum on a particular variable after both study nights. If a subject scores the maximum on a test after both study nights the test cannot differentiate between conditions. Two or more subjects scored the maximum of 60 correct additions after both limbs on the PASAT 4 second test. Again 2 or more subjects stayed awake for the maximum of 40 minutes on all individual naps on the MWT after both study limbs. Two or more subjects scored a minimum of zero misses on the RVIP test. These variables were subsequently analysed using the Wilcoxon matched pairs test.

7.3 RESULTS

Sleep Architecture

There was no difference in total sleep time (TST) (p=0.4), or the percentage of wakefulness (p=0.9) between the clustered and regular fragmentation study nights (table 7.1). There was significantly more stage 2 (p=0.05) and less slow wave sleep (SWS) (p=0.002) on the regular fragmentation study night (table 7.1).

	CLUSTERED	REGULAR	p Value
TST (mins)	391 SD 26	384 ± 35	0.4
% Wake (SPT)	11 ± 4	11 ± 7	0.9
% Stage 1	5 ± 2	4 ± 3	0.3
% Stage 2	55 ± 4	61 ± 7	0.05
% SWS	22 ± 3	14 ± 6	0.002
% Stage REM	19 ± 4	22 ± 3	0.1

Table 7.1; Comparison of sleep stages on clustered and regular fragmentation study nights. All values are mean ± standard deviation (SD). Values for stages 1 to REM are expressed a percentage of TST. TST; total sleep time, SPT; sleep period time.

Arousals

There was no significant difference between study nights in the arousal frequency, number of tones that were presented to subjects (p= 0.3) or the percentage of those tones that caused arousals (p= 0.9) (table 7.2).

	Clustered	**Regular**	**p value**
Arousal frequency	42 ± 4	43 ± 5	0.5
R&K awakenings/ hr. slept	6 ± 3	5 ± 2	0.6
number of tones	215 ± 21	224 ± 26	0.3
% tones causing arousals	79 ± 10	79 ± 12	0.9
%tones causing R&K	9 ± 4	9 ± 4	0.7

Table 7.2; Comparison of arousal statistics on clustered and regular fragmentation nights. Arousal frequency; number of microarousals + R&K awakenings per hour slept. All values are mean ± SD.

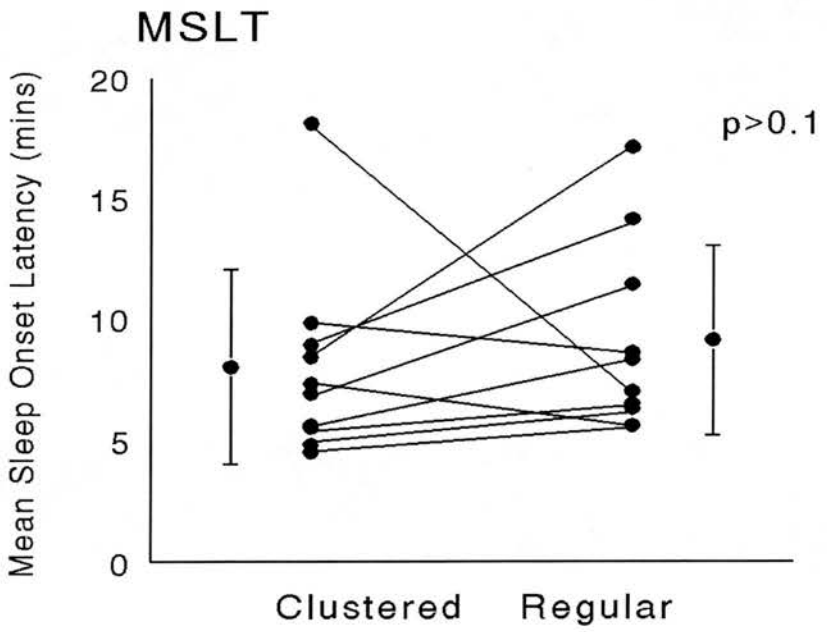
The arousal frequency was divided into arousal frequencies of different durations (table 7.3). There was no significant difference between study nights in the frequencies of arousals of different durations except arousals of duration 5 to 10 seconds. There was a small but significantly greater frequency of arousals of this duration on the regular fragmentation study night (p=0.05) (table 7.3).

Duration (s)	**3-5**	**5-10**	**10-15**	**15+**	**R&K**
CLUSTERED	20.5 ± 4.2	11.4 ± 5.3	3.1 ± 1.0	1.3 ± 0.7	4.1 ± 1.1
REGULAR	19.4 ± 4.0	12.8 ± 5.0 *	3.7 ± 1.9	1.2 ± 0.6	5.7 ± 1.9

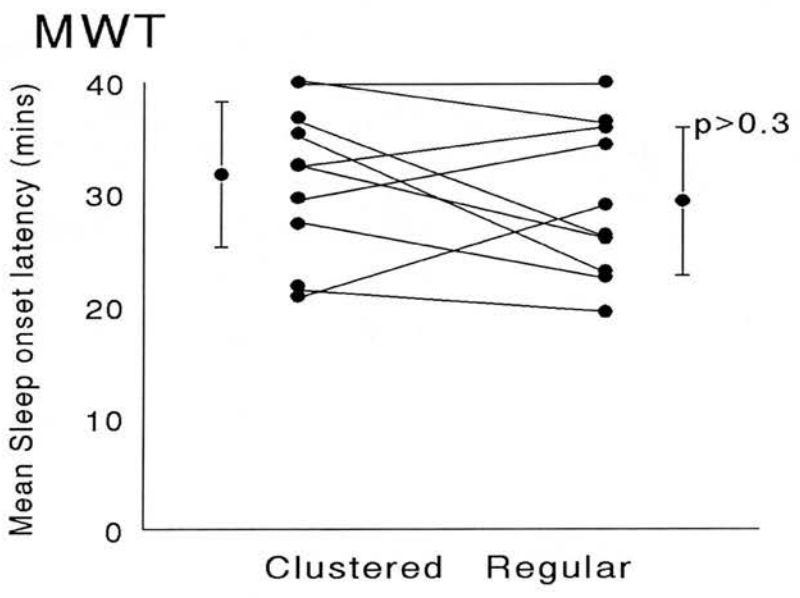
Table 7.3; Microarousal and R&K frequencies per hour slept for varying durations of microarousals. Values are mean ± standard deviation. *p=0.05 significantly different between study nights.

Daytime Sleepiness

There was no difference between clustered or regular fragmentation in their effects on mean sleep onset latency on the MSLT (clustered; 8 SD 4, regular; 9 ± 4 mins) (figure 7.1a) or on the MWT (clustered; 32 SD 7, regular; 29 SD 7) (figure7.b).



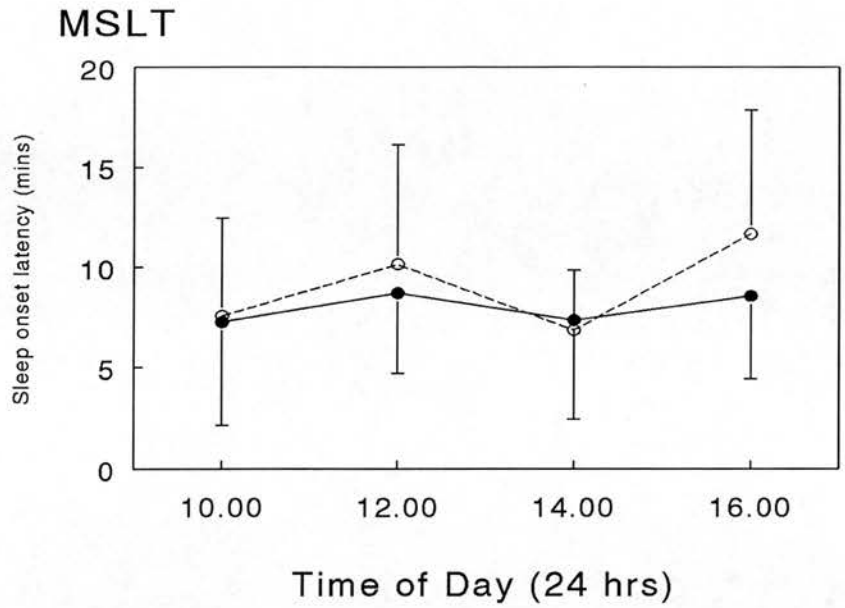
(a)



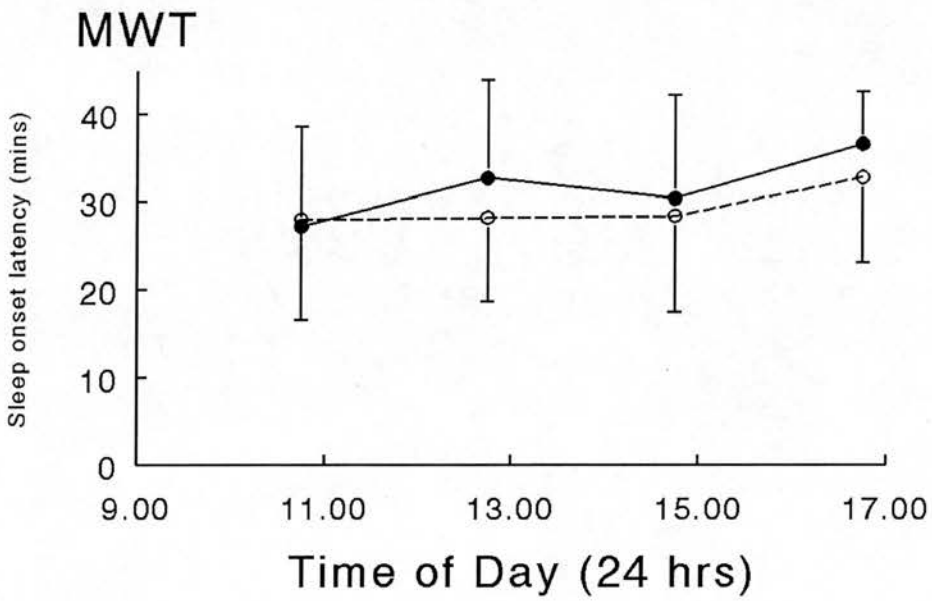
(b)

Figure 7.1; Paired point data of mean sleep onset latency on the (a) MSLT and (b) MWT after both study nights. Single points are mean ± SD for all subjects.

There were no significant differences in individual nap latencies on either the MSLT (all p> 0.1) (figure 7.3a) ot the MWT (all p> 0.2) (figure 7.3b) after the 2 types of sleep fragmentation.



(a)



(b)

Figure 7.2; Sleep onset latencies for individual naps on the (a) MSLT and (b) MWT. ---●--Clustered, - - - ❍ - - - Regular. Values are mean ± SD.

There was no difference in subjective sleepiness on the SSS at any time of day after clustered or regular fragmentation (all $p > 0.2$).

Cognitive Function and Mood

There was no difference between clustered and regular fragmentation in their effects on the cognitive function tests that were used in this study (all $p>0.1$) (table 7.4).

	Clustered	**Regular**	**p value**
Digit Symbol	73 ± 12	74 ± 11	0.3
Block Design	47 ± 3	45 ± 4	0.5
Est. Perf. IQ	131 ± 15	132 ± 14	0.9
Steer Clear	39 ± 27	37 ± 30	0.7
Trailmaking A	20 ± 5	20 ± 4	0.9
Trailmaking B	40 ± 9	38 ± 9	0.4
RVIP hits	122 ± 55	124 ± 51	0.9
RVIP misses	14 ± 15	7 ± 6	0.1
PASAT 4 sec	58 ± 2	57 ± 3	0.7
PASAT 2 sec	48 ± 8	46 ± 10	0.1

Table 7.4; Mean ± SD for cognitive outcome measures after both study nights. Est. perf. IQ; estimated performance IQ.

There was no difference between either fragmentation paradigm in their effects on mood dimensions at any time of day: Energetic Arousal; all $p>0.1$, Tense Arousal; all $p>0.2$, Hedonic Tone; all $p>0.4$, (table 7.5).

	Clustered	**Regular**	**p value**
Mean EA	16 $\pm$ 4	15 $\pm$ 4	0.4
Mean HT	27 $\pm$ 3	26 $\pm$ 3	0.9
Mean TA	12 $\pm$ 3	11 $\pm$ 2	0.5

Table 7.5; Mean ± SD values for all 5 mood assessments for the 3 different mood dimensions. EA; energetic arousal, HT; hedonic tone, TA tense arousal.

7.4 DISCUSSION

This study shows no difference between clustered or regular sleep fragmentation in their impacts on daytime sleepiness, mood or cognitive function. This was despite the fact that there was significantly more slow wave sleep and less stage 2 sleep on the clustered sleep fragmentation night. The clustered sleep fragmentation night was designed to allow subjects to obtain some uninterrupted sleep and this is reflected in the decreased stage 2 and increased slow wave sleep on the clustered fragmentation night.

There was no difference between study nights in their relative impacts on daytime sleepiness as measured by the MSLT or MWT. Although Philip et al (1994) found that slow wave sleep was the best predictor of daytime sleepiness on the MSLT they did not report on any relationship, significant or otherwise, between arousal frequency and daytime sleepiness. In chapter 5 of this thesis SWS duration decreased as arousal frequency increased, indicating that arousal frequency and SWS duration are interrelated. In this study however the arousal frequency has been manipulated on the clustered limb to allow for minimal loss of SWS with no subsequent differences in mood or cognitive function compared to after the regular fragmentation study night. This suggests that the increased SWS found on the clustered study night is not sufficient to lead to improved scores on the daytime sleepiness, mood and cognitive function tests that were used in this study.

These data are in agreement with Bonnet (1986a) who compared daytime function after induced sleep disruption -not sleep fragmentation- with that after a similar frequency of sleep disruption targeted to eliminate slow wave sleep. There were no significant differences in performance, mood and daytime sleepiness scores between study limbs. This in conjunction with the current results suggest that deficits in daytime function caused by sleep fragmentation may not be dependent on SWS.

On the clustered study night there were periods of uninterrupted sleep which were not sufficient to allow improved daytime function compared to one night of regular sleep fragmentation. These results suggest that it is the overall frequency of sleep disruption rather that its spacing which determines subsequent daytime function. This is in contrast to the suggestion that there may be a minimum period of uninterrupted sleep required for it to be restorative. This is known as the sleep continuity theory. Drawing together results from Badia et al (1985), Magee et al (1987), Levine et al (1987) and Bonnet (1986b) 4 minutes was suggested as that minimum. These differences cannot be explained by differences in the techniques used to assess daytime sleepiness as the studies of Magee et al (1987) and Levine et al (1987) tested daytime sleepiness with the MSLT. In 6 out of 10 subjects in the current study there was a cluster of fragmentation which terminated within 25 minutes of wakening which may have negated the restorative effects of the previous hour of sleep and would account for the similarity of daytime function after clustered and regular fragmentation. This is unlikely to be the case as in the study by Bonnet (1986b) performance was best after 2.5 hours uninterrupted sleep followed by regular disruption for the remainder of the night suggesting that any restorative effects of periods of uninterrupted sleep would last throughout the night regardless of subsequent disruption. Bonnet (1986b) however did not use a full MSLT but used one morning nap to test daytime sleepiness.

Alternatively the lack of significant differences in daytime function between fragmentation study limbs may be due to a type 2 statistical error as there were only 10 subjects in this study. However these results agree with those of Bonnet (1986a) who studied 12 subjects over 2 conditions. The power of the current study and that of Bonnet (1986a), although low, may be greater than that of Bonnet (1986b) who studied 8 subjects over 4 conditions and Downey and Bonnet (1987) who studied 5 subjects over 3 conditions. As these studies (Bonnet 1986b, Downey and Bonnet 1987)are used as evidence for the sleep continuity theory these conlcusions may be based on

studies with low power. Badia et al (1985) and Magee et al (1987) studied more subjects, 20 and 16 subjects respectively, however these were split into 2 groups and a parallel study design used to compare different sleep fragmentation conditions. Therefore there were only 10 (Badia et al 1985) and 8 (Magee et al 1987) subjects in each sleep fragmentation condition again suggesting that their conclusions are based on results from studies which may have inadequate power.

The lack of a control limb in this study was deliberate as it has been established in this thesis (chapter 5) and by previous studies (Bonnet 1987, Philip et al 1994, Roehrs et al 1994) that regular sleep fragmentation has marked effects on daytime sleepiness. Indeed the results from the regular limb of the current study are similar to those found after regular sleep fragmentation in chapter 5 of this thesis. Using unpaired t-tests a post hoc comparison of daytime sleepiness (MSLT and MWT) after regular sleep fragmentation in this study and in the previous cortical sleep fragmentation study (chapter 5) was performed. There was no significant difference between objective sleepiness measured by either the MSLT or MWT in the regular fragmentation limb in this study and those in the previous study (MSLT; $p>0.1$, MWT; $p=0.3$). The aim of the current study was to determine whether clustered arousals had similar affects on daytime function to regular arousals and that could only be assessed by a direct comparison between these two limbs. The addition of a third, control, limb would not only have decreased the power of the study but also may have made subject recruitment more difficult as the subjects would have been required to spend 6 nights and 3 days in the sleep laboratory.

In this study the fragmention of normal subjects' sleep was successful in increasing arousals and in inducing similar numbers of arousals on both study nights. It may be expected that allowing subjects to have blocks of uninterrupted sleep may lower their acclimatisation thresholds to tones however this did not appear to be the case as there was no difference in the number of tones that were presented to subjects. Seventy nine percent of

tones caused arousals, and 9% of tones caused full awakenings on both study nights. These figures include repeat tones if the initial tone was not successful in inducing the standard microarousal response.

These study results may be applicable to the excessively sleepy patient who has intermittent sleep fragmentation, due to sleep apnea which only occurs during REM sleep (Kass et al 1996) or while the patient is lying supine. They may also have relevance to patients with PLMS, whose limb movements normally occur in a clustered fashion during NREM sleep (Montplaisir et al 1994) and therefore these patients may have periods of uninterrupted sleep, during the night. Recently Kass et al (1996) demonstrated that a group of patients with mild SAHS (AHI<15) who had moderately severe daytime sleepiness had a high AHI specific to REM sleep. They also demonstrated that AHI and arousal frequency during REM sleep alone are significantly correlated with sleepiness on the MSLT. Furthermore Guilleminault et al (1991) and Guilleminault et al (1993) have found that milder forms of sleep disordered breathing such as snoring and increased upper airway resistance may also lead to fragmentation of sleep and subsequent daytime sleepiness.

Patients who have respiratory events during REM or light sleep may snore or have increased upper airway resistance during SWS. Series et al (1994) have suggested that sleep fragmentation may contribute to increased upper airway collapsibility during sleep. Subjects in this study either had a night of sleep fragmentation or a night of sleep deprivation, followed by recovery sleep during which upper airway collapsibility was monitored. They found that upper airway collapsibility during recovery sleep after sleep fragmentation was increased compared to that after sleep deprivation. These data suggest that respiratory events during REM sleep alone may lead to increased upper airway collapsibility during subsequent sleep stages. Furthermore this may suggest that sleep fragmentation is instrumental in the aetiology of sleep apnoea along the continuum from mild to severe sleep disordered breathing.

These results indicate that clustered arousals may produce similar degrees of sleepiness, mood and cognitive function to that found after regular arousals in patients with fragmented sleep.

Chapter 8

Fast Fourier Transformation (FFT) analysis of the EEG during arousals from sleep in normal subjects.

8.1 INTRODUCTION

The process of manual evaluation of sleep fragmentation is time consuming and highly laborious. It requires expert technician time and in patients with severe sleep apnoea may take a considerable length of time to score fully (Biernacka and Douglas 1993). Although the relationships between arousal frequency and daytime sleepiness or cognitive function in SAHS patients are significant arousals do not explain much of the variance in daytime sleepiness (Roth et al 1980, Roehrs et al 1989). There may be many contributing factors to this finding. Primarily current methods of measuring arousals may not be accurate enough to reflect true sleep fragmentation in patients with sleep disordered breathing. In chapter 4 of this thesis a range of manual arousal definitions were equally poor predictors of daytime sleepiness. In addition although more apnoeas and hypopnoeas were terminated by shorter arousals (1.5 second definitions) the arousal definitions used still left at least 17% of respiratory events terminating without any indication of sleep disturbance. This suggests that there may not be any change in the EEG at the termination of these apnoeas. Evidence from Rees et al (1995) demonstrates that this is not the case.

Rees et al (1995) found that computer detectable changes in EEG frequency occur at apnoea termination even when there is no visible change in the EEG. Accompanied by these changes in EEG there are transient blood pressure increases suggesting some form of increased autonomic activation. In chapter 6 of this thesis there were increases in EEG power in the alpha frequency bandwidth, as detected by FFT analysis, in response to tones whether or not they induced visible EEG arousals. These results are in agreement with Davies et al (1993). Further to this Davies et al (1993) have

found transient increases in blood pressure in response to tones that caused no computer detectable change in the EEG. However the evidence suggesting that these blood pressure arousals have any impact on daytime function is contradictory. Preliminary evidence from Sahloul et al (1995) in 4 subjects only found no increase in daytime sleepiness following 3 hours of induced non-visible sleep fragmentation whereas in chapter 6 of this thesis a whole night of sleep fragmentation to cause non-visible arousals on the EEG made subjects significantly sleepier during the day on the MSLT and MWT.

Automatic detection of sleep fragmentation would cut the current workload involved in scoring microarousals in clinical sleep studies. Manual definitions as described in section 3.5 (Roehrs et al 1989, Cheshire et al 1992) are currently the best validated methods of measuring sleep fragmentation and therefore have to be used as a starting point for the development of any automatic arousal analyser. Ultimately this could be used as a basis for development of a system which could detect more subtle forms of sleep fragmentation as described by Davies et al (1993), Rees et al (1995) and in chapter 6 of this thesis. Given that this kind of sleep fragmentation can increase daytime sleepiness, albeit by small amounts, there may be patients with subtle forms of sleep disordered breathing, such as increased incidences of inspiratory flow limitation (Guilleminault et al 1993, Condos et al 1994), whose daytime sleepiness may be explained by increased incidences of this kind of sleep fragmentation.

Therefore in this study EEG signals were analysed using the Fast Fourier Transformation (FFT) system as described in section 3.7. Using this technique the present study examines EEG frequency changes during visible and non-visible EEG arousals in normal subjects where sleep was fragmented by auditory tones.

8.2 METHODS

Visible EEG Arousals

Ten overnight sleep studies were selected from those recorded onto computerised polysomnography using the Compumedics (Melbourne, Australia) system. Studies recorded on computerised polysomnography could be downloaded digitally for further computerised analysis. The studies were selected from the clustered versus regular sleep fragmentation protocol, as described in chapter 7, as I wished to study sequences of visible EEG arousals. There were 10 subjects in this protocol however only the last 7 subjects had overnight studies recorded on the Compumedics system. For this reason 3 subjects had both clustered and regular overnight sleep studies sampled. Sections of stage 2 sleep which contained, where possible, a continuous sequence of 30 arousals, were selected and downloaded into raw data files. The visible EEG arousals selected contained both spontaneous and induced arousals. Arousals which contained obvious EEG artifact were excluded from the analysis. Visible EEG arousals had been scored according to the sleep fragmentation definition described in section 3.5.

Non-Visible Arousals

All 12 overnight studies from the fragmentation limb were selected from the non-visible sleep fragmentation protocol as described in chapter 6. Ten events from each study in which tones did not cause visible EEG arousals, as defined in section 3.5, were selected from stage 2 sleep and the raw data downloaded into data files.

EEG Analysis

Using programmes generated by departmental computing support (see acknowledgement) Fast Fourier Transformation (FFT) was performed on the raw data files. FFT was performed on the central EEG signals derived from bipolar electrodes at positions CZ/PZ. EEG power was calculated separately for the four predominant stage 2 sleep EEG frequencies; sigma (12 to 16 Hz), alpha (8 to 11 Hz), theta (4 to 7 Hz), and delta (0 to 3 Hz). The analysis programme allowed calculation of EEG power within these specified frequencies in 2 second moving windows with a resolution of 1 second. Therefore FFT data points were generated every second. In addition I made time marker files containing start times (hr: min: sec) for each microarousal, and control time points 10 seconds prior to the beginning of each visible EEG arousal. For the non-visible arousals time marker files were generated at each tone and control time points 10 seconds prior to each tone. A further computer programme then searched the transformed EEG data to select the peak EEG power within 5 seconds of the start of each arousal event, or tone, and also during the 5 seconds after each control time point.

Statistical Analysis

The difference in peak EEG power after control and arousal or after control and tone time points was calculated. These differences were displayed as frequency plots and examined for normality. All outcome variables were normally distributed and therefore parametric statistics were used. Peak EEG power after control and microarousal time points, or control and tone time points, were compared using paired t-tests. The changes in peak EEG power during spontaneous and induced arousals were compared using unpaired t-tests. Changes in EEG power during visible and non-visible arousals were compared with unpaired t-tests. Bonferroni corrections were made for multiple comparisons where appropriate.

8.3 RESULTS

Visible EEG Arousals

Three hundred visible EEG arousals were studied. The mean duration of all arousals was 7.4 seconds (range 3 to 92 seconds). There were 51 spontaneous and 249 induced arousals in the sample. The total number of arousals longer than 5 seconds in duration was 110.

Subject ID number/ study number	**mean duration (secs)**	**max. duration (secs)**	**no. spontaneous arousals**	**no. arousals > 5 sec.**
310 clustered /1	6.1	25	0	8
304 " /2	8.7	41	2	16
305 " /3	6.9	35	1	8
306 " /4	7.8	92	2	11
307 " /5	9.1	43	0	14
308 " /6	7.4	28	3	12
309 " /7	5.3	24	3	7
304 regular /8	5.0	16	6	5
305 " /9	8.1	18	17	16
310 " /10	9.6	59	17	13

Table 8.1; Description of the visible EEG arousals used in this study according to the 10 individual studies.

Visible EEG arousals were divided into those that occurred spontaneously and those that were induced by tones. There were significant increases in peak EEG power during arousals compared to control periods within all frequencies regardless of whether the arousal was spontaneous or occurred in response to a tone.

	SPONTANEOUS		INDUCED	
	Control	**Arousal**	**Control**	**Arousal**
Sigma	4.4 ± 1.8	6.2 ± 1.7*	4.2 ± 1.9	5.6 ± 2.0*
Alpha	5.6 ± 2.4	10.3 ± 3.6*	4.5 ± 2.1	8.1 ± 3.6*
Theta	6.9 ± 2.7	11.3 ± 4.1*	6.5 ± 3.4	9.1 ± 4.7*
Delta	17.4 ± 11.0	39.1 ± 19.1*	14.2 ± 12.9	26.1 ± 21.6*

Table 8.2; Mean ± SD values for EEG power in the different frequencies for spontaneous and induced visible EEG arousals. * $p<0.001$ significantly different between control and arousal.

Changes in EEG power during arousals were calculated separately for spontaneous and induced arousals by subtracting control peak EEG power from the peak EEG power during arousal. There was no significant difference between spontaneous and induced arousals in the change in EEG power during arousals in any of the frequency bandwidths studies (figure 8.1).

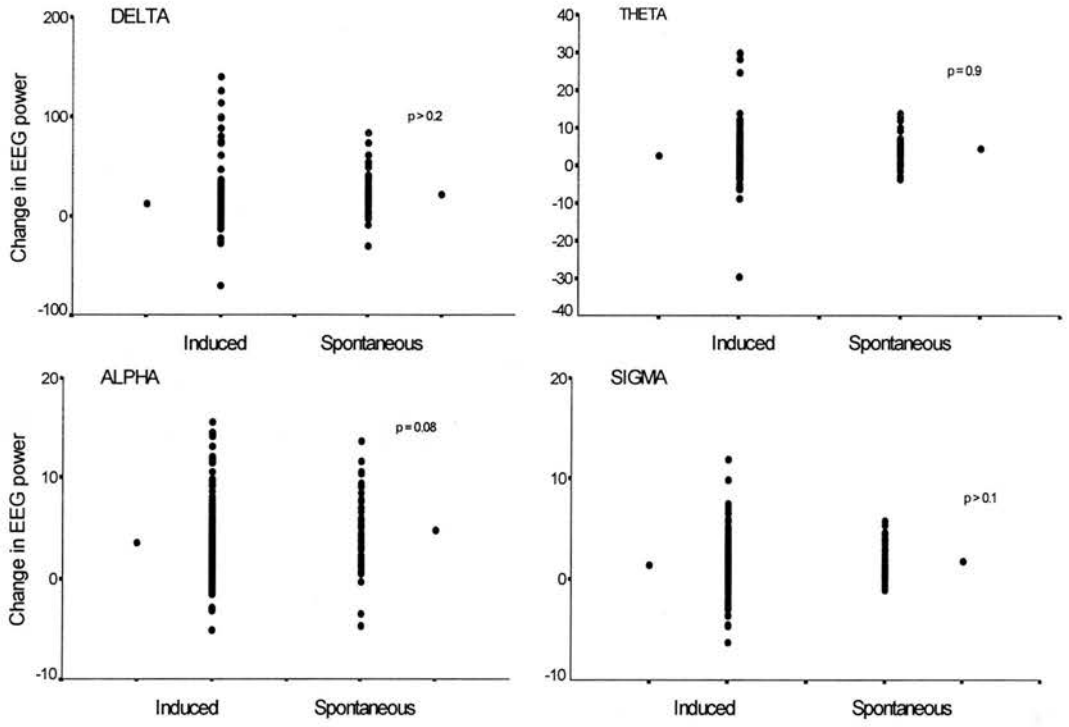


Figure 8.1; Individual data points for the comparison of changes in EEG power during arousals between spontaneous and induced arousals in the various EEG frequency bands studied. Single points indicate mean.

Changes in EEG power in all frequency bands after control times and during visible EEG arousals, both spontaneous and induced, were compared separately for each of the 10 individual studies (figure 8.2). There were significant increases in EEG power during arousals in all studies, in all frequencies, apart from in study numbers 2 and 6, where there were no significant increases in peak EEG power in the delta and theta frequencies (figure 8.2).

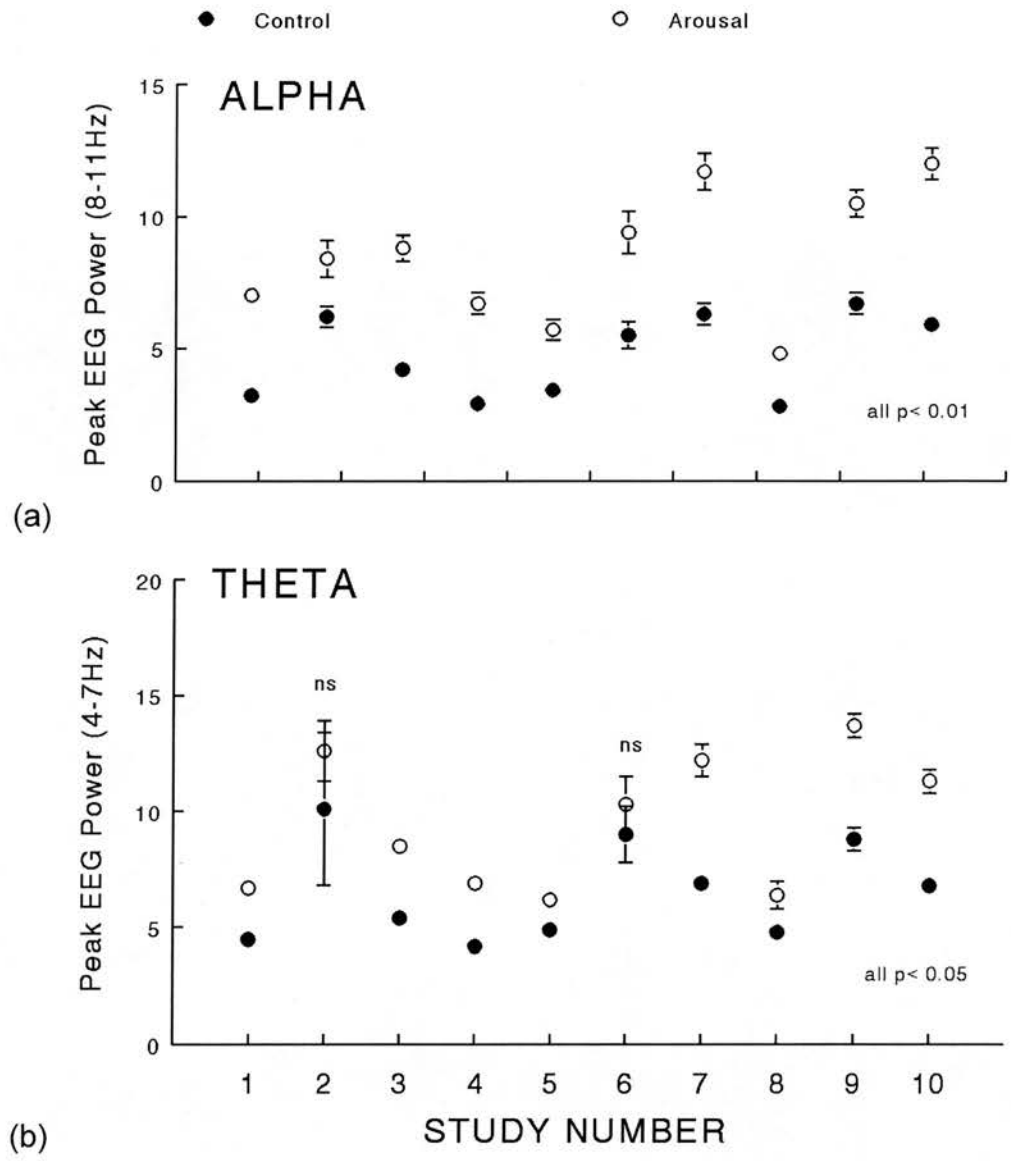


Figure 8.2 (a) and (b); Mean ± SEM of individual study's increases in EEG power in alpha and theta EEG frequencies during arousals compared to during control periods. ns; non-significant. ---●--- control, - - ○- - - arousals.

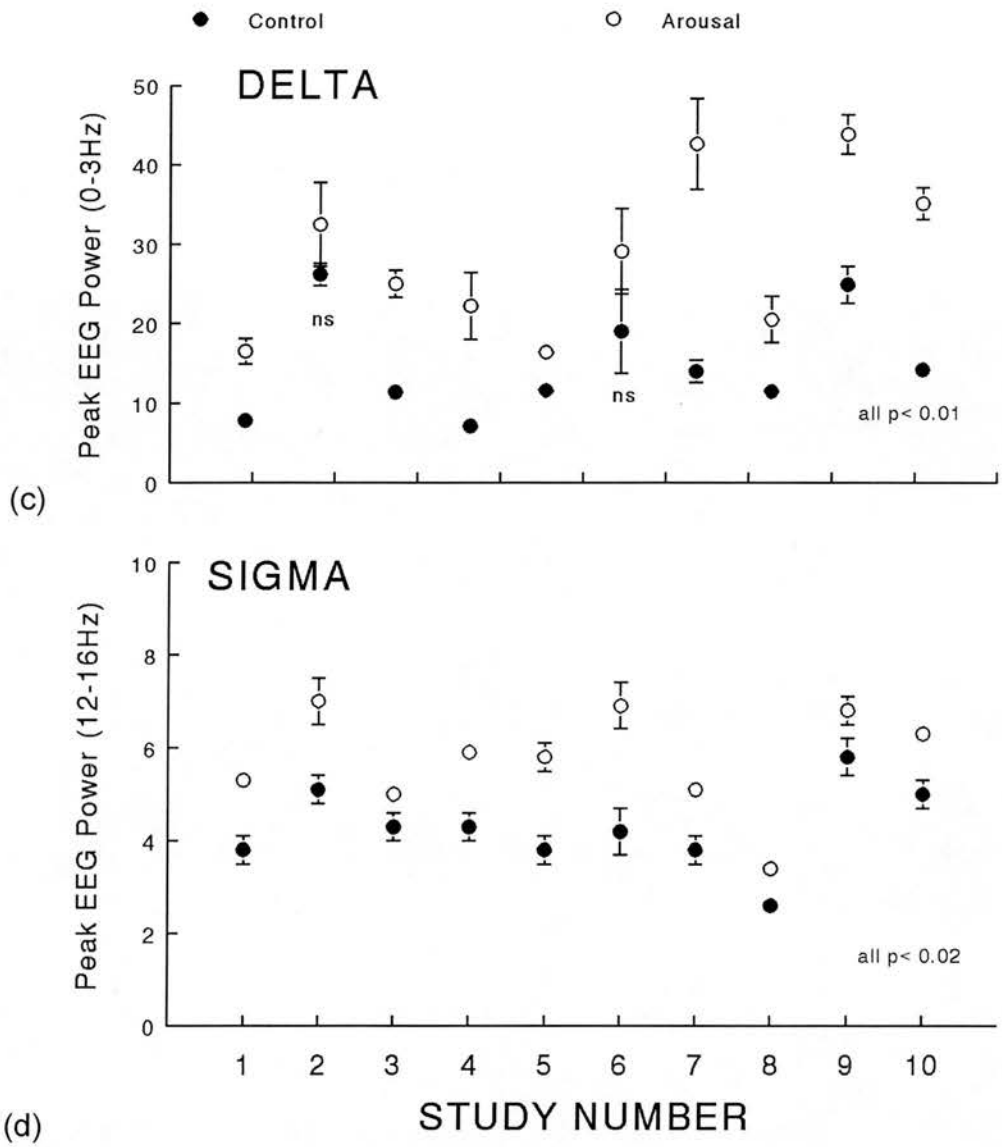


Figure 8.2 contd. (c) and (d); Mean ± SEM of individual study's increases in EEG power in delta and sigma EEG frequencies during arousals compared to during control periods. ns; non-significant. ---●--- control, - - ○- - - arousals.

Non-visible Arousals

Changes in EEG power in all frequency bands after control times and during non-visible arousals were compared separately for each of the 12 individual studies (figure 8.3). Peak EEG power in the delta frequency was significantly increased during non-visible arousals in 9 out of 12 subjects. Peak EEG power in the theta frequency was increased in 4 out of 12 subjects. There were significant increases in peak alpha EEG power in 5 out of 12 subjects. There were significant increases in peak sigma EEG power in 2 out of 12 subjects (figure 8.3).

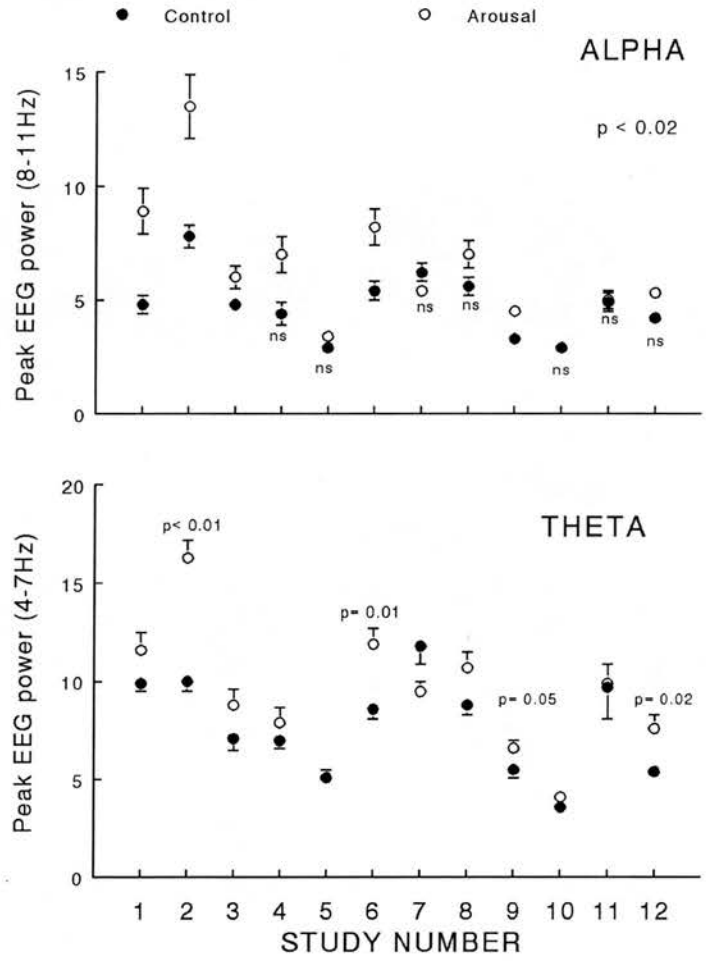


Figure 8.3 (a) and (b); Mean ± SEM of individual study's increases in peak EEG power in the alpha and theta frequencies during non-visible arousals compared to during control periods. ns: non-significant.

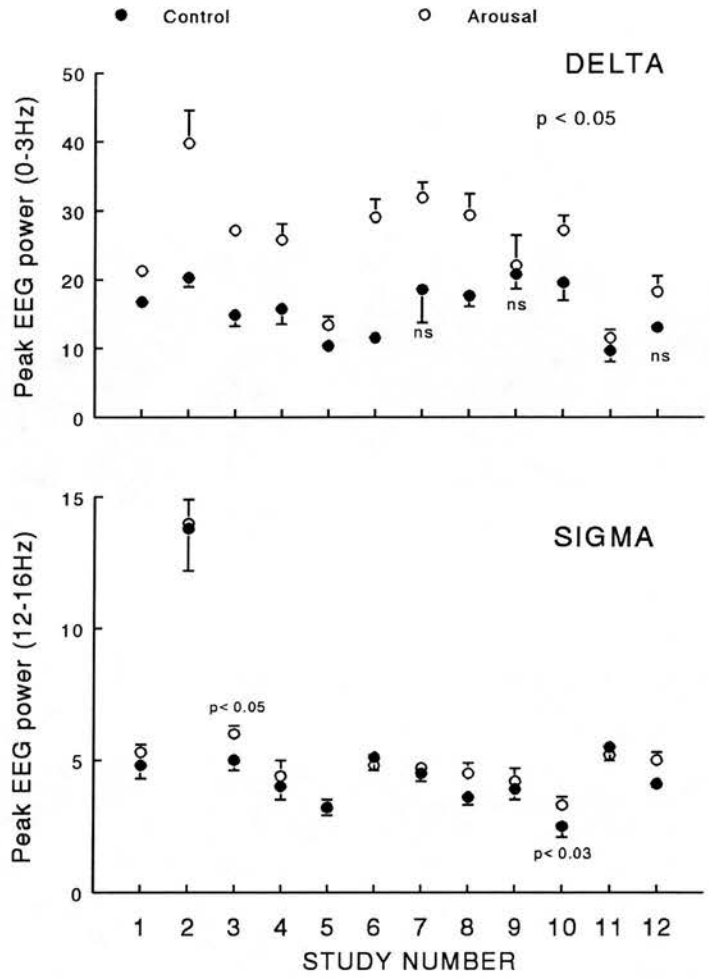


Figure 8.3 contd. (c) and (d); Mean ± SEM of individual study's increases in peak EEG power in delta and sigma EEG frequencies during arousals and during control periods. ns: non-significant.

All Arousals

Spontaneous and induced visible EEG arousals were analysed together. For visible arousals there were significant increases in peak EEG power in all the EEG frequencies studied ($p< 0.001$) (table 8.3). In response to tones there were significant increases in peak EEG power during non-visible arousals in delta, theta and alpha EEG frequencies ($p< 0.001$) (table 8.3). During non-visible arousals there was a trend towards a significant increase in peak EEG power within the sigma frequency ($p<0.08$).

	VISIBLE AROUSALS		**NON-VISIBLE AROUSALS**	
	Control	**Arousal**	**Control**	**Arousal**
Sigma (12-16 Hz)	4.2 SEM 0.1	5.7 ± 0.1*	4.9 ± 0.3	5.3 ± 0.3
Alpha (8-11 Hz)	4.7 ± 0.2	8.5 ± 0.1*	4.8 ± 0.2	6.4 ± 0.3*
Theta (4-7 Hz)	6.5 ± 0.2	9.4 ± 0.3*	7.7 ± 0.3	9.1 ± 0.4*
Delta (0-3 Hz)	14.7 ± 0.7	28.3 ± 1.3*	15.9 ± 0.7	24.5 ± 0.9*

Table 8.3; Comparison of peak EEG power after control and arousal time points for the various EEG frequencies for visible and non-visible arousals. Values are mean ± SEM. * $p< 0.001$.

The change in EEG power during arousals compared to control times was calculated as a percentage of the control value for individual EEG frequencies during both visible and non-visible arousals. Unpaired t-tests compared absolute changes in EEG power (Arousal - control) between visible and non-visible arousals. There was a significantly greater change in delta EEG power and a trend towards significantly greater change in alpha EEG power during visible EEG arousals compared to during non-visible arousals (table 8.4).

	Visible Arousals	**Non-visible Arousals**	**p value**
% Δ Delta	139 SEM 14	74 ± 8	0.008
% Δ Theta	55 ± 4	24 ± 4	0.2
% Δ Alpha	100 ± 5	40 ± 6	0.06
% Δ Sigma	56 ± 5	18 ± 4	0.2

Table 8.4; Percentage change in EEG power in the different EEG frequencies during visible and non-visible arousals. Δ; difference.

8.4 DISCUSSION

This study demonstrates that there are group mean increases in all physiologically relevant EEG frequencies during visible and non-visible EEG arousals from stage 2 sleep. It confirms findings of increased EEG frequency during visible EEG arousals and that FFT can be used to look at frequency changes in the EEG during short events such as arousals (Rees et al 1995, Drinnan et al 1996). However there appears to be a large amount of inter-individual variability, with two subjects showing no change at all in delta and theta EEG frequencies.

FFT analysis of the EEG in this study is very different to the process of manual scoring of the EEG. In manual scoring of visible EEG arousals the EEG is scanned for the reappearance of theta and/ or alpha frequencies and the disappearance of delta frequencies when identifying arousals in SWS. FFT analysis determines the relative amounts of the different frequencies and therefore is a more quantitative approach. This finding of increases in all EEG frequencies from 0-16 Hz during arousals confirms in a quantitative fashion the qualitative results of Halasz (1993). The results of that study show that there were increases in all EEG frequencies from 0-20Hz in response to tones however there were no statistical tests performed on this data. The sigma and delta frequencies are not usually used in manual scoring associated with arousals. However this study was performed during stage 2 sleep only and arousals from this stage of sleep may often include or begin with a K- complex (ASDA 1992). In addition tones inducing non-visible EEG arousals often produced a K complex as shown in figure 6.2. K complexes have a similar frequency bandwidth to delta waves (Rechtschaffen and Kales 1968) and this could therefore account for the increase in delta EEG power seen during arousals. It is unclear whether K complexes appear during arousals as an arousal phenomenon or as a defensive mechanism against arousal. Johnson and Lubin (1967) have suggested that K complexes are part of the "Orienting Reflex"; an evolutionary arousal mechanism which enables the brain to remain in a state

of readiness for physical activity during sleep. They found that K complexes are followed by transient increases in arterial blood pressure similar to those found in association with arousals in response to tones in normal subjects (Davies et al 1993, chapter 6) and respiratory events in SAHS patients (Rees et al 1995). In contrast to this Wauquier et al (1995) suggested that K complexes are sleep protective. They found better defined and more K complexes in stage 2 sleep in normal subjects compared to patients with sleep disorders and they reasoned that this lack of K complexes in patients with epilepsy, narcolepsy, insomnia and SAHS may have contributed to their poor sleep quality.

Guidelines for manual arousal scoring specifically exclude sleep spindles (sigma waves) as arousal phenomena. This is due to their role in the maintenance of sleep and more specifically the generation of deep sleep (Steriade et al 1992). It may be that increased EEG activity in this waveband is present during visible EEG arousals as a sleep protective mechanism, as suggested by Halasz (1993). A further reason for their presence during visible EEG arousals is that they are often associated with K complexes as a physiological marker for scoring of stage 2 sleep (Rechtschaffen and Kales 1968). If K complexes can be found during or at the start of arousals it is logical to suggest that co-existing EEG activity within the frequency range of sleep spindles may also occur. This would account for the significant increases in sigma waves seen during arousals in this study.

There was no significant difference between spontaneous and induced EEG arousals in increases in peak EEG power during arousals. There was however a trend towards a larger change in alpha EEG power during spontaneous arousals. This suggests that cortical arousals induced by tones are similar to those occurring spontaneously. In chapter 5 of this thesis there were more arousals of short durations (3 to 5 seconds) on the fragmented study night than on the undisturbed study night. The longer duration of spontaneous arousals however does not appear to allow waveforms to become more pronounced.

There may be different neural pathways involved in the generation of spontaneous and induced arousals. Spontaneous arousals may be a side effect of undergoing polysomnography (Mathur and Douglas 1995b) or they may occur as a result of increased upper airway resistance which is as yet undetected in routine clinical sleep studies and which could have an impact on daytime sleepiness. Indeed what constitutes a normal or pathological number of events of increased upper airway resistance during sleep is unknown. Induced arousals were generated by auditory tones. However these examples of different sensory inputs into arousal pathways did not lead to increases of different magnitude in the various EEG frequencies as expressed at the cortex.

As is evident from figures 8.2 and 8.3 there is a large amount of variability between individuals in the changes in EEG frequencies during visible and non-visible arousals. This largely reflects the inherent inter-individual variability in EEG signals. Therefore it is impossible to suggest that increases in various frequencies above a certain amount constitute arousals. A method of standardisation could be to use some multiple of the standard deviation of the EEG frequency change during arousals, similar to the mobility index of EEG used by Drinnan et al (1996). This would require screening of the EEG signals for artefacts which could skew the data. However the global EEG frequency changes found in this study would make it difficult to select a frequency upon which to focus. Drinnan et al (1996) applied automated analyses to manually scored arousals and investigated changes in the EEG before and during arousals. They found that the three best analyses, i.e. those that found the most significant differences in EEG between before, and during an arousal, (zero cross, mean frequency, and mobility) were all indices of total EEG frequency. They did investigate alpha EEG power alone and found significant increases during arousal, however the overlap between before and during arousal was greater than with other indices of EEG frequency and therefore it was not selected as an EEG index which warranted further study. These results suggest that more than one

EEG frequency may be required to accurately detect arousals from EEG frequency analyses.

In SAHS patients using changes in delta EEG frequencies may lead to inaccuracies in automated arousal detection. Krieger and Kurtz (1978) reported that bursts of slow waves can occur prior to apnoea termination. More recent data from Stradling et al (1995) and Svanborg and Guilleminault (1996), found that there were computer detectable increases in slow wave and delta activity prior to apnoea termination. Both studies suggest that this constitutes a sleep protective mechanism against arousal. This is a similar suggestion to that of Halasz et al (1985) who found that, in patients with parasomnias who had confusional arousals, there was an increased incidence of arousals preceded by a burst of slow waves. They concluded that this may constitute a sleep protective mechanism. These results suggest that using changes in delta frequency to detect arousals in patients with sleep apnoea may be unreliable.

This study has demonstrated global EEG frequency changes during visible arousals in normal subjects and suggests that quantitative EEG changes can be used to detect arousals automatically in SAHS patients. Furthermore this method detects increases in EEG power in non-visible induced arousals. The present data suggest that the best combination of frequencies with which to detect arousals may be alpha and theta EEG frequencies.

Chapter 9

CONCLUSIONS AND FUTURE WORK

The data presented in this thesis shows that some of the daytime impairments in patients with SAHS can be modeled by inducing cortical sleep fragmentation in normal subjects. Not only does this suggest that nocturnal hypoxemia need not necessarily be present for SAHS to be diagnosed but also that at least some of the deficits in daytime function found in these patients are reversible. Given that in chapter 5 the arousal frequency increased from 15/ hr to 34/ hr, this is equivalent to an apnoea + hypopnoea index of 20 per hour of sleep which is in the moderate range of severity of disease. This suggests that these induced impairments may be applicable to patients with moderate sleep apnoea.

However results in chapter 4 show that at best only 83% of respiratory events are terminated by cortical arousals. In addition cortical arousals scored by a range of definitions are only weakly related to daytime sleepiness. This leads to the question of whether the apnoeas and hypopnoeas that do not terminate in a visible EEG arousal but do terminate in an autonomic arousal are pathological in terms of daytime sleepiness. Furthermore are the weak relationships between cortical arousals and daytime sleepiness found by ourselves and others caused by the lack of routine measurement of more subtle arousals from sleep?

Results from chapter 6 suggest that these autonomic arousals do have a small but significant impact on daytime sleepiness. As previously shown, using a different computer technique, by Davies et al (1993) there were computer detectable changes in EEG, calculated by FFT analysis in this thesis, during these non visible arousals from sleep. These subtle changes in EEG may have lead to the increased daytime sleepiness after autonomic fragmentation. Although changes in EEG have been detected after induced autonomic arousals there is no evidence as yet how often these blood pressure rises occur during a normal night's sleep. In addition

Davies et al (1993) demonstrated that not all blood pressure increases in response to tones occur with concurrent detectable EEG change, as measured by Neural network analysis. Studies in normal subjects are required to determine how often these blood pressure arousals occur during a night's sleep and how often they are associated with changes in the EEG. Furthermore studies of a similar nature in patients with different severities of sleep disordered breathing may go some way to determining whether current diagnosis techniques are missing significant sleep fragmentation. As an adjunct to this the identification of significant non-visible sleep fragmentation and its relationship to daytime sleepiness needs to be investigated as it may account for the poor relationships found between visible arousals and daytime sleepiness.

The clustered versus regular sleep fragmentation protocol is a more subtle examination of the distribution of microarousals and their effects on daytime function. There were similarities in daytime function outcome measures after both types of fragmentation despite there being increased SWS on the clustered limb. Although this contradicts the sleep continuity theory of Downey and Bonnet (1987), this theory was developed using results from sleep disruption studies (Bonnet 1986b, Downey and Bonnet 1987). As this kind of study decreases total sleep time the results, upon which this theory is based, include a component of sleep deprivation. Therefore the results from sleep fragmentation studies such as that described in chapter 7 may not have relevance for this theory.

There is at least one potential further sleep fragmentation protocol which is an extension of the 3 fragmentation protocols presented in this thesis. The question of whether arousals during REM sleep are pathological is contentious. This is mainly due to the phenomena of alpha intrusion and EMG bursts being regarded as normal aspects of REM sleep. In addition respiratory instability is inherent in REM sleep suggesting that arousals resulting from hypo/ hyper ventilation is part of the normal sleep process. Measuring daytime function after fragmentation during REM sleep only may

go some way to answering this question. In addition it would more closely model REM related sleep apnoea than the sleep fragmentation protocol described in chapter 7.

There were significant changes in daytime function tests after cortical sleep fragmentation. These impairments are similar to those found in SAHS patients prior to CPAP therapy. The tests of daytime function used however have limitations and further work using different technology may give additional relevant information about the potential effects of sleep apnoea on daily living. Daytime sleepiness testing using the MSLT/ MWT is never ideal as these tests do not allow for testing in subjects' real-life situations. In addition a component of the MSLT includes measuring subjects' ability to sleep which is known to vary between individuals (Harrison and Horne 1996a). The recent development of reliable portable systems for monitoring of EEG signals (Compumedics; Melbourne, Australia) has made it feasible to send a subject about their normal daily routine after one night of sleep fragmentation. A true picture of their daytime sleepiness could be obtained by examining their EEG for epochs of sleepiness or, in a slightly more sensitive fashion, by looking for the occurrence of microsleeps (Harrison and Horne 1996b). A further application of the FFT technique described in this thesis may be to ascertain daytime sleepiness by looking at changes in EEG power as an indicator of sleep onset.

The cognitive tests that were used in these sleep fragmentation studies give little indication of the neural pathways involved in their execution and therefore cannot give any information about specific areas of the brain that are affected by sleep fragmentation. The exception is the RVIP test which examines information processing (Wesnes and Warburton 1983, Petrie and Deary 1989). Wesnes and Warburton (1983) suggest that the efficiency of this function is controlled by ascending reticular cholinergic pathways. This test however did not show any significant changes in any of the sleep fragmentation protocols. Future work in this area should focus on

using more targeted theory based tasks for the measurement of cognitive function.

Measuring topographic mapping of sensory evoked potentials may be an improvement in the measurement of cortical function. Sensory evoked potentials are usually performed either with visual or auditory stimuli. They are usually performed using one electrode recording site at CZ however topographic mapping of these potentials using the full 10/20 electrode placement is now available. This increases the amount of information that can be recorded from a test of this kind and allows for closer examination of discrete areas of the cortex. A study using this technique may pinpoint which areas of the cortex have altered function after one night of sleep fragmentation.

There is evidence that sleep fragmentation itself may have an impact on the development of sleep disordered breathing. Snoring and sleep apnoea are likely to be part of the same disease process, (Lugaresi et al 1983) both resulting from narrowing of the upper airway. The mechanisms whereby a snorer becomes a patient with sleep apnoea are uncertain however both snoring and respiratory events result in arousals from sleep (Guilleminault et al 1991). Espinoza et al (1991) found that there was a significant increase in AHI during 2 nights of fragmented sleep in normal subjects. During fragmentation sleep efficiency was decreased and stage 1 sleep was increased. Respiratory instability is greater during sleep onset and stage 1 sleep, leading to a greater likelihood of respiratory events occurring (Trinder et al 1992). The increase in AHI may have been due to the above effect or it may reflect a direct effect of sleep fragmentation on upper airway compliance and muscle function.

A study by Series et al (1994) addresses this question by investigating upper airway collapsibility (P_{crit}) during recovery sleep after a night of sleep deprivation and after a night of sleep fragmentation. P_{crit} was significantly lower after fragmentation than after deprivation indicating increased upper airway collapsibility. There was no control limb in this study however it would

have been difficult to obtain data during recovery sleep in the morning following a normal nights' sleep. However this data suggests that increased upper airway narrowing that could lead to a period of increased upper airway resistance or snoring during a normal night's sleep, may, due to an increase in upper airway collapsibility, become a hypopnoea or apnoea during or after a night of sleep fragmentation.

The mechanism whereby upper airway collapsibility is increased after fragmentation may be due to fragmentation itself causing an increase in arousal threshold. Recently Berry et al (1996) demonstrated that in SAHS patients on the 3rd night off CPAP respiratory events are longer, and the maximum negative inspiratory effort prior to arousal is increased by 10 cm H_2O compared to 1 night off CPAP. This suggests that the increased drive to sleep due to sleep fragmentation increases the negative pressure threshhold for termination apnoeas and hypopnoeas with arousals. This and the increased drive to sleep caused by sleep fragmentation may lead to an occurrence of respiratory events. The resulting increase in upper airway oedema may lead to increased upper airway collapsibility.

Further studies investigating the effects of sleep fragmentation on upper airway muscle function are required to understand the links between sleep fragmentation, upper airway collapsibility and the occurrence of respiratory events.

It is clear that the sleep fragmentation model for sleep apnoea/ hypopnoea syndrome is a useful tool in dissecting out the causes of the clinical problems that are associated with sleep apnoea. However animal models may reveal more information about the underlying physiological mechanisms involved in SAHS. Preliminary evidence from Brooks (1996a, 1996b) and Horner et al (1996) in a dog model of sleep apnoea demonstrates that obstructive sleep apnoea or sleep fragmentation can be induced over a 2-3 month period thus enabling more realistic modeling of sleep apnoea than one night. Furthermore animal modeling in smaller mammals may allow more invasive recording, particularly in a cellular

fashion, from discrete nuclei in the brain controlling aspects of function which are impaired in SAHS.

An approach in this direction may involve a series of experiments starting with sleep fragmentation studies to determine the anatomical location of neuronal pathways involved in the generation of cortical arousal from sleep. Once located the neurones can be described in terms of their neurotransmitter control. An obstructive model may then be applied to determine the pathways which control apnoea termination prior to cortical arousal. It is the interaction of these above pathways in conjunction with sleep generating mechanisms that may determine what kind of respiratory event occurs, its duration and its termination with or without cortical involvement. Once established the model can be applied in conditions of varying severity to explore whether SAHS could be the product of a positive feedback mechanism. This kind of approach allows for the identification of neural pathways involved in the aetiology of sleep apnoea and may lead to suggestions of neuropharmacological alternatives to CPAP in the treatment of sleep disordered breathing.

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Appendix 1

This is the in house sleep/ wake questionnaire used to assess subjects prior to recruitment for sleep fragmentation studies. The Epworth Sleepiness Scale (Johns 1991) is contained in question 8.

NAME : ..... DATE .....

SLEEP/ WAKE QUESTIONNAIRE

Please find enclosed a questionnaire for you to fill out and return.

You may get help, from your partner in answering Questions 9, 11 and 20.

For most questions several options are available, underline the answer which is most appropriate.

The answers will remain confidential.

Thank you for your co-operation.

PERSONAL INFORMATION: DATE: .....

Name: ..... Age: ..... Date of Birth : .....

Address : ..... Tel No: .....

..... Marital Status: single/married/divorced/widowed

..... Collar Size : .....

	Age	Sex
Children: Number :	.....	.....
	.....	.....
	.....	.....

Occupation: current ..... for ..... years
previous ..... for ..... years
..... for ..... years
..... for ..... years

Are you a : smoker / non-smoker / ex-smoker (for ..... years)

What did / do you smoke:	cigarettes	yes/no	Number per day .....
	cigars	yes/no	Number per day .....
	tobacco (own rolled)	yes/no	Oz. per week .....
	tobacco (pipe)	yes/no	Oz. per week .....
Do you drink:	tea	yes/no	cups per day .....
	coffee	yes/no	cups per day .....
	wine	yes/no	glasses per day .....
	beer	yes/no	pints per week .....
	spirits	yes/no	drinks per week .....
	sherry/port	yes/no	glasses per week.....

Any alcohol immediately before going to bed: yes/no

What medication, including sleeping pills are you taking at present?

	Name	Dose	How long have you been taking it?
1.	.....	.....	.....
2.	.....	.....	.....
3.	.....	.....	.....
4.	.....	.....	.....
5.	.....	.....	.....
6.	.....	.....	.....
7.	.....	.....	.....

PAST MEDICAL HISTORY

If you have had the following illnesses, please give details:

Illness			
Asthma	yes/no		.....
Bronchitis		yes/no	.....
Emphysema		yes/no	.....
Diabetes		yes/no	.....
Heart attacks		yes/no	.....
High blood pressure		yes/no	.....
Ankle swelling		yes/no	.....
Tonsillitis		yes/no	.....
Hay fever		yes/no	.....
Broken nose		yes/no	.....
Bed wetting		yes/no	.....
Nerve problems	yes/no		.....
Nose operations	yes/no		.....
Throat operations	yes/no		.....

****

1. When do you go to bed at night on average?

2. When do you finally wake up in the morning on average?

3. How long do you take to fall asleep at night?

4. How often do you wake between going to bed and getting up in the morning?

   never / 1-3 times / 3-6 times / more than 6 times per night

5. Do you do shift work? If so, please specify shifts and how long you are on each shift

   ....

6. How many times have you wet the bed in the last year?

   never / occasionally / 2-6 times / more than 6 times

7. How often have you woken with a headache each week?

   never / 1-2 times / 2-5 times / more than 5 times

8. How likely are you to doze off or fall asleep, in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0	=	would **never** doze
1	=	**slight** chance of dozing
2	=	**moderate** chance of dozing
3	=	**high** chance of dozing

Situation	Chance of Dozing
Sitting and reading	.....
Watching TV	.....
Sitting, inactive in a public place (eg a theatre or a meeting)	.....
As a passenger in a car for an hour without a break	.....
Lying down to rest in the afternoon when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after a lunch without alcohol	.....
In a car, while stopped for a few minutes in traffic	.....
	TOTAL

==========

9. Do you snore during sleep?

Yes/No

If yes:

a) How long have you snored loudly?

Always (since childhood / last 5 years / 3 years / 1 year

b) Do you snore every night / most nights/ occasional nights

c) Do you snore on your back only / on back and side / in all positions

10. Do you have a regular bed-partner or room-mate?

yes / no / previously but not currently

11. Has your bed-partner/room-mate ever noticed that you stop breathing when asleep?

yes / no

12. Do you need to go to the toilet at night?

never / occasionally / 1-2 times / more than 2 times per night

13. Do your ankles swell? If so, for how long

yes / no ..... months / years

14. Have you ever had hallucinations when you have been falling off to sleep or waking up?

yes / no

15. Have you ever had episodes when you body or part of your body has become floppy in response to an emotional stimulus?

yes / no

16. Have you ever had episodes when you have woken up and been unable to move?

yes / no

If so, how often?

once / less than 5 times / more than 5 times

17. In the morning do you feel that your nights sleep was refreshing/satisfactory?

always / 4-6 nights per week / 1-3 nights per week / never

18. Have you or your partner noticed any change in your sex drive?

increased / unchanged / decreased / non-existent

19. How many times have you woken choking or suffocating in the past month?

never / 1-2 times / 3-6 times / more than 6 times

20. How often is your bed-partner or room-mate, disturbed each week because of excessive arm and/or leg movements?

never / 1-5 times / 5-10 times / more than 10 times / no bed partner

21. Are you ever forced to have a nap during the day?

yes /no

If so, how many naps (5 minutes) do you have per day?

1-2 / 2-4 / 4-6 / more than 6

22. How many times have you fallen asleep against your will (for example, while eating, driving or in company) in the last year?

never / 1-2 / 2-4 / more than 4 (give details below)

23. For how long have you been sleepy during the day?

3 months / 3-6 months / 6-12 months / over 12 months / over 10 years

24. Do you drive?

yes / no

25. Have you ever had, or nearly had an accident because of falling asleep while driving?

yes / no (give details below)

26. Have you, your partner or family noticed any change in your personality?

yes / no

If so, specify : .....

.....

.....

27. Has you weight changed in recent years?

yes / no down / up

If so, what is the change ..... stones ..... lbs

When did your weight change occur : .....

28. Have you any comments on the questions above?

.....

.....

.....

.....

Additional comments:

.....

.....

.....

.....

.....

NAME : ..... DATE : .....

Appendix 2

Articles and presentations resulting from studies presented in this thesis.

Original Articles

Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. Am J Respir Crit Care Med. 1996; 153: 1328-1332.

Douglas NJ, Martin SE. Arousals and the sleep apnea/ hypopnea syndrome. Sleep 1996; 19: S196-S197.

Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of non-visible sleep fragmentation on daytime function. Am J Respir Crit Care Med. 1997; 155:1596-1601.

Submitted Articles

Martin SE, Engleman HM, Kingshott RN, Douglas NJ. Microarousals in patients with sleep apnea/ hypopnea syndrome (SAHS). Submitted to J Sleep Res.

Abstracts and Presentations

The effect of autonomic arousals on daytime function. Martin SE, Deary IJ, Douglas NJ. Am J Respir Crit Care Med. 1996; 153: A354.

The effect of sleep fragmentation on daytime function (II). Martin SE, Deary IJ, Douglas NJ. Am J Respir Crit Care Med. 1996; 153: A354.

Comparison of microarousal definitions in patients with sleep apnea. Martin SE, Engleman HM, Deary IJ, Douglas NJ. Am J Respir Crit Care Med. 1995; 151: A154.

The effect of sleep fragmentation on daytime function. Martin SE, Deary IJ, Douglas NJ. Am J Respir Crit Care Med. 1995; 151: A154.

Microarousal scoring and daytime function. Martin SE, Engleman HM, Deary IJ, Douglas NJ. Proceedings of the British Sleep Society. London; September 1995.

The effect of sleep fragmentation on daytime function (II). Martin SE, Deary IJ, Douglas NJ. Proceedings of the British Sleep Society. London; September 1995.

The effect of sleep fragmentation on daytime function. Martin SE, Deary IJ, Douglas NJ. Proceedings of the British Thoracic Society. London; December 1994.

The effect of sleep fragmentation on daytime function. Martin SE, Deary IJ, Douglas NJ. Proceedings of the British Sleep Society. Bristol; September 1994.

The Effect of Sleep Fragmentation on Daytime Function

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Patients with the sleep apnea/hypopnea syndrome suffer from impaired daytime function. This has been attributed to both sleep fragmentation and hypoxemia. To help understand which is casual, we studied the effects of sleep fragmentation alone on daytime function. Sixteen normal subjects were studied on two pairs of two nights. The first night of each pair was for acclimatization, and on the second the subject either slept undisturbed or had sleep fragmented with sound pulses every 2 min. Sound volume and duration was titrated to cause a return to theta or alpha rhythm on the EEG for at least 3 s. Study nights were followed by daytime testing of psychometric function and mood and by a multiple sleep latency test (MSLT) and a maintenance of wakefulness test (MWT). Total sleep time did not differ between study nights (400 ± 20 SD min undisturbed, 396 ± 24 min fragmented; $p = 0.6$). Fragmentation decreased sleep latency on both the MSLT (11 ± 3, 7 ± 2 min; $p = 0.001$) and the MWT (34 ± 8, 24 ± 10 min; $p < 0.001$). Energetic arousal (22 ± 4, 19 ± 4; $p = 0.005$) and hedonic tone (29 ± 4, 27 ± 4; $p = 0.05$) decreased after fragmentation. Fragmentation impaired daytime function adjudged by the Trailmaking B ($p = 0.05$) and PASAT 4-s tests ($p < 0.03$). One night of sleep fragmentation makes normal subjects sleepier during the day, impairs their subjective assessment of mood, and decreases mental flexibility and sustained attention. Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function.

AM J RESPIR CRIT CARE MED 1996;153:1328–32.

Patients with the sleep apnea/hypopnea syndrome (SAHS) suffer from impaired daytime function (1–4). They are severely sleepy during the day as measured by the multiple sleep latency test (MSLT) (5) and they suffer from impaired cognitive function compared with age- and educationally matched control subjects (1, 4). The nocturnal sequelae of apneas and hypopneas in patients with SAHS are recurrent drops in oxygen saturation and frequent sleep fragmentation in the form of short (< 15-s) microarousals (2, 6). There is controversy (1, 2, 7–11) as to which of these is the cause of the daytime sleepiness and cognitive dysfunction seen in patients with SAHS.

Excessive daytime sleepiness in patients with SAHS has been reported to be best predicted by the level of nocturnal sleep disturbance (7) and sleep fragmentation (8). However, Bedard and colleagues (9) found that daytime sleepiness was predicted by severity of nocturnal hypoxemia, whereas Cheshire and colleagues (2) found no relationship between daytime sleepiness and nocturnal hypoxemia or sleep fragmentation. Cognitive dysfunction in patients with SAHS has been related to both their nocturnal hypoxemia (1, 2, 4, 9, 10) and their sleep disruption/fragmentation (2, 9). We have previously found that patients with SAHS have altered anxiety and depression (2), and Kribbs and colleagues (11) reported that the mood of patients with SAHS, which had improved after CPAP therapy, returned to pretreatment levels after one night without receiving CPAP (11).

Unfortunately, the magnitude of sleep disruption and the extent of desaturation in patients with SAHS are correlated (2), confounding attempts to determine in patients with SAHS what specifically causes daytime dysfunction. Sleep disturbances in normal subjects causes increased daytime sleepiness (12), impaired mood, and altered daytime function (13). However, these studies had decreased total sleep time on the disruption nights compared with baseline, and they did not all mimic the short repetitive microarousals found in SAHS. We have therefore tested the hypothesis that such sleep fragmentation may cause the increased sleepiness and impaired mood and daytime function found in patients with SAHS.

METHODS

Subjects

Subjects were recruited from the local student population using advertisements that did not refer to sleep. Subjects responding with possible sleep disorders were excluded using our in-house sleep/wake questionnaire, which is used to assess patients prior to attendance at the Scottish National Sleep Laboratory. Ethical permission for the study was obtained from the Lothian Research Ethics Committee and the University of Edinburgh. We studied 16 subjects (eight men) with a mean age of 24 ± 3 SD yr. They were all nonobese (body mass index, 23 ± 3 kg/m^2) and had low Epworth sleepiness scores (14) (4; range, 0 to 9).

Protocol

Subjects spent two pairs of two nights in the sleep laboratory. Prior to the first night in the laboratory subjects received instructions on each test of mood and cognitive function that we used in this study and underwent one practice session. The nights were divided into two pairs of two nights a week apart. The first night of each pair was for acclimati-

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zation to the laboratory to avoid any "first night effect." On the second night subjects were randomly assigned to having an undisturbed night's sleep or to having their sleep fragmented with manually delivered acoustic stimulations.

Every 2 min from the onset of Stage 2 sleep we varied the duration and volume of tones of 1,000 Hz to try to produce a standard microarousal response, i.e., a return to alpha or theta rhythm for longer than 3 s but, when possible, not longer than 15 s on the EEG channels. If we achieved this response, we began the next 2-min intertone interval from the reappearance of Stage 2 sleep defined as the first occurrence of a well-defined K complex or sleep spindle. If we did not achieve an arousal response on the first tone we allowed a 10-s lapse before repeating with a louder and/or longer tone.

Lights-out on all nights was standardized to 11:00 P.M., and the study time finished at 6:30 A.M. on all nights except the fragmented night when study time was extended by 20 min in all subjects regardless of previous sleep quality to allow for any possible sleep loss caused by the fragmentation. Fragmentation continued throughout this additional 20 min.

On study nights, sleep was recorded by our standard techniques (15) and manually scored according to standard criteria (16) from electroencephalography (EEG), electrooculography (EOG), and submental electromyography (EMG). The arousal frequency consisted of the number of microarousals plus the number of Rechtschaffen and Kales awakenings (16) per hour of time slept. Arousals were further divided into durations of 3 to 5, 5 to 10, 10 to 15, and 15+ s (if not scored as a stage shift to wakefulness). We also calculated mean duration of undisturbed slow wave sleep (SWS), and the mean interarousal duration.

Subjects spent the day after each pair of nights undergoing testing of daytime sleepiness, cognitive function, and mood.

Daytime Assessment

We assessed subjective daytime sleepiness at 7:00 A.M. using only the Stanford Sleepiness Scale (17). We measured objective daytime sleepiness using the multiple sleep latency test (MSLT) (18) and maintenance of wakefulness test (MWT) (19). Both tests consisted of four naps at 2-h intervals throughout the day. We stopped all naps after one epoch of Rechtschaffen and Kales Stage 1 sleep, thus preventing subjects from obtaining any recuperative sleep that might affect their subsequent daytime function.

We assessed mood using the UWIST mood adjective checklist (20) at 7:00 A.M. and prior to each nap during the MSLT, at 10:00 A.M. and 12:00 noon and at 2:00 and 4:00 P.M. This scores mood dimensions of energetic arousal, hedonic tone, and tense arousal. Energetic arousal is assessed by asking the subject to rate their feelings at the time according to eight adjectives, e.g., vigorous, sluggish; hedonic tone uses eight adjectives, e.g., depressed, contented; tense arousal uses eight adjectives, e.g., relaxed, anxious. On each adjective subjects rate themselves on a four-point scale ranging from definitely feeling, e.g., sluggish to definitely not. Scores range from 8 to 32 for each dimension of mood, with high scores being positive indications for all three dimensions.

Prior to the first daytime nap, subjects underwent a battery of performance tests. They were selected to test a broad range of function; WAIS-R subtests—digit symbol substitution and block design (21)—testing general cognition; Trailmaking A and B (21), testing mental flexibility and attention; Steer Clear testing vigilance (22) and rapid visual information processing (RVIP) (23) and paced auditory serial addition test (PASAT) at 4 and 2 s (21), testing sustained attention and information processing. In addition we previously found that some of these tests relate significantly to nocturnal hypoxemia and sleep fragmentation in patients with SAHS (2) and that they are sensitive to improvements in performance in these patients after CPAP therapy (24).

Statistical Analysis

We analyzed our data using a mixed two-way analysis of variance (SPSS-PC+) for repeated measures with order of conditions as a between-subjects effect. The only test with an order effect was the Stanford Sleepiness Scale. These data were therefore analyzed as suggested by Hills and Armitage (25) using an unpaired *t* test on first-limb data only.

RESULTS

Sleep Architecture

There was no difference in total sleep time between the undisturbed and fragmented study nights; however, there was a trend towards a greater percentage of time awake on the fragmented night ($p = 0.06$) (Table 1). There was a significant general shift towards lighter sleep on the fragmented night, with significantly more Stages 1 ($p < 0.02$) and 2 ($p < 0.001$) sleep and significantly less SWS ($p < 0.001$) and REM sleep ($p < 0.02$) (Table 1).

Arousals

We presented a mean of 183 ± 20 SD tones to each subject during the fragmented night, of which a mean of 150 (82%) ± 20 (8%) resulted in arousals. Fragmentation more than doubled the arousal frequency ($p = 0.0001$ (Table 1). There were significantly more Rechtschaffen and Kales awakenings on the fragmented night (undisturbed, 27 ± 2; fragmented, 37 ± 3; $p = 0.02$). There were significantly more arousals per hour slept of any duration on the fragmented night (Table 2). On the fragmented night, 31% of arousals were less than 5 s in duration compared with 25% on the undisturbed night. Furthermore, 68% of arousals were less than 10 s in duration on the fragmented night compared with 55% on the undisturbed night.

Daytime Sleepiness

There were significant decreases in the mean sleep onset latencies on the MSLT (11 ± 3, 7 ± 2 min; $p = 0.002$) and the MWT (34 ± 8, 24 ± 10 min; $p < 0.0001$) after fragmentation. On the MSLT there were significant decreases in individual naps at 10:00 A.M. and at 2:00 and 4:00 P.M. (Figure 1) after fragmentation. On the MWT there were significant decreases in naps at 2:45 and 4:45 P.M. (Figure 2) after fragmentation. There was no change in subjective sleepiness on the Stanford Sleepiness Scale after fragmentation ($p = 0.8$).

TABLE 1

COMPARISON OF SLEEP STAGES AND MICROAROUSALS ON UNDISTURBED AND FRAGMENTED STUDY NIGHTS*

	Undisturbed	Fragmented	p Value
TST, min	400 ± 20	396 ± 24	0.6
Wake (SPT), %	8.0 ± 3.9	11.2 ± 5.8	0.06
Stage 1, %	3.2 ± 2.0	5.4 ± 2.5	0.02
Stage 2, %	42.9 ± 7.1	59.3 ± 6.7	0.0001
SWS, %	29.1 ± 11.2	15.4 ± 9.1	0.0001
Stage REM, %	23.0 ± 5.0	19.1 ± 3.3	0.02
Arousal frequency†	15.4 ± 3.7	34.1 ± 5.0	0.0001
R&K	27 ± 7	37 ± 11	0.02

Definition of abbreviations: TST = total sleep time; SPT = sleep period time; R&K = total number of Rechtschaffen and Kales awakenings per night.

* Values are mean ± SD. Values for Stages 1 to REM are expressed as a percentage of TST.

† Number of microarousals + R&K awakenings per hour of sleep.

TABLE 2

MICROAROUSAL AND R&K FREQUENCIES PER HOUR OF SLEEP FOR VARYING DURATIONS OF MICROAROUSALS*

	Duration (s)				
	3–5	5–10	10–15	15+	R&K
Undisturbed	3.8 ± 2.6	4.7 ± 1.7	1.9 ± 1.2	1.0 ± 0.6	4.1 ± 1.1
Fragmented	10.9 ± 3.8	12.3 ± 2.2	3.5 ± 1.7	1.9 ± 1.2	5.7 ± 1.9

For definition of abbreviations, *see* Table 1.

* Values are means ± SD. All $p < 0.01$ for comparisons between study nights.

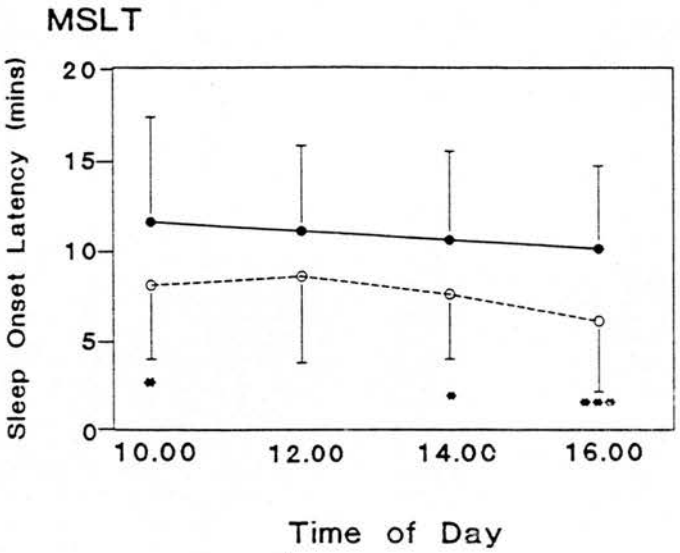

Figure 1. Sleep onset latencies for individual naps on the MSLT. Values are expressed as mean ± SD at each time of day. *Closed circles* indicate undisturbed; *open circles* indicate fragmented (* $p < 0.05$; *** $p < 0.001$).

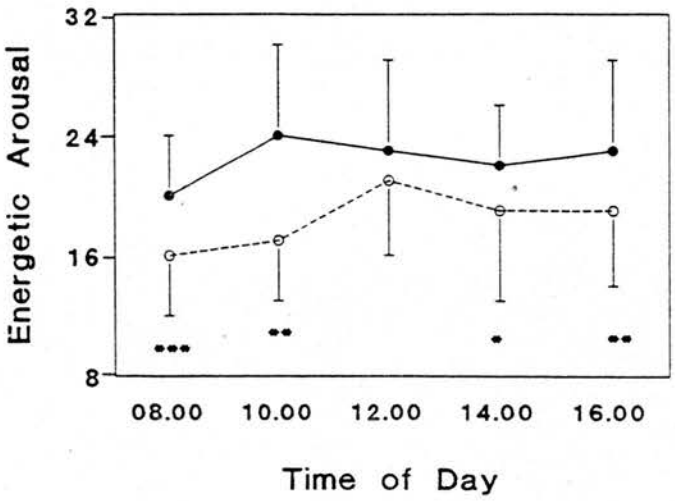

Figure 3. Energetic arousal scores throughout both test days. Values are expressed as mean ± SD. *Closed circles* indicate undisturbed; *open circles* indicate fragmented (* $p < 0.05$; ** $p < 0.01$; *** $p = 0.001$).

Mood

The mean energetic arousal score (22 ± 4, 19 ± 4, scores from 32; $p < 0.001$) and the mean hedonic tone score (29 ± 4, 27 ± 4; $p = 0.05$) were significantly lower after fragmentation. The mean tense arousal score did not change. The individual energetic arousal scores were significantly lower after fragmentation at all times except 12:00 noon (Figure 3). Individual hedonic tone scores were significantly lower after fragmentation at 10:00 A.M. (undisturbed, 30 ± 3; fragmented, 27 ± 4; $p = 0.005$) only. The individual tense arousal scores were increased after the fragmented night at 8:00 A.M. (undisturbed, 11 ± 3; fragmented, 13 ± 3; $p = 0.01$) and at 10:00 A.M. (10 ± 2, 12 ± 2; $p = 0.05$) only.

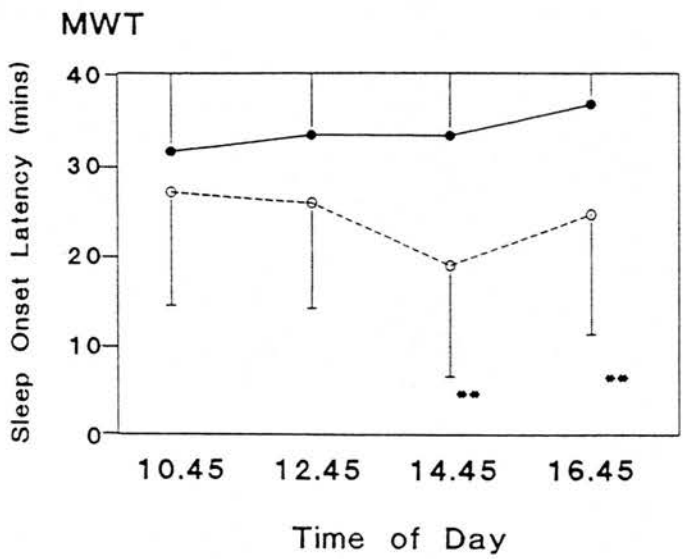

Figure 2. Sleep onset latencies for individual naps on the MWT. Values are expressed as mean ± SD at each time of day. *Closed circles* indicate undisturbed; *open circles* indicate fragmented (** $p < 0.01$).

Cognitive Function

Subjects had a significantly slower time to complete the Trail-making B task (40 ± 14, 43 ± 10 s; $p = 0.05$) and scored significantly fewer correct additions on the PASAT 4-s test (60 ± 2, 58 ± 3; $p < 0.03$) after the fragmented night. No other cognitive variables were altered significantly by sleep fragmentation.

Correlations with Daytime Sleepiness

Mean sleep onset latency on the MSLT and the MWT correlated significantly with many nocturnal variables (Table 3). Multiple linear regression analysis found that arousal frequency was the single best predictor of daytime sleepiness measured by the MSLT and that the percentage of SWS was the best predictor of mean sleep onsent latency on the MWT. Mean length of undisturbed SWS did not correlate with sleep onset latency on the MSLT or the MWT.

DISCUSSION

This study confirms recent findings (26, 27) that one night of sleep fragmentation with short arousals causes increased objective daytime sleepiness, and it also shows that it causes decrements in mood and performance of normal subjects. Our sleep fragmentation design improves on previous studies, which did not include an acclimatization night in the laboratory (26, 27) or a control undisturbed night (26). Previous studies have induced longer and more marked arousals than often occur in SAHS (12, 13, 28), with a subsequent decrease in total sleep time (12, 13, 28). We improved on daytime assessments in previous studies (12, 13, 26–28) as they did not all include investigating daytime sleepiness with the MSLT (12, 13, 28), the MWT (12, 13, 26–28), or by looking at the effects of fragmentation on mood (25, 27). Our subjects became sleepier than in previous studies (26, 27), and we also demonstrated that maintenance of wakefulness was impaired. The instruction to "stay awake" without stimulation mimics more closely daytime situations in which the excessively sleepy patients may find themselves and thus give more relevant clinical information than how quickly the patients can fall asleep. Our results show that after a single night of sleep fragmentation normal subjects have as much difficulty staying awake as untreated patients with SAHS (19, 29). Clearly, patients

TABLE 3

CORRELATION MATRIX SHOWING RELATIONSHIPS BETWEEN DAYTIME SLEEPINESS AND NOCTURNAL EEG VARIABLES

		Wake (%)	Stage 2 (%)	SWS (%)	Arousal Frequency	R&K Frequency	Interarousal Duration
Mean MSLT	r	−0.24	−0.35	0.32	−0.39	−0.26	0.32
	p	0.09	0.02	0.04	0.01	0.08	0.04
Mean MWT	r	−0.39	−0.52	0.45	−0.42	−0.40	0.32
	p	0.01	0.001	0.005	0.007	0.01	0.04

Definition of abbreviations: SWS = slow-wave sleep; R&K = total number of Rechtschaffen and Kales awakenings per night; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test.

with SAHS may clinically respond in a way different from that of normal subjects with a similar degree of objective daytime sleepiness. For example, their ability to alert themselves may be affected by years of experience of sleepiness.

Sleep fragmentation impaired performance in two tests: Trail-making B, testing mental flexibility and attentional capacity, and the PASAT 4-s test, a sustained attention task. Thus, sleep fragmentation is probably affecting attention. We have previously found both these measures to be improved by treatment in patients with SAHS (24). Previous studies have found that two nights of sleep disruption (not fragmentation) decreased performance on a simple reaction time task (12), the Wilkinson addition task (12, 13, 28), and the digit symbol substitution (12). In contrast to our results, however, studies inducing short arousals similar to those seen in patients with SAHS (26, 27) found no change in performance after fragmentation. They did not use either Trailmaking or PASAT, but they had selected tests for their monotonous quality. We used Steer Clear (30 min) to assess vigilance and did not find any change in performance. It appears that normal subjects can overcome the effects of sleep fragmentation on such monotonous tasks.

In this study, one night of fragmentation resulted in energetic arousal scores in the subjects similar to those of untreated patients with SAHS (24). Decrements in energetic arousal after fragmentation mirror the decreases seen on the individual MSLT and MWT naps, suggesting that the energetic arousal dimension of mood may be a subjective indicator of objective daytime sleepiness. Mood is most susceptible to an external stress in the early part of the day as demonstrated by the global changes in mood at 10:00 A.M. after fragmentation. Sleep deprivation has similar global effects on mood (20). Our results suggest that sleep fragmentation is as detrimental to mood as sleep deprivation.

In our study the arousal frequency during the fragmented night was similar to that seen in untreated patients with SAHS (1, 30). The arousal frequency, even when altered for spontaneously occurring arousals from sleep, was still greater than that of Roehrs and colleagues (26), whereas Philip and coworkers (27) refer to the number of stimulations during the fragmented night and not to the number of arousals.

Our decrements in daytime function may be due to the small but significant changes in sleep architecture on the fragmented night. Our data indicate that sleepiness on the MSLT and the MWT correlated with a range of EEG variables, many of which were themselves interrelated. Our regression analysis showed that the single best predictors of daytime sleepiness was arousal frequency for the MSLT and SWS duration for the MWT. Philip and colleagues (27) found a significant relationship between nocturnal slow wave sleep and mean sleep latency on the MSLT, but they did not examine the relationship with arousals. Bonnet (31) found that eliminating SWS does not affect performance, mood, or daytime sleepiness decrements after sleep disruption in normal subjects. In patients with SAHS, daytime sleepiness was best predicted by sleep disruptions (7) and respiratory-associated arousals (8). However, neither ourselves (2) nor others (1) found any significant relationships between sleep stages and daytime function, whereas we have found a relationship between microarousals and daytime function (2).

This study shows that a single night of sleep fragmentation can induce objective sleepiness and altered mood and psychometric function similar to that found in patients with SAHS.

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Arousals and the Sleep Apnea/Hypopnea Syndrome

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Summary: As daytime deficits in sleep apnea/hypopnea syndrome (SAHS) correlate poorly with earlier definitions of arousals, we investigated the relationship between microarousals and sleepiness in o3 patients with SAHS. There was a poor correlation between mean sleep latency and microarousal frequency. To determine whether arousals not detected by current definitions could account for some of the residual variance in normal subjects we used sound to induce "arousals" that were detected by rises in blood pressure but produced no visible EEG change. Such autonomic arousals produced an increase in sleepiness. We conclude that arousals not scored currently on polysomnography may contribute to the sleepiness of patients with SAHS. **Key Words:** Sleep apnea—Arousals—Cognitive function—Sleepiness.

Repetitive arousal from sleep is a key component of the sleep apnea/hypopnea syndrome (SAHS). This paper describes investigations into the consequences of recurrent brief arousals in both patients with the syndrome and normal subjects.

In early studies, we showed that the daytime cognitive deficits in patients with the sleep apnea/hypopnea syndrome correlate best with the apnea + hypopnea frequency and more weakly with 1.5 second definitions of microarousals (1). However, there was no significant relationship in that study between arousal and objective daytime sleepiness measured by the multiple sleep latency test (MSLT) (1), while others have found weak relationships between arousals and objective sleepiness (2,3). We have now extended those studies by looking at a group of 63 patients and examining the coincidence between breathing irregularity at night and microarousals using three different definitions of microarousals (4). Three-second ASDA microarousals occurred at the termination of 75 SEM 4% of apneas and hypopneas, whereas significantly more ($p < 0.01$) apneas and hypopneas were terminated by 1.5-second (1) microarousals (81 ± 4%) or a 1.5-second microarousal definition based on the ASDA neurophysiological criteria (83 ± 4%). There was a significant relationship between apnea + hypopnea frequency and the mean sleep latency on the multiple sleep latency test ($r = -0.3$, $p < 0.01$) and even weaker but still significant relationships between mean sleep latency and microarousals ($0.24 > r > 0.2$). Many of the patients with sleep apnea/hypopnea syndrome had arousal frequencies that were within the normal range for one night polysomnography in our laboratory (5). We conclude that there is a weak relationship between visible electromyelograph (EMG) arousal and objective daytime sleepiness but that the variance in objective sleepiness is not explained by this relationship.

To further investigate the consequences of arousal and the potential sources of variance in the above relationship, we first examined the effect of fragmenting sleep by sound in 16 normal subjects (6). The study was carried out in a randomized blinded fashion with acclimatization nights and showed that the induction of repetitive microarousals by sound impulses every two minutes decreased sleep latency both on the MSLT ($p = 0.001$) and the MWT ($p < 0.001$). There were also impairments in cognitive function on the Trailmaking B and Paced Serial Addition Test. We then performed a study inducing arousal that was detectable by a blood pressure increment but no visible electroencephalograph (EEG) change. Such "autonomic" arousals also produced increased sleepiness as detected by the MSLT and MWT ($p < 0.05$). However, no changes in cognitive function were observed.

It is possible that some of the unexplained variance in the relationship between microarousals and objective sleepiness in the patients with the sleep apnea/hypopnea syndrome are due to "autonomic" type arousals occurring in these patients that are not detected by visible scoring of the EEG (7).

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The Effect of Nonvisible Sleep Fragmentation on Daytime Function

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Patients with sleep apnea/hypopnea syndrome (SAHS) suffer from impaired daytime function that correlates with hypoxemia and visible electroencephalographic (EEG) arousals. However, not all breathing irregularities during sleep terminate with visible EEG arousal. We hypothesized that sleep disturbance without visible EEG change may impair daytime function. Twelve normal subjects spent two pairs of 2 nights each in the laboratory. The first night of each pair was for acclimatization. On the second night, subjects either slept undisturbed or had sleep fragmented every minute to cause a transient increase in arterial blood pressure or increase in heart rate without visible EEG arousal. We tested daytime function after each study night. We presented 253 ± 23 tones (mean ± SD), 79 ± 7% of which did not cause visible EEG arousals. Fragmentation did not alter total sleep time (undisturbed: 419 ± 27 min; fragmented: 414 ± 32 min; $p = 0.5$) or arousal frequency (undisturbed: 22 ± 4/h; fragmented: 25 ± 6/h; $p = 0.4$). Fragmentation reduced slow-wave sleep (undisturbed: 24 ± 5%; fragmented: 20 ± 4%; $p < 0.01$), mean sleep onset latency on the multiple sleep latency test (MSLT) (undisturbed: 8.0 ± 3.1; fragmented: 6.2 ± 2.1 min; $p = 0.01$) and the maintenance of wakefulness test (MWT) (undisturbed: 29.0 ± 10.0 min; fragmented 25.7 ± 9.7 min; $p = 0.04$). Fragmentation decreased hedonic tone at 7 A.M. (27 ± 4, 25 ± 6; $p = 0.03$). Nonvisible (autonomic) sleep fragmentation makes normal subjects sleepier and impairs their mood. Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. AM J RESPIR CRIT CARE MED 1997;155:1596–1601.

Patients with sleep apnea/hypopnea syndrome (SAHS) suffer from impaired daytime function (1–3). They are pathologically sleepy during the day as measured by the multiple sleep latency test (MSLT) (4), and they have impaired cognitive function and mood as compared with those of control subjects (1, 3). These impairments in daytime function have been associated with both the nocturnal hypoxemia and the sleep fragmentation/disruption seen in patients with SAHS (2). They are, however, strongly interrelated, making it difficult to elucidate which is the specific cause of daytime dysfunction.

Previous studies modeling the effects of sleep disruption found that normal subjects had impaired daytime function after sleep disturbance (5, 6). In these studies, subjects had to respond behaviorally to tones presented during sleep, and consequently had disturbed sleep. Recently, we have investigated the effects of induced sleep fragmentation, with recurrent brief cortical arousals (3 to 15 s), on daytime function in normal subjects (7). We found that one night of sleep fragmentation made the subjects sleepier during the day on the MSLT and the maintenance of wakefulness test (MWT), and impaired their mood and cognitive function (7).

Recently, patients with mild sleep apnea (8), snoring (9), and upper airway resistance syndrome (10) have shown improvement in daytime function with continuous positive airway pressure (CPAP) therapy. These milder forms of sleep-disordered breathing are invariably characterized by relatively normal nocturnal oxygenation, but with more cortical arousals, and it is the elimination of these arousals that is believed to lead to the improvement in daytime function.

In SAHS patients, sleep fragmentation accounts for about 16% of the variance in daytime sleepiness (11), and many SAHS patients have a similar number of cortical arousals as normal subjects when studied in a sleep laboratory (12). Thus, their daytime symptoms are not explained by sleep fragmentation caused by visible electroencephalographic (EEG) arousals. Not all sleep-related apneas and hypopneas are terminated by cortical arousals (13). Because apneas and hypopneas unaccompanied by visible EEG change may result in the blood-pressure (BP) increase of arousals (14), we hypothesized that sleep disturbance unaccompanied by visible EEG change may impair daytime function. We therefore studied the effects on daytime function of recurrent induced arousals detected by transient BP and/or heart rate (HR) increases in normal subjects.

METHODS

Subjects

We recruited subjects from the local student population, using advertisements that did not refer to sleep. Responding subjects were screened for sleep disorders with our in-house sleep–wake questionnaire, which we use to assess patients prior to attendance at the Scottish National Sleep Laboratory. We obtained ethical permission for this study from the Lothian Research Ethics Committee and the University of Edinburgh.

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We studied 12 subjects (seven men and five women) with a mean age of 25 ± 6 yr. They were all nonobese (body mass index [BMI]: 22 ± 2 kg/m²) and had Epworth sleepiness scores in the normal range (mean 5, range 2 to 8) (15).

Protocol

Subjects spent 4 nights and 2 d in the laboratory. Prior to the first night, subjects were familiarized with the tests of cognitive function used, and underwent one practice session. The nights were divided into two pairs of 2 nights a week apart. The first night of each pair was for acclimatization to the laboratory to avoid any "first night" effect. On the second night of each pair, subjects were randomly assigned to having an undisturbed night's sleep or having their sleep fragmented with tones.

On both study nights, sleep was recorded with our standard techniques (16), using a computerized recording system (Compumedics, Melbourne, Australia), and was staged manually according to standard criteria (17) through electroencephalography, electrooculography, and submental electromyography. In eight subjects we also recorded two frontal electroencephalographic (EEG) channels from standard EEG recording sites Fp1 to F3 and Fp2 to F4. We monitored arterial blood pressure with a digital infrared plethysmograph (Finapres; Ohmeda) set in beat-to-beat digital data-stream mode and attached to a personal computer (PC). Beat-to-beat systolic, diastolic, and mean arterial BP and pulse rate were recorded in serial ASCII string format on both study nights (18).

In order to assess the plethysmograph for use in whole-night studies we performed pilot studies with two normal subjects. Subjects tolerated the device for the first sleep cycle (approximately 1.5 h), but had profoundly disturbed sleep for their remaining study time. We therefore aimed to record BP continuously for the first 1.5 h of sleep, from the onset of slow-wave sleep (SWS). If subjects had a full awakening, the device was switched off and subjects were allowed to go back to Stage 2 sleep before the device was again switched on. During BP recording, HR responses to tones that produced nonvisible arousals were closely monitored and used as a guideline for nonvisible responses to tones during the remainder of the study night after the plethysmograph had been removed from the subject's hand. The volume and duration of tones were increased during the night in accordance with data showing that normal subjects acclimatize to arousing stimuli (5, 6). Subjects were monitored with a video camera to check for any movement that may have affected BP recording.

At every 1-min interval from the onset of SWS, we varied the duration and volume of tones to produce not a visible EEG change, but an autonomic response (i.e., a minimum increase in systolic BP of 4 mm Hg or, when the subject was not connected to the plethysmograph, an increase in HR of at least 4 beats/min without any visible cortical arousal response on the EEG channels that could be scored as an arousal). Brief (less than 3 s) EEG changes in response to tones, including K complexes or sleep spindles, were not counted as visible EEG responses to tones. The response should occur within 15 s of a tone, and because BP varies with the respiratory cycle, should be sustained over at least 3 beats as compared with BP over the 15 s prior to the tone. BP responses were assessed by the experimenter from a real-time display on a PC situated next to the Compumedics polysomnography computer. HR was also assessed from a real-time display on a cardiac rate monitor. If we achieved this response, the next tone came 1 min after the previous tone. If tones produced cortical arousals, we waited until the reappearance of the first sleep spindle or K complex, and then waited 1 min before applying the next tone. If we did not achieve this nonvisible response on the first tone, we allowed a 30-s lapse before repeating the process with a louder or longer tone. Sample visible and nonvisible EEG responses to tones are depicted in Figure 1. In Figure 1b, it can be argued that there is a visible response to the tone in the form of a K complex. During this study, sleep spindles and K complexes were seen on the electroencephalogram in response to tones, but were not counted as visible EEG arousals because they did not meet the criteria for scoring of arousals. Tones of 1,000 Hz were presented to subjects via a loudspeaker positioned above the subject's head.

Lights out on all nights was at 11:00 P.M., with the study time ending at 6:30 A.M. on all nights except for the fragmented night, when the study time was extended by 15 min to allow for any sleep loss due to fragmentation regardless of prior sleep quality. Fragmentation of sleep continued throughout this extended study time.

On the fragmented study night, the increase in systolic BP in response to tones was calculated for 10 s prior to each tone and for 10 s surrounding the maximum BP response. The mean delay to maximum BP response was noted for each subject. In order to compare BP responses to tones on different study nights, we randomly marked BP records from the undisturbed study night with an equal number of sham tones as of real tones on the fragmented study night. We took the "maximum" BP response to the sham tone as the BP at x seconds after each tone, x being the mean delay to maximum blood pressure within 20 s of a tone on the subject's fragmented study night. We then calculated the mean systolic BP for the 10 s prior to each "tone" and for the 10-s period from 5 s before to 5 s after the "maximum" BP response.

Arousals were defined as a return to alpha or theta frequency on the electroencephalograph channels for a minimum of 3 s (7, 19), regardless of sleep stage and without taking into account whether arousals

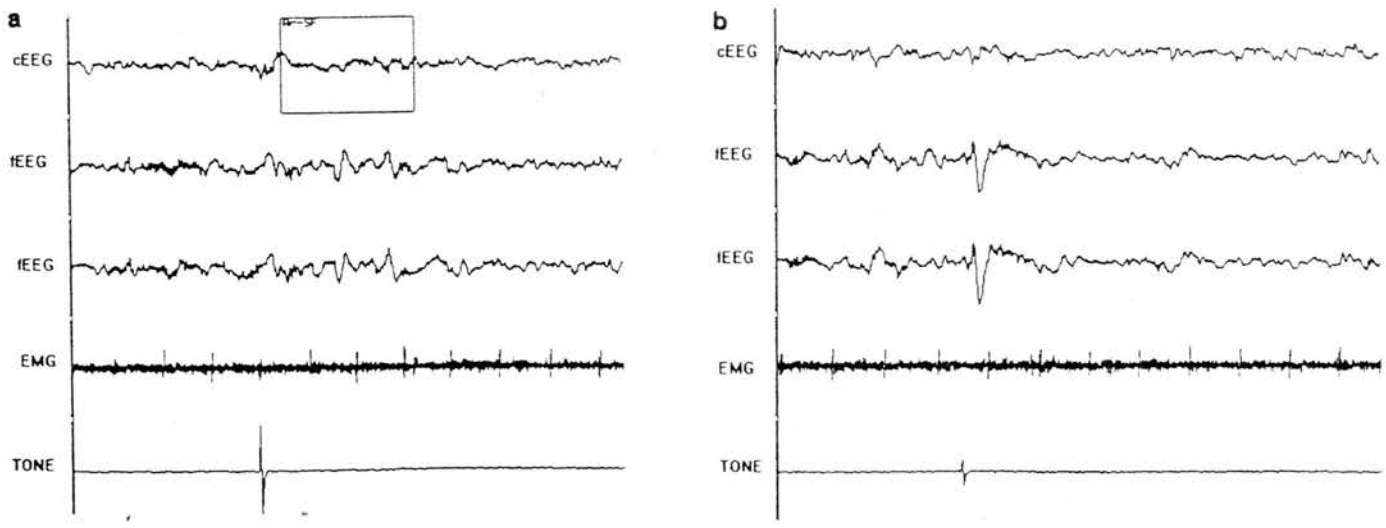

Figure 1. Sample visible (*a*) and nonvisible (*b*) EEG responses to tones. The channels depicted are central EEG (cEEG); (CZ/PZ) and frontal EEG (fEEG); Fp1/F3, Fp2/F4; chin EMG; and the tone marker channel. Tones were administered at the marks shown. In *a*, Ar-SF indicates visible EEG arousal. In *a*, the peak EEG power (in the range of 8 to 11 Hz) within 5 s of the tone was 3.3Hz, and the maximum BP increase within 15 s of the tone was 16 mm Hg. In *b*, the peak EEG power was 2.6 Hz and maximum BP increase was 5 mm Hg.

were induced by tones or not. We did not use any electromyographic (EMG) criteria for scoring of arousals, as we had found that we could not induce increases in EMG tone without causing full awakenings. The arousal frequency consisted of the number of arousals plus the number of Rechtschaffen-and-Kales awakenings per hour of sleep. Frontal (Fp1/F3, Fp2/F4) and occipital (CZ/PZ) arousal frequencies were scored separately. We also scored 1-h segments of Stage 2 sleep for 1.5-s arousals from the frontal leads.

Frontal EEG data from Stage 2 sleep were analyzed with fast Fourier transformation to calculate EEG power in the alpha frequency band (8 to 11 Hz). Peak power was selected within 5 s of tones and control time points either 30 s before or after tones. Subjects spent the day after each pair of nights undergoing testing of daytime sleepiness, cognitive function, and mood.

Daytime Assessment

We assessed objective daytime sleepiness with the MSLT (20) and MWT (21). Both tests consisted of four naps at 2-h intervals. We terminated all naps after one epoch of Rechtschaffen-and-Kales Stage 1 sleep, thus preventing subjects from obtaining any recuperative sleep that might have affected their subsequent daytime function. We assessed subjective daytime sleepiness with the Stanford sleepiness scale (SSS) at 7:00 A.M. and prior to each nap on the MSLT, at 10:00 A.M., 12:00 P.M., 2:00 P.M., and 4:00 P.M. (22).

We assessed mood with the University of Wales Institute of Science and Technology mood adjective checklist (23) at 7:00 A.M. and prior to each nap on the MSLT. This checklist scores mood dimensions of energetic arousal, hedonic tone, and tense arousal, as previously described (7).

Prior to the first daytime nap, subjects underwent a battery of performance tests designed to examine a broad range of cognitive functions. We have previously found that these tests relate to nocturnal hypoxemia and sleep fragmentation in patients with SAHS (2), and are sensitive to improvements in cognitive function in SAHS patients after 1 mo of CPAP therapy (24). The tests were the Wechsler Adult Intelligence Scale-R (WAIS-R) subtests of digit-symbol substitution and block design (25), trailmaking tests A and B (25), the steer clear test (26), and the paced auditory serial addition test (PASAT) at 4 and 2 s (25).

Statistical Analysis

We analyzed our data with a mixed two-way analysis of variance (ANOVA) (SPSS/PC+ software; SPSS Inc., Chicago, IL) for repeated measures, with the order of conditions as a between-subjects effect. We examined our outcome measures for nonnormal distributions and found ceiling effects on all individual naps on the MWT and all measures of hedonic tone. We analyzed these variables with Wilcoxon's matched pairs test.

We used paired *t* tests to compare peak EEG power after control times and tones. Tones were divided into those that induced arousals and those that did not. ANOVA was performed on the difference between tones and controls, with outcome (whether tones caused arousals or not) and intrasubject variability as factors. In order to reduce the number of outcome measures from the cognitive-function test battery, we subjected them to principal-components analysis (27).

TABLE 1

COMPARISON OF SLEEP ARCHITECTURE ON UNDISTURBED AND FRAGMENTED STUDY NIGHTS

	Undisturbed	Fragmented	p Value
TST, min	419.0 ± 27.4	414.0 ± 32.2	0.5
Wake (SPT), %	7.4 ± 4.2	8.3 ± 4.4	0.5
Stage 1, %	3.3 ± 1.9	3.7 ± 1.8	0.5
Stage 2, %	49.8 ± 4.8	53.8 ± 6.2	0.1
SWS, %	23.9 ± 5.0	19.5 ± 4.3	0.007
Stage REM, %	23.0 ± 4.2	23.1 ± 4.2	0.9

Definition of abbreviations: TST = total sleep time, SPT = sleep period time, SWS = slow wave sleep.

Values are expressed as mean ± SD.

TABLE 2

AROUSAL FREQUENCIES PER HOUR OF SLEEP

	Undisturbed	Fragmented	p Value
Central arousals/h	22.4 ± 4.3	24.5 ± 5.7	0.4
Frontal arousals/h	22.8 ± 6.0	26.3 ± 5.0	0.1
1.5-s arousals/h	26 ± 12	27 ± 12	0.7
R&K awakenings/h	3.7 ± 1.6	3.8 ± 1.2	0.8

Values are expressed as mean ± SD.

Central; CZ/PZ: frontal: Fp1/F3 and Fp2/F4; 1.5-s arousals scored from frontal leads.

RESULTS

Sleep Architecture

There were no significant differences between study nights in total sleep time (TST), amounts of wakefulness, or Stage 1, Stage 2, or rapid eye movement (REM) sleep (Table 1). However, there was significantly less SWS on the fragmented study night (Table 1).

Arousals

The minimum tone volume and duration was 38 db for 0.25 s. The maximum volume and duration of tones required to produce a nonvisible arousal response was 65 db for less than 4 s in all subjects. We presented a mean of 253 (SD = 23) tones to subjects during the fragmented study night, 21 ± 7% of which caused central arousals and a similar number (23 ± 9%; $p = 0.3$) of frontal arousals. The frequency of arousals induced by tones was 7.8 ± 2.2 per hour of sleep. The spontaneous arousal frequency on the fragmented night (16.7 ± 4.4 per hour of sleep) was significantly smaller than the arousal frequency on the undisturbed night (Table 2, $p = 0.001$). There were no significant differences between study nights in central, frontal, or 1.5-s arousal frequencies (Table 2). The mean systolic BP increase in response to tones was 8 ± 2 mm Hg, which was significantly greater than the response to control "tones"; (− 0.2 ± 0.1 mm Hg; $p < 0.0001$). The mean delay time to the maximum BP response was 9 ± 2 s.

Fast Fourier Transformation

Peak alpha EEG power was significantly greater after tones than for controls, both when tones induced visible EEG arousals ($n = 191$ events; control: 4.9 ± 2.2 μV; tone: 10.6 ± 4.9 μV; $p < 0.0001$) and when tones did not induce visible arousals ($n = 575$ events; control: 5.3 ± 2.7 μV; tone: 7.4 ± 3.3 μV; $p < 0.0001$). There was a significantly greater increase in peak EEG power after tones that caused arousals than after those that did not ($p = 0.008$), with no significant contribution from intrasubject variability.

Daytime Sleepiness

There were significantly shorter mean sleep-onset latencies in the MSLT (8.0 ± 3.1 versus 6.2 ± 2.1 min; $p = 0.01$) (Figure 2) and MWT (29.0 ± 10.0 versus 25.7 ± 9.7 min; $p = 0.04$) (Figure 3) after nonvisible sleep fragmentation. On the MSLT there were significantly shorter sleep onset latencies for individual naps at 10:00 A.M. ($p = 0.01$) and at 4:00 P.M. ($p = 0.01$) after fragmentation. On the MWT there were trends toward significant differences in sleep-onset latencies for individual naps at 10:45 A.M. ($p = 0.09$) and at 4:45 P.M. ($p = 0.07$) after nonvisible fragmentation. There was no difference in subjective daytime sleepiness as measured by the SSS (mean SSS score: undisturbed: 3 ± 1; fragmented: 3 ± 1; $p = 0.7$) after either study night.

Mood

There was a significant decrease in hedonic tone at 7:00 A.M. ($p = 0.03$; Figure 4), and there was a trend toward a significant in-

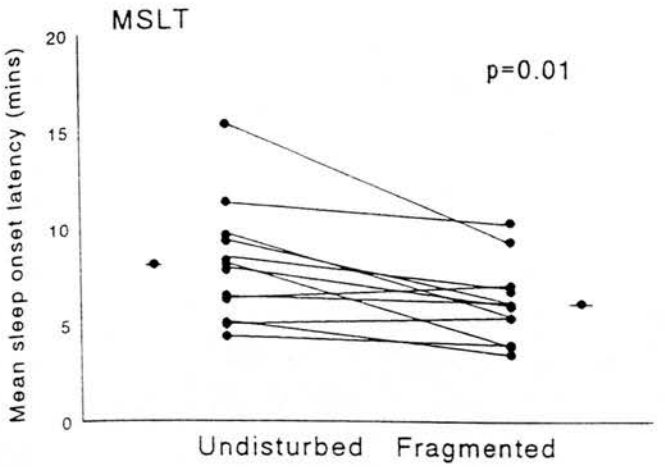

Figure 2. Paired points for individual subjects' mean sleep-onset latency on the MSLT after undisturbed and fragmented study nights.

crease in tense arousal at 7:00 A.M. ($p < 0.09$; Figure 4) after fragmentation. There was no change in energetic arousal at any time of the day after fragmentation.

Cognitive Function

We extracted the first cognitive factor from our principal-components analysis, which accounted for 39% of the total variance. This factor correlated significantly with all cognitive-function measures. We therefore standardized each measure, assigned equal weightings to them, and summed them, to produce one outcome variable for each subject for each study limb. Scores for tests in which high scores indicated poor performance were subtracted as opposed to added. Fragmentation did not cause significant impairment of cognitive function (undisturbed: 0.6 ± 2.8; fragmented: -0.01 ± 4.0; $p = 0.7$).

DISCUSSION

This study shows that nonvisible sleep fragmentation affects sleep architecture, daytime sleepiness as measured with the MSLT and MWT, and mood upon awakening. There was no coincident significant increase in the number of visible cortical arousals on the electroencephalogram; however, we have shown that small but significant increases in EEG power do occur in response to tones that do not cause visible EEG arousals. We have previously found that one night of cortical sleep fragmentation makes normal subjects sleepier during the day on the MSLT and MWT, and impairs mood and cognitive function (7).

We previously found that inducing visible EEG arousals every 2 min decreased the MSLT from 11 to 7 min and the MWT from 34 to 24 min, impaired all mood dimensions in the morning and energetic arousal for the rest of the day as well, and caused decrements in cognitive function. Nonvisibly detected arousals decrease the MSLT from 8 to 6 min and the MWT from 29 to 26 min, cause mood impairment on awakening only, and have no deleterious effect on cognitive function. The current results contrast with preliminary results from Sahloul and coworkers (28), who found, in four subjects, that there was no difference in sleep-onset latency on the MSLT after nonvisible sleep fragmentation during 3 h of recovery sleep as compared with a baseline night. We believe that our results differ from those of Sahloul and coworkers (28) because we studied more subjects and performed whole-night studies after acclimatization nights on both study limbs, tested mood and cognitive function, and tested daytime sleepiness with the MWT as well as the MSLT.

We found small but significant changes in daytime sleepiness in response to nonvisible sleep fragmentation. Despite the changes in MSLT and MWT results, there was no difference in subjective sleepiness after fragmentation. Previous studies have shown that SSS scores and objective sleepiness do not always move in parallel (4). We presented 34 tones per hour to induce nonvisible arousals, as compared with 30 tones per hour inducing visible EEG arousals (7), and the more subtle changes in daytime sleepiness reflect this difference. On the MSLT, this small change is similar in magnitude to that seen in patients with sleep apnea after they have been established on CPAP therapy (29, 30). Sangal and associates (21) found that sleepiness on the MWT improves with CPAP therapy by a magnitude (8 min) that is smaller than the decrease seen in normal subjects after induced visible EEG arousals (10 min) (7) but greater than the decrease seen after nonvisible arousals (4 min) in the present study. Our subjects appeared to be sleepier after the undisturbed night than those in our previous study (7). We therefore looked closely at our subjects' working habits, and found that three of our student subjects had evening jobs on weekends which ran into the early morning. Each was studied at the same time of the week in both limbs of the study, and always after at least 2 nights of normal sleep at home plus the acclimatization night before the study night. These three subjects may have increased the overall sleepiness of our study sample.

We monitored BP for the first sleep cycle only, because during pilot studies we showed that normal subjects were not sleepy enough to tolerate BP monitoring for the whole night without sleep disruption. The plethysmography device used in our study may have increased arousal frequency on study nights, since the arousal frequency on the undisturbed night in the study was 22 per hour, as compared with 15 per hour on the undisturbed night in our previous fragmentation study (7). Mood, cognitive function, and daytime sleepiness in normal subjects are impaired by sleep disruption (5, 6), and we therefore felt that monitoring BP over the whole night would have compromised the present study.

We found no significant difference in arousal frequencies measured centrally or frontally (either 3-s or 1.5-s duration) on different study nights. There was no significant difference between cortical areas in the number of tones that caused arousals. We decided to monitor frontal EEG channels because O'Malley and cowork-

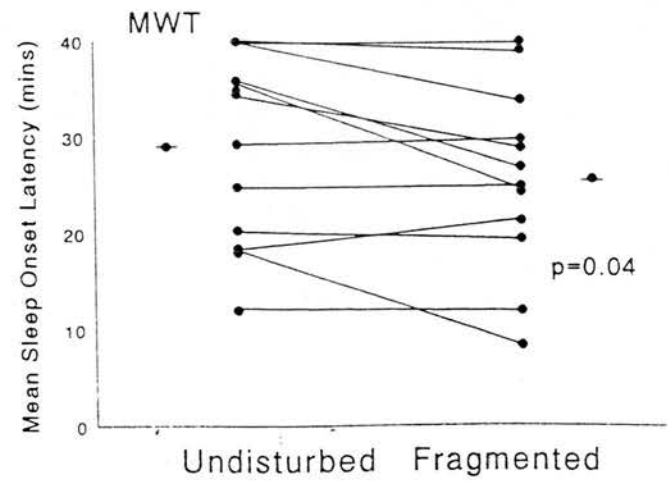

Figure 3. Paired points for individual subjects' mean sleep-onset latency on the MWT after undisturbed and fragmented study nights.

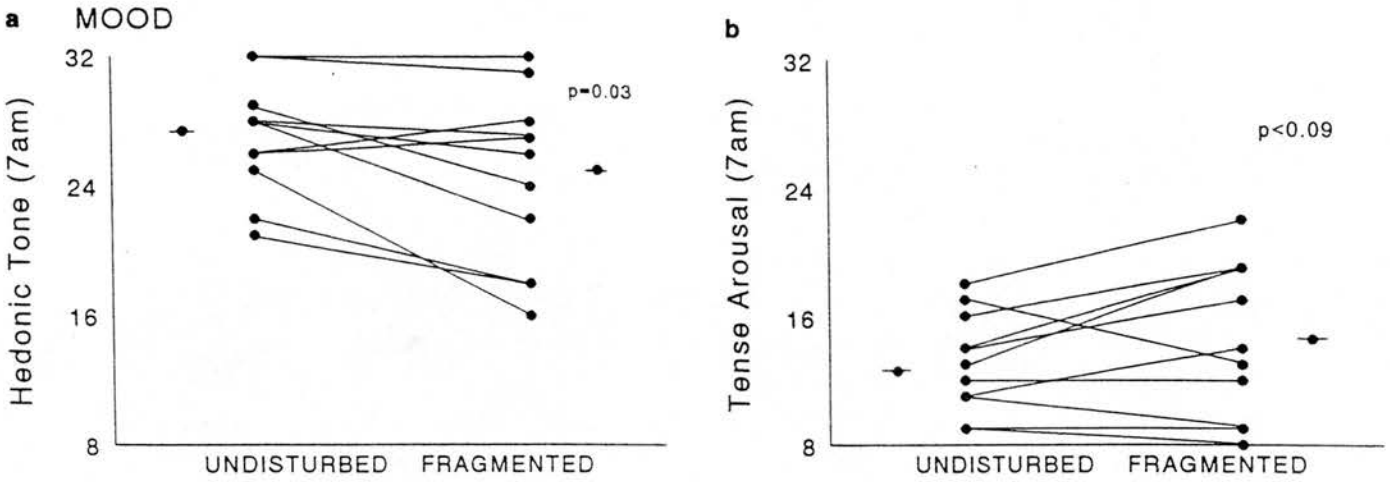

Figure 4. Paired point values for (*a*) hedonic tone and (*b*) tense arousal mood dimensions at 7:00 A.M.

ers (31), in a provisional study with topographic brain mapping, found that in patients with mild sleep apnea, frontal arousals were seen at the termination of 95% of respiratory events, whereas only 73% of such arousals were detected at occipital sites. In contrast, we did not find that visual scoring of frontal EEG signals increased the detection of visible EEG arousals in response to tones in normal subjects. The maximum volume and duration of tones required to produce a nonvisible arousal response was 65 db for less than 4 s, which is much smaller than that required to induce visible cortical arousal in our previous fragmentation study (100 db for up to 12 s).

We performed fast Fourier transformation on the frontal electroencephalogram from Stage 2 sleep. We found significant increases in EEG frequency in response to tones that did not cause visible EEG arousals. Davies and colleagues (18) tracked EEG changes in normal subjects in response to auditory stimuli, using a computerized artificial neural network without seeing visible cortical arousals. These changes were always accompanied by transient increases in arterial BP (18). Rees and coworkers (14) used fast Fourier transformations of the electroencephalograms of SAHS patients and found increases in EEG frequency coincident with increases in BP at the end of respiratory events whether or not they terminated in cortical arousals. This evidence, taken together with the induced decreases in daytime sleepiness that we have demonstrated in the present study, suggests that perhaps a more sophisticated analysis of the electroencephalogram or a nonvisible marker of arousal (32) should be included in routine sleep studies to assess the true extent of sleep fragmentation suffered by patients being assessed for sleep disorders.

We found a decrease in hedonic tone and a trend toward an increase in tense arousal on awakening after nonvisible sleep fragmentation. This is consistent with findings in studies using acute hypoglycemia as a physiologic stressor. Normal subjects had decreased hedonic tone and increased tense arousal, which was maximal with the onset of autonomic reactions to acute hypoglycemia (33), whereas adrenalectomized subjects, who do not have the normal adrenaline response to hypoglycemia, did not show these changes (34). Together, these results suggest that changes in hedonic tone and tense arousal could be autonomically mediated, whereas changes in energetic arousal are due to cortical stimulation. This hypothesis is supported by our findings in the present study of transient changes in mood due to repetitive nonvisible arousal from sleep, and in our previous study (7) of longer lasting impairment of energetic arousal due to cortical sleep fragmentation.

In this study, we have shown that one night of induced nonvisible sleep fragmentation causes increased daytime sleepiness and impaired mood upon awakening. The importance of sleep fragmentation with nonvisible EEG arousals in patients with sleep disorders needs to be assessed.

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