Contents - Chapter 1

Background

BACKGROUND CHAPTER

1.1 The role of hypoxia in the genesis of cognitive dysfunction.

This chapter will seek to define the relationship between cognitive dysfunction and hypoxia, using previous experimental data from studies in normals, as well as data collected from patients with chronic lung disease. The two models, of acute hypoxia and chronic hypoxia will be discussed separately.

1.1.1 Acute hypoxia in normals.

In the early 1980's, Gibson et al[1] reported that levels of ATP (adenosine triphosphate) are unaltered in mild to moderate hypoxia, in contrast to severe hypoxia or ischaemia. However, the turnover of several neurotransmitters such as acetylcholine are diminished even by mild hypoxia. There is, indeed, a proportional decline in acetylcholine synthesis relative to the reduction in carbohydrate oxidation.

Experimental data[2-4] in vivo and in vitro, support the hypothesis that the turnover of acetylcholine (and other neurotransmitters) is depressed by metabolic insults such as hypoxia. Gibson postulated this finding as an important mechanism in mediating the cerebral effects of even mild hypoxia. This hypothesis is supported by early data from Luft[5] and Siesjo[6], which examined the effects of hypoxia in young healthy men exposed to rapid decompression. Their findings ranged from impaired dark adaptation (5,000ft) to loss of consciousness above 20,000 ft (PaO_2 = 35mmHg).

In the presence of experimental hypoxia ability to concentrate is initially affected. Subsequently, short term memory, new learning and critical judgment become

impaired[7]. Similar findings were reported by West[8] in climbers ascending Everest. He noted a decline in verbal learning and short term memory.

In 1993, Noble[9] performed a double-blind, placebo controlled study of acute hypoxia on cognitive function. While moderate acute hypoxaemia (mean saturation 78%) in this setting was shown to cause a significant impairment in the simple unprepared reaction time, all of the changes seen were small.

More severe hypoxic insults correlate with more profound memory impairment and have been linked at post mortem to specific lesions of the anterior thalamus and hippocampus[10]. The patients in this amnestic group appeared orientated and did not confabulate, suggesting that the insult incurred differs from other forms of amnestic injury.

Thus, while acute hypoxia can give rise to small measured changes in cognitive function, this appears to be plastic and reversible. More sustained periods of hypoxia such as those demonstrated by West, would indicate that the duration of the insult is as potent as the magnitude of the hypoxia. This is best demonstrated in the chronic obstructive lung disease (COPD) patient group and will be discussed later. Severe hypoxic injury results in an irreversible insult which is demonstrable histologically and is the result of irreparable cell damage.

1.1.2 Cognitive dysfunction in chronic lung disease.

Early studies by Krop et al[11] evaluated the effect of chronic hypoxia on cognitive function. They demonstrated abnormalities of motor speed and perceptual motor integration. Significant improvements in function were demonstrated by Block[12] when oxygen was administered.

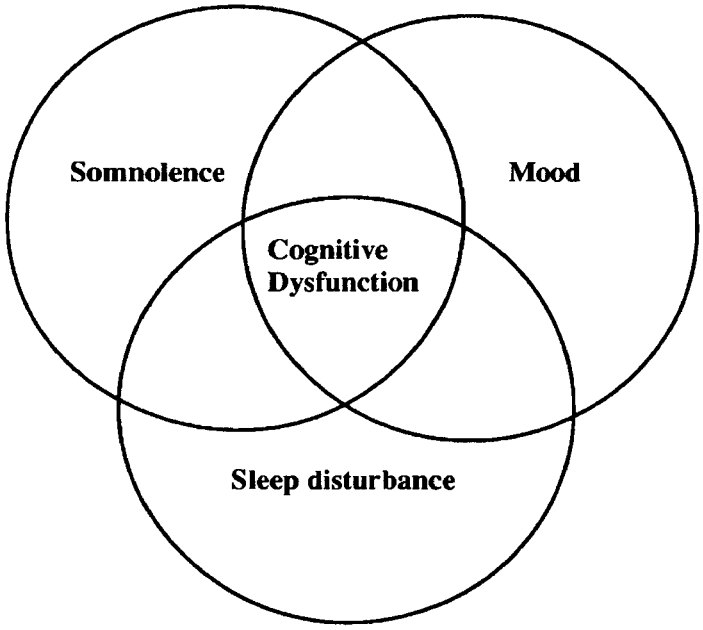
A matched control study of 203 COPD patients was carried out by Grant[13]. In the pre treatment group 42% of patients had moderate to severe test impairment in contrast to 14% in the normal group. Higher cognitive functions (abstracting ability and perceptual motor integration) were most dramatically abnormal. A significant correlation between impairment and PaO2 as well as resting oxygen saturation was demonstrated. The authors then studied the patients after six months and 12 months treatment. The treated group was subclassified into continuous and nocturnal oxygen treatment. While the groups showed similar improvements at six months, the continuous oxygen patients registered better cognitive performances at twelve months. Of note, only 42% of the total group showed modest improvement at six months suggesting a significant proportion of brain injury is irreversible in this setting.

Corroborative work by Prigatano[14] substantiated the findings of cognitive abnormality particularly those of abstract reasoning, memory and speed of performance. They, like Grant and Heaton, found statistically significant correlations between dysfunction and resting daytime levels of hypoxia.

In reviewing the available data, Berry[7] drew together these studies to conclude that clearly tests of abstract reasoning and motor speed are "sensitive to the effects of cerebral hypoxia". The level of chronic daytime hypoxia is similarly correlated with cognitive dysfunction although the level of statistical significance is lower than for the entire CAL group. This finding most likely relates to the presence of nocturnal hypoxia with sleep hypoventilation in the absence of daytime hypoxia in a proportion of the CAL patient group. Thus there is a bias in favour of a greater cognitive deficit when there is a co-existing daytime hypoxic insult, although nocturnal hypoxia alone is sufficient to generate measureable cognitive decline.

1.2 The role of non-hypoxic arousals in the genesis of cognitive dysfunction, somnolence and mood disturbance.

The inter-relationship between sleep fragmentation/deprivation, somnolence, mood and cognitive dysfunction is very complex. Each separate variable usually co-exists with one or more of the others in any given clinical scenario or research model. The following chapters (1.2.1-1.2.5) will seek to unravel the various components, analysing each relationship in turn. Given that many variables are often measured in any one study, several studies will be sub-analysed to extract the requisite data. The following diagram seeks to simplify the equations acting as an overall reference to the chapter 1.2.



1.2.1 Sleep fragmentation and cognitive dysfunction.

Early work by Bonnet [15] examined the memory for events during arousal from sleep. Fourteen patients were studied. They were aroused in both Stage 2 and slow wave sleep (SWS) and asked to perform the Williams Word Memory Task (Stage 2) and an additional maze-tracking task when aroused from SWS. This experiment demonstrated three important features. 1) Recall is significantly impaired when patients are aroused from SWS as compared to Stage 2 sleep. 2) Memory ability improves as a function of the period of wakefulness prior to the test performance. 3) Overall ability is the same two minutes post Stage 2 arousal as compared to eight minutes post SWS arousal. This work was not performed during REM sleep, but does demonstrate the importance of arousal timing to immediate cognitive dysfunction. Bonnet dubbed this effect as "sleep inertia".

In 1985, Bonnet [16] induced arousals each minute (to a level of behavioural response) in eleven normal adults. The very small amounts of SWS and REM recorded was reflective of the severity of sleep fragmentation. In this setting, the subjects performed more poorly and self ratings of somnolence increased.

Following this work Downey [17] in concert with Bonnet [18] proceeded to demonstrate the effects of arousal timing on cognitive function. Five young normal adults were subjected to sleep fragmentation over two consecutive nights at one minute and ten minute intervals and following an uninterrupted two and a half hour sleep period. A cognitive task of addition (two digits, two numbers randomly selected) was performed after each arousal. The results demonstrated that when sleep disruption occurred more frequently, cognitive inertia developed more rapidly. That is to say, the latency to problem solving from the time of arousal was greatest with the shortest interval (one minute) protocol. This effect was more pronounced on the second experimental night suggesting that the total effect may be cumulative.

This early work suggests that the timing and frequency of experimental, non-hypoxic arousal is important in the genesis of cognitive dysfunction. Supportive evidence for the role of non-hypoxic arousals was later demonstrated by Jennum et al[19] In a cohort questionnaire study of 1,670 snorers, a subgroup (n = 808) were self reported good sleepers. They demonstrated an increased odds ratio for memory problems (2.3) and concentration problems (2.5) in this group. While this may be a reasonable model for non-hypoxic arousal, only 60 patients were subjected to polysomnography (PSG) putting into question the overall validity of this study. Later work published by the same author [20] did examine the group in a more detailed manner with PSG. These subjects were then divided into those with a respiratory disturbance index (RDI) of less than five and those with an RDI greater than five. This further sub-analysis found a statistically significant difference favouring concentration problems in the OSA group. There was no difference for memory disturbance between the two groups. Analysis of this work suggests that snoring alone, over and above apnoea, may be sufficient to increase self reporting of memory disturbance and would confirm the findings of Bonnet that memory disturbance correlates with non-hypoxic arousal.

An elegant, recent study by Martin et al[21] performed a controlled study of auditory arousal (two minutely) in sixteen subjects. Of note, the intention was not to create arousal to a level of behavioural response as per Bonnet, but rather simply to induce the fragmentation of sleep that most closely mimics that of OSA. The outcome measures included those of somnolence, assessment of mood and cognitive function (Trails B and Pasat - 4 second tests). They found significant decline in cognitive function could be induced in the fragmented sleep model. This decline was best demonstrated in tasks of mental agility as opposed to those of sustained vigilance (Steer Clear). Measurements of mood and sleepiness were also significantly correlated with sleep fragmentation. This group has thus postulated that the

repetitive arousals disrupt the micro-architecture of sleep which results in a number of cognitive changes and mood disturbance.

Thus from the work of Bonnet and others, it is clear that nocturnal sleep arousal contributes to cognitive dysfunction. The timing and duration of arousal, and the stage of sleep in which they occur is also relevant. Fragmentation of sleep induces excessive somnolence and mood disturbance which may act as a co-variable in this setting and are discussed separately.

1.2.2 The relationship between non-hypoxic arousals and somnolence.

Measurements of somnolence are complex and fraught with overlapping issues. The validation of tests varies according to their clinical setting, they are numerous and there is no gold standard. It is therefore appropriate to review the current methods of measurement and subsequently their relationship to cognitive dysfunction.

One of the earliest attempts to quantify somnolence was the development of the Stanford Sleepiness Scale[22]. This self reporting questionnaire, while subjective, did correlate with sleepiness. Easy to administer, it has been used repeatedly in subsequent studies of sleepiness.

The first genuine attempt at an objective measure of sleepiness was the development of the Multiple Sleep Latency Test (MSLT)[23]. A standardised protocol of five twenty minute napping opportunities at two hourly intervals was adopted. The latency to sleep onset was time averaged to give an overall measure of sleep propensity. The finding of sleep onset REM helped to confirm the presence of somnolence and has become the standard test for the diagnosis of narcolepsy. The MSLT remains therefore, both a useful clinical and research tool. Despite these valid techniques, the indefinable nature of sleepiness has continued to plague researchers.

In a thoughtful review of the issues Dement[24] wrote "At our current state of knowledge, we can only speculate whether they {sleepiness and alertness} are two reciprocal mechanisms, or whether alertness is simply the lack of sleepiness, or vice versa".

In order to look at the inverse relationship between wakefulness and sleepiness, Sangal et al[25] performed MSLT on 258 consecutive patients. The test of sleep latency was run in concert with a new tool, the Maintenance of Wakefulness Test (MWT). The MWT directly examines the subject's ability to stay awake, rather than their sleep propensity. They concluded that indeed, the two tests were measuring different parameters and proffered their alternate tool as a useful adjuctive test. In a related article[26] the same authors examined this ability to maintain wakefulness in 47 patients with a documented sleep disorder. The subjects were tested by MSLT and MWT pre and post treatment. The investigators found a marked improvement in the maintenance of wakefulness post treatment but no treatment related change in the MSLT. Thus, they proposed that the two states of wakefulness and sleepiness represent different physiological processes. In this setting, the MWT may have more relevance if it is vigilance that is important to the subjective improvements in symptoms, and objective improvements in activities of daily living (eg driving a car) that are seen after treatment for conditions of somnolence.

Because of the cumbersome and resource consuming nature of the MSLT and MWT, subsequent authors have re-examined the use of subjective scoring tools to measure sleepiness. One of the most widely used of these is the Epworth Sleepiness Scale (ESS) [27]. A short questionnaire regarding the potential for an individual to fall asleep in circumstances of low stimulation, it has been validated by comparison to MSLT [28] and by factor analysis [29]. No comparison to the MWT has yet been performed.

In an effort to devise other objective measures of vigilance, which are easier and cheaper to perform, Findley et al[30] developed the Steer Clear Driving Test (SC). In a study of patients with OSA and narcolepsy, compared to normals matched for sex and age, they determined that the pathological group hit more obstacles. The usefulness of this test lay in the sub-analysis of automobile accident rates amongst the somnolent group when compared to normals. Impaired vigilance as measured by SC correlated with a larger number of road accidents in the group with sleep pathology. No direct comparisons between this driving simulator and the aformentioned tests of sleep propensity (MWT, ESS, MSLT) have been published to date. The importance of vigilance and vehicle accidents is discussed later.

Finally, both pupillometry[31, 32] and cerebral evoked potentials[33] have been verified as measures of sleepiness. Their expense and requirement for specialised skills has led them into disfavour as common tests of sleepiness.

Early work by Carskadon[34, 35] sought to explore the relationship between daytime function and experimental sleep deprivation. This work demonstrated the significant increase in daytime sleepiness, associated with sleep loss. At the same time, Roth[36] et al demonstrated a correlation between sleep disruption and an increased sleep tendency in a group of OSA patients and a group of normals. Corroborative animal work using a dog model [37] demonstrated that experimental sleep fragmentation (generated by a response to hypoxia and hypercapnia) would also decrease subsequent nap latencies.

Based on this earlier work, the relationship between non-hypoxic sleep arousal and subsequent somnolence was explored by Stepanski et al[38]. In a study of 55 patients, 4 subgroups were analysed. Insomniacs (n=15), OSA patients (n=15), patients with periodic limb movement (n=15) and normals (n=10). The authors developed an arousal scoring system, based upon EEG and EMG criteria. The levels of arousal

were stratified according to the degree of sleep disruption, from an increase in EMG or EEG frequency (level 1) to an awakening from sleep (level 4). The study demonstrated a small correlation between the total arousal index and daytime sleepiness (MSLT). This correlation was evident in the PLM and OSA groups only and accounted for 21 - 33% of the variance. Of more importance was the relationship between the level of arousal and somnolence. Indeed, level 1 and 2 arousals (ie those of a lesser magnitude and shorter duration) correlated best with Excessive Daytime Somnolence (EDS). These lower order arousals also occurred in greatest frequency. They surmised that in the EDS group (OSA and PLM's) short arousals are more important in predicting the sleepiness index.

In 1987 Levine et al[39] examined the effect of experimentally induced arousal (by auditory tone) and EDS in 40 normal subjects. One night of sleep deprivation was followed by a further night of sleep deprivation or arousals at 12 second, 20 second or minutely intervals. Somnolence was measured by MSLT subsequent to the experimental night. These investigators demonstrated an inverse linear relationship between the rate of arousal and the mean sleep latencies. This work suggests, therefore, the rate of arousal is probably as important as the level.

Guilleminault et al[40] examined the role of non-hypoxic arousals (snorers without desaturation) and somnolence in a study of 15 men. Although the MSLT's performed pre-treatment with CPAP were within the normal considered range ($\geq$ 10 minutes) there was a very significant improvement post-treatment. Although levels of sleepiness in this patient group were not within the reported pathological range for the MSLT, the increase in sleep latency with control of sleep disordered breathing suggests that somnolence was present but at sub-clinical levels. This study indirectly confirms the role of non-hypoxic arousals in the genesis of somnolence.

An experimental model of sleep fragmentation devised by Roehrs et al [41] explored the role of auditory arousals and the relationship to daytime sleepiness (MSLT). Unlike the Levine model, arousal was not to a level of behavioural awakening, more closely mimicking the type 2 arousals of Stepanski. They demonstrated a correlation between significant disruption and heightened somnolence. The same authors also demonstrated that a greater number of tones of longer duration were necessary for arousal from SWS as opposed to Stage 1 or 2 sleep. This work suggests that an increased stimulus is required for a similar level of arousal between different sleep stages and thus the rate (as per Levine) as well as the stage of sleep may be important.

In order to confirm this finding and to explore the question as to whether sleep stage is important, Martin et al[21] performed a similar sleep fragmentation study. Experimental sleep disruption was produced at two minute intervals by auditory tone. The end point being a three second or longer return to alpha or theta activity. Excessive somnolence was confirmed by both measures of wakefulness (MWT) and sleep latency (MSLT). Arousal frequency was the best predictor of EDS by multiple regression analysis. The percentage of SWS was the best predictor of sleep onset latency on the MWT, but was only of statistical significance in the last two nap periods. In other words, increasing amounts of SWS prolong the latency to sleep onset, possibly by relieving sleep pressure on the day following a night of fragmented sleep. Earlier, but unrelated work, by Bonnett[42] confirmed that virtually eliminating SWS (occasional epochs of stage3 only) in normals did not increase sleepiness. The combined analysis of these two studies suggests that SWS is of value in reducing sleep propensity, but its absence does not infer that excessive daytime sleepiness will be present.

Thus, experimental data supports the notion that an increase in non-hypoxic arousals correlates with an increase in daytime somnolence. The frequency of the arousals is

probably the best predictor of the magnitude of subsequent sleepiness. Contrary to what one might expect, in adequate numbers, arousals of lesser magnitude will more reliably generate somnolence. A greater arousal threshold is evident in SWS versus stages 1 and 2 sleep, but the placement of arousals into either light or slow wave sleep is not as important as the total degree of fragmentation.

1.2.3 The relationship between somnolence and cognitive dysfunction.

This chapter will seek to explore the fundamental relationship between sleepiness and performance. Much of the current data relates performance to measures of artificial or pathological sleep fragmentation. This has been discussed previously. In order to look at the effects of somnolence alone as a separate cause for cognitive dysfunction, one must examine models of sleep deprivation or acts of nature e.g. narcolepsy in which there is excessive daytime somnolence unrelated to arousal.

Early work by Carskadon[34] demonstrated that sleep loss on two consecutive nights would significantly alter performance on the Wilkinson Addition Test and Serial Alternation Task. In later work by Bonnet[43] similar findings with respect to immediate recall and reaction time were demonstrated in 36 subjects totally deprived of sleep for 64 hours. Furthermore, the recovery time for older patients (55 - 71 years of age) was the same as the their younger matched controls.

Subsequent work by Bonnet[44] demonstrated that performance (computer administered testing) and alertness improved in a dose response manner to the length of the 'prophylactic' nap period preceeding two consecutive nights of sleep deprivation. In addition, he demonstrated that no nap of any duration could reverse the loss of alertness and function during the second night of sleep loss.

A proposed mechanism for cognitive decline with sleep deprivation was demonstrated by McCann[45]. In a study using 40 healthy volunteers, the group were randomly allocated to total sleep deprivation (TSD) or 40.5 hours of rest. These groups were further randomised to placebo or 2 days of treatment with alpha-methyl-para-tyrosine (AMPT) a catecholamine synthesis inhibitor. This group of investigators measured cognitive function by a computerised test battery. The study demonstrated that the group with both sleep deprivation and catecholamine inhibition were substantially more impaired than the control groups. They hypothesized that the cognitive impairment arising from sleep deprivation was possibly mediated by brain catecholamines.

In 1994 How[46] and Foo[47] demonstrated abnormalities in cognitive and perceptual skills after approximately 30 hours of total sleep deprivation. They demonstrated no threshold for manual tasks or sleepiness (Stanford Sleepiness Scale). This experiment not only confirmed previous work but now sought to determine a 'break point' for the development of cognitive impairment. One wonders if this is the threshold for catecholamine synthesis in the absence of a recuperative nap, although this hypothesis remains speculative. Work by Lorenzo[48] in 1995, demonstrated that there was a linear relationship between the length of sleep deprivation (baseline to 40 hours) and the increase in a reaction time test. This correlated with a linear increase in EEG theta wave activity, a measure of increased daytime somnolence.

Further to the 'break-point' hypothesis, Dotto[49] in a review article described "vulnerable windows" during which learning and memory are impaired by sleep loss. Dotto summarised the cumulative understanding to-date which demonstrated that memory required to perform cognitive procedural tasks is affected by specifically inducing REM sleep deprivation. Declarative memory (memory for specific facts) is not similarly affected.

Thus, it would seem that increased somnolence, induced by sleep deprivation and possibly mediated by catecholamine synthesis, can give rise to cognitive dysfunction. The nature of the cognitive abnormality relates not only to the length of TSD but probably also to the kind of sleep which is lost. This finding is supported by the very large meta-analysis of Pilcher[50]. Their mathematical summation of 19 previous studies found good evidence that overall sleep deprivation strongly impairs cognitive function. Of note, they found that partial sleep deprivation(less than 5 hours sleep/24 hours) was worse than short or long term sleep deprivation, a finding which has ramifications for the OSA patient group.

Using the narcolepsy model of EDS, Aguirre[51] demonstrated subjective memory problems in a group of 10 untreated narcoleptics compared with 10 matched controls. However this author found there was no objective difference when the group was formally measured by psychometric battery. The authors surmised that the subjective abnormality related to irrepressible somnolence during testing rather than to a true organic memory deficit. Subsequent work by Mitler[52] demonstrated improved performance (to normal levels) in narcoleptics given large doses of stimulants. This work, contrary to that of Aguirre, demonstrated the effect of alleviating somnolence on cognitive function and may be reflective of a different psychometric methodology in this study group.

Thus, the narcolepsy model, although not as well studied as sleep deprivation would also lend credence to the strong relationship between somnolence and cognitive impairment.

1.2.4 The relationship between non-hypoxic sleep fragmentation, sleep deprivation and mood.

There is little data in the current literature that has looked specifically at the effect of sleep fragmentation (ie. disruption without sleep loss) on mood and personality. Most of the work has focused on other outcomes, such as cognitive dysfunction or somnolence, measuring mood changes in passing. Much of this literature has been reviewed in the preceding chapters, thus the findings with respect to mood will be summarised. The specific relationship between the arousals of OSA and mood will be discussed separately.

In 1985 Bonnet[16] demonstrated that severely fragmented sleep, with only one hour loss of normal total sleep time (TST) was sufficient to elicit statistical abnormality on the Clyde Mood Scale. Of note, the strongest subjective ratings were for sleepiness (in the morning) with difficulties with respect to clear thinking and increased unhappiness rating higher in the evening. Similarly, Martin et al [21] demonstrated abnormalities in hedonic tone and energetic arousal scores in their subjects following the sleep fragmentation night.

Several studies [53-58] have demonstrated the negative impact of sleep deprivation on the mood of hospital resident staff. The majority of these studies involved a sleep period of less than 4 - 5 hours in 24, although the lack of polysomnography in some, and the unreliability of using diaries in at least one of these studies [58] makes the assessment of TST questionable. A recent paper by Richardson [59] demonstrated that in the Intern model, their subjects were chronically sleep deprived. This was reflected in the presence of daytime micro-sleeps following control nights when they were not on-call. Thus, the value of much of the previous data should be set in the context of abbreviated sleep, possibly with a background of chronic sleep debt.

Indeed, Pilchers[50] review demonstrated only 6 studies of partial sleep loss that were of sufficient calibre for analysis.

The meta-analysis by Pilcher[50] is the most comprehensive assessment of the data to-date. The most striking abnormality being the comparative effects of short term, long term and partial sleep loss on mood outcomes. Short term was defined as less than or equal to 45 hours of sleep deprivation. Long term was defined as greater than 45 hours of sleep deprivation and partial sleep deprivation being less than 5 hours sleep in a 24 hour period. They determined that, on average, the subjective mood ratings of sleep deprived individuals were 3 standard deviations worse than controls. In addition, the effect of partial deprivation was far greater than that demonstrated for short or long term deprivation.

One can surmise that certain mood changes are more than likely to be a function of sleep loss and are reflective of the type of insult. Despite Bonnet's study [16] which all but eliminated SWS and demonstrated mood changes, there are no data looking at which changes in sleep architecture are related to specific changes in mood. The same is not true for patients presenting with mood disorder, i.e. depression, about which much is known with respect to disorders of sleep These associations are explored in the following chapter.

1.2.5 Depression and cognitive dysfunction.

Recent neurophysiological studies have been performed in patients with depression in an effort to examine whether there is a measureable electrical delay to account for the cognitive inertia which characterises clinical depression. Using the P300 component (late component) of the event-related potential (ERP), patients were examined for reaction-time and task accuracy during an auditory discrimination task. These physiological studies by Sara[60] demonstrated that there is no measurable

difference for the event-related potential (ERP), between depressed patients and normals. This study documented poor task performance in the depressed group, although clearly this was not thought to be a function of synaptic delay.

It has been demonstrated by Hubain[61] that the amount of SWS and the REM latency are reduced in exogenous and endogenous depressed patients versus controls. Furthermore, when REM latency is dichotomised at 50 minutes, there is a measurable difference between endogenous versus reactive depression with statistically more endogenously depressed patients having a REM latency below 50 minutes. These physiological sleep variables in depressed adolescents have been reproduced in work by Dahl et al[62], who also found dysregulation near sleep onset to be a psychobiological change in early - onset depression.

The relationship between cognitive dysfunction and depression has been well studied although the cross-over with dementia often makes this difficult. To ascertain whether cognitive decline is an inevitable function of depression or is specific to a subgroup of depressed patients,. Brown[63] examined cognition in 29 patients. Global function was measured, the group was normally distributed, and then divided into unimpaired, borderline or impaired. This was done so as to examine depressed unimpaired patients (ie. those at the statistically 'normal' end of the depressed range) with normals. The model also allowed examination of the gradient of specific abnormality across the three functional categories. The major findings were that the unimpaired depressed group when compared to a non-depressed control group demonstrated significant deficits including language function, memory (recall and recognition) as well as attention and behavioural regulation. This suggests that even at the 'normal' end of the depressed range patients are dysfunctional. Furthermore, there was a gradient of dysfunction across the three groups with measureable differences in immediate recall, behavioural regulation and attention. These

abnormalities of cognitive dysfunction in depression are confirmed by the work of others [64-70].

Finally, Perlis et al[71] demonstrated a correlation between sustained facial muscle activity (as measured by sleep EEG) in REM sleep and the severity of depression measured by the Beck Depression Inventory (BDI). The authors hypothesised that dysregulation of arousal mechanisms in REM sleep may promote mood disturbance, at least during the depressive episode - a finding of great relevance to the OSA patient group.

The relationship between cognitive dysfunction and sleep disturbance may therefore be augmented by the development of depression secondary to sleep loss or fragmentation as demonstrated in chapter 1.2.4. Depression itself, either as an end point of sleep abnormality or as a disease state in its own right, may further impair cognition and must be considered as an important co-variable in any work that relates sleep to measures of intellectual function.

1.3 The links between OSA and cognitive dysfunction.

This chapter will attempt to detail the studies which to-date have examined cognitive dysfunction in OSA. The specific findings of each study will be further analysed in an effort to examine the inter-relationships between hypoxia and arousal as well as mood and sleepiness in this patient group.

1.3.1. A review of previous studies and a summary of their findings.

The earliest studies of cognitive impairment were reported in 1985 by Kales[72] and Yesavage[73]. Kales examined cognitive parameters using the Bender Gestalt Test and Wechsler memory Scales. This work also included measures of personality (MMPI - Minnesota Multiphasic Personality Inventory) and the Symptom Distress Check List (SCL-90-R). They studied 50 patients with disease of sufficient severity to warrant tracheostomy. They demonstrated mild to severe deficits in thinking, perception, memory and communication in 76% of the patients. Additionally, they found abnormalities in new information learning. Unfortunately they did not define the magnitude of the hypoxic injury or the severity of sleep fragmentation. Thus, while demonstrable abnormalities were detected, the lack of PSG correlates renders the study largely observational. It did however, confirm the previous findings of Guilleminault[74] in a 25 case review in which 60% of patients reported difficulties with attention and concentration.

In the same year, Yesavage et al published an analysis of 41 non demented male subjects with a mean age of 69.5 years. Their test battery included tests of verbal and visuo-spatial reasoning, memory and psychomotor speed. They proceeded to calculate the RDI (including obstructive apnoeas, hypopnoeas and central events), however no oximetric data was recorded. They found a correlate between increasing

RDI and poorer performance, but did not assess the magnitude of hypoxia or the distribution of respiratory events in non REM versus REM sleep.

The association with hypoxia was first explored by Findley et al[75], and later by Greenberg et al[76]. Findley demonstrated abnormalities in attention and concentration as well as complex problem solving and short term memory. Greenberg assessed similar skills finding deficits of motor and perceptual organisational ability. The detail of the relationships to hypoxia are discussed later.

Telakivi et al[77] in a study of 46 habitual snorers, found abnormalities in short term memory (recall of logical stories of the Wechsler memory scale) even when the group was adjusted for age and obesity. The authors concluded that the degree of sleep fragmentation and excessive daytime somnolence were the main causes of memory dysfunction with mild hypoxia. Unfortunately the cognitive battery was administered on the evening prior to the assessment of sleep making this relationship less valid. Previous work by Schneider-Helmert[78] had also suggested that morning assessment is more sensitive than evening testing (at least in insomniacs). No direct causal relationship between the polysomnographic results and cognitive function can be made in the circumstance where preceding total sleep time or efficiency were not calculated.

In a more organised study, Bedard et al[79] administered a daytime neurocognitive battery preceded by a night of PSG and followed by a second night of sleep study. Of note they studied only 20 patients (10 severe and 10 moderate apnoeics) and compared them to 10 normal controls. They measured somnolence by MSLT. The patients were not randomly selected and the severity of their disease was known to the test administrators. This design flaw is important to note given the potential bias in test performance secondary to the manner of administration. That is to say, it is possible to administer or score a cognitive test in such a way as to, in part, determine

the outcome. Despite this, the data set is useful in demonstrating progressively increasing deficits from moderate to severe patients in tests of attention, immediate and delayed recall, visual learned material, planning and sequential thinking and manual dexterity tasks. There is no indication of the impact of more mild disease with the emphasis in analysis looking primarily at the effect of hypoxia without accounting for arousal. The independent effect of somnolence (while measured) was not considered and there was no measurement of mood. The cognitive results were 'normed' within each group, and then compared by post hoc testing, without a global measure of cognitive ability being considered for each individual. Thus while demonstrating many features of cognitive dysfunction, the manner of analysis and the size of the groups makes reference to the general sleep apnoea population difficult.

In 1992, Cheshire et al[80] undertook a study of 29 OSA patients in an effort to explore the relationship between arousal, hypoxia and cognitive impairment. The data with respect to arousal will be discussed separately. They measured somnolence by MSLT and the partial effects of mood were controlled for in the analysis. Unfortunately the MSLT did not immediately follow the PSG so the validity of the somnolence data cannot accurately be analysed. Furthermore, the cognitive battery was administered on a day subsequent to the PSG, when again the test administrator would have had prior knowledge of the disease severity. Additionally, direct correlations to the magnitude of hypoxia and arousal and subsequent cognitive dysfunction are deemed indirect given the night-to-night variability of total sleep time and RDI in any individual. Despite these flaws, the data confirmed the finding of the previous authors with respect to abnormalities of problem solving, visuo-spatial organisation, sustained attention, response speed and visuo-motor co-ordination. The small sample size and the other design problems again make it difficult to define cut-offs for how much apnoea is required to confer a risk ratio for cognitive impairment, other than to determine that it is present and measurable.

Telakivi[81] studied 31 consecutive patients who were being evaluated for presumptive OSA. They excluded 7 patients leaving only 24 subjects for analysis. A battery of tests, predominantly designed for dementia and neurological disease was administered. No correlation was found between any of the test battery and measurements of arousal or hypoxia. While this study does not confirm the work of others, it does demonstrate the difficulty of cognitive testing in OSA and the need for the correct tools to elicit pathology - namely tests for sustained concentration and attention.

Jennum and Sjol[20] in a large epidemiological study of 1504 adults, demonstrated elevated odds ratios for the correlations between snoring and concentration (OR = 1.9) as well as snoring and memory problems (OR = 1.58). Additional evaluation of patients with OSA (RDI $\geq$ 5) demonstrated even greater odds ratios for concentration (OR = 3.53) and an equivalent ratio for memory problems (OR = 1.51). This study confirms the subjective awareness of cognitive dysfunction in the sleep disordered breathing group. Unfortunately only half the group had polysomnography, which was performed by modified domiciliary PSG without oximetry. No objective measures of cognitive dysfunction were performed.

In a later study by Naegele[82] a small group (n = 17) of OSA patients, were compared to a group of matched controls. The neurocognitive battery focused particularly on frontal lobe function. The tests were administered on the evening following polysomnography whereupon the RDI had already been determined and the patients categorised according to severity and the magnitude of the hypoxic injury. These authors found memory deficits related to the number of apnoeas/hypopnoeas per hour, while the frontal lobe abnormalities correlated with the magnitude of the hypoxic injury. Their numbers were small and the test battery specific. Again,

sample size does not permit broader reference to the OSA group and no relationship between graded severity and increasing dysfunction can be demonstrated.

In summary, all of the documented studies (bar one) have found evidence of cognitive dysfunction related to sleep disordered breathing, despite design flaws and in some cases small numbers. The relative contributions of hypoxia and arousal are often contradictory and difficult to assess. The following chapters will attempt to interpret the aforementioned data sets in an effort to highlight these relationships.

1.3.1.1. Supportive evidence for the role of arousal in the genesis of cognitive dysfunction in OSA.

Findley et al[75] used a rudimentary arousal scoring system to assess the relationship between sleep fragmentation and cognitive function. The authors defined awakenings (30 seconds or longer) between two 30 second epochs of sleep as an arousal. Additionally, a movement arousal was defined as 15 seconds or less of alpha activity again between two sleep epochs. Movement was associated with increased electromyogram (EMG) activity. No relationship to upper airway events was defined in this unique arousal scoring system. The total arousals were compared by unpaired t-testing between patients with hypoxia and those with normoxic polysomnography. The differences between the two groups was not statistically significant. They found no correlation between sleep fragmentation and cognitive dysfunction. However, the similarity in overall arousal scores between the 'hypoxic' and 'non-hypoxic' groups may well have buried a correlation between arousal only and cognitive outcomes, since both groups had equivalent sleep fragmentation. Furthermore, the definition of arousal is non-standard and was not analysed by level or sleep stage.

Telakivi et al[77] reported an abnormality in a spatial orientation test (Clock test) in habitual snorers. The authors concluding later[81] that fragmentation without desaturation may therefore be important in the development of cognitive dysfunction. Unfortunately they did not analyse the data according to standard criteria, choosing instead to calculate the periodic breathing index (PBIf), defined as the mean number of drops to zero level per hour in the respiratory graph. Oximetry was used to calculate the mean number of drops exceeding 4% (DESA 4). The conclusion was drawn from the group with low DESA 4 scores and elevated PBIf scores. That is to say, those with numerous respiratory events without significant desaturation. Unfortunately, while EMG/EEG data was collected, the authors failed to define sleep arousal so any true measure of sleep fragmentation can only be extrapolated from the non-hypoxic snoring group.

In an effort to better define arousal, Cheshire[80] used the conventional criteria of Rechtschaffen and Kales[83]. An arousal was defined by a 1.5 second return to alpha or theta rhythm associated with an increase in EMG tone of any duration. This tighter definition found correlations with the Block Design Test, Simple Reaction Time and a decrement in IQ. Of note, when entered into multiple regression the apnoea/hypopnoea indices (AHI) and the lowest oxygen saturation acted as strong co-variables. Inversely, the correlations between AHI and lowest oxygen saturation versus the decline in IQ were not improved by the addition of the arousal index to the multiple regression matrix. The numbers in the study were small (n = 29) and the patients were preselected for an AHI $\geq$ 15. Thus, much of the independent effect of arousal is likely to have been overwhelmed by the preponderance of respiratory events associated with desaturation.

Using a different sleep model, that of older (mean age 64.6 years) insomniacs, Stone et al[84] demonstrated that when the severity of sleep disruption is controlled, there are minimal differences between mild - moderate OSA sufferers and those without

sleep disordered breathing. They calculated sleep efficiency which was diminished in all patients (TST < 5 hours) and defined arousals as those of greater than 15 seconds duration or awakenings of greater than 5 minutes. While the conclusion is supported by analysis of the data according to their criteria, there was no control group with normal sleep time and sleep efficiency. Indeed, much of the power of the study is diminished by the probable effects of sleep deprivation across the entire study group.

Thus, cognitive deficit relating to sleep fragmentation in OSA has been demonstrated in previous work. The major problem in analysing the data probably reflects small patient numbers in some studies and the selection of more severe apnoeics in whom the relative addition of moderate hypoxia makes the input of arousal alone difficult to analyse. There is little standardisation of arousal scoring across the literature, and few studies have attempted to model out the effects of somnolence and mood as co-variables.

1.3.1.2. The role of hypoxia in the genesis of cognitive dysfunction in OSA.

The early work by Findley[75] examined correlations between hypoxia and cognitive outcomes, comparing two groups both with nocturnal desaturation. One group demonstrated co-existing daytime hypoxia (PaO2 63+/-3 mm Hg - defined as the 'hypoxic group), the other had normal resting daytime gas exchange ('non-hypoxic'). Subanalysis of the whole patient group reveals that, in fact, all the patients had moderate to severe OSA (defined as 4% or greater desaturations per hour). The 'non hypoxic' group had 43+/-5 events per hour sleep and the 'hypoxic' group had 86+/-14 events per hour sleep. The 'hypoxic' group were substantially heavier (BMI = 47+/-4) and would most likely represent patients with concomitant Obesity Hypoventilation Syndrome. No control group was used. The authors demonstrated correlations between the median SaO2 and awake PaO2 to overall cognitive

impairment. They failed to demonstrate a correlation between sleep fragmentation and cognitive impairment in this study. One would suggest that the patient selection bias in favour of more severe hypoxia most likely overwhelmed any subtle changes brought about by arousal alone.

The later work by Greenberg et al[76] endeavoured to examine the same relationship using 14 patients with OSA, a control group of 14 normal volunteers and a group of patients with excessive daytime somnolence (EDS) but without OSA. The non OSA EDS group included 4 patients with nocturnal myoclonus, 5 non-cataplexic narcoleptics, and 1 patient with Idiopathic Hypersomnolence. Furthermore, the subjects were independently assessed by a neuropsychologist blinded to the patient diagnosis with controls for age and level of education being considered. In this study of only 10 matched subjects, they demonstrated correlations between tests of perceptual organisation (block design) and bilateral motor speed (peg board) and the hypoxic variables - lowest saturation and total time not breathing. They were unable to demonstrate similar correlations between hypoxia and global cognitive scores - perhaps a reflection of their small numbers and the unusual methods of defining hypoxia. No measure of arousal was included in the analysis although measures of sleep latency, efficiency and percentages of sleep time were assessed between the two groups. Further subanalysis shows that both the somnolent groups (EDS only and OSA) performed many tests more poorly than the 14 normal volunteers. Unfortunately, their objective analysis of somnolence (MSLT) was incomplete in 3 EDS patients, and a number of Stanford Sleepiness Scales were similarly poorly completed and not evaluated in the analysis. An interesting observation was made when the 3 EDS (without MSLT) patients were compared to the EDS control subjects who had performed the MSLT. Those without MSLT performed more poorly. The practice of administering a cognitive test battery following MSLT should be considered with caution. It is likely that the naps would decrease sleep pressure and possible improve performance as the co-variable of sleepiness is diminished.

In 1991 Bedard et al[79] demonstrated that indeed vigilance acted as a co-variable with nocturnal hypoxia in the genesis of cognitive dysfunction. They performed the test battery over the course of the day, interspersed with MSLT naps and the performance of the Four Choice Reaction Time Test (FRCTT) as a measure of vigilance. They defined the hypoxic variables in two ways. 1) The lowest saturation during total sleep time. 2) The percentage of total sleep time with a saturation below 80%. This secondary criteria was then used to divide the groups into OSA with more than 5% TST (with a saturation below 80%) and those with less than 5% TST (saturation below 80%). This arbitrary division into moderate or severe does not include any measure of sleep fragmentation, indeed arousals scores, if measured, are not reported. The data demonstrated that global intellectual function, shifting and constructive abilities were impaired only in the severely hypoxic group and related to the magnitude of the insult. While the study demonstrates clear abnormalities at the more extreme end of the hypoxic range, insufficient numbers make linear relationships and cut-offs difficult to extract from the data. Additionally, there is no physiological basis for the selection of 80% saturation proposed by the authors. A lesser cut-off may have yielded more subtle change. Of note, the same authors in a different article[85] proceeded to analyse the data from a 20 subject group studied via identical means. In this analysis they determined hypoxia as the percent of sleeptime with a saturation below 90%. They also used a rudimentary arousal score, measured as the number of awakenings. They determined that measures of hypoxia were the best predictors of daytime alertness (FCRTT) and sleepiness (MSLT). Furthermore the FRCTT is sensitive to the number of awakenings. No formal cognitive tasks are included for analysis in this revised model.

Later work by Cheshire[80] confirmed the relationship between the magnitude of hypoxia and cognitive impairment. Again, they used the lowest SaO2 as one parameter of hypoxia, the other defined as the number of 4% desaturations per night

(AHI). They demonstrated, by multiple regression, that the lowest oxygen saturation and the AHI were independently associated with IQ decrement and respectively accounted for 38% and 31% of the variance.

A more recent study by Naegele[82] defined hypoxia as the cumulated time with a saturation less than 85%. The physiological reason for this cut-off proffered by the authors was that it had been derived from previous cognitive studies of function at altitudes over 8,000 metres and in patients with COPD. RDI was defined in the standard manner. The cognitive battery was specifically designed to detect several frontal lobe deficits. Indeed, analysis of the data by regression techniques demonstrated abnormalities in tests of initiation of new mental processes and a lack of ability to inhibit automatic processes of thinking, in the OSA group as a whole. More specifically they demonstrated a prominent abnormality in the Wisconsin Card Sorting Test related to the severity of hypoxaemia. This abnormality thought to be a test of "abstract of behaviour" and "shift of set"[86] suggests that a frontal lobe-type deficit may be related to hypoxic injury in OSA.

Thus, it is evident from the literature to date that cognitive impairment is measurable in OSA and correlates with the degree of hypoxic injury. Although many of the studies involved only small numbers and the magnitude of the hypoxic insult was often arbitrary, the body of supportive evidence for the role of hypoxia in cognitive dysfunction in OSA remains firm. The co-variables, somnolence and arousal, have been in part addressed but remain to be explored in conjunction with hypoxia in sufficient numbers of patients such that they may be independently evaluated.

1.3.2. The role of OSA in the genesis of daytime somnolence.

Excessive daytime somnolence has long been a key pointer to the possible diagnosis of OSA. It is a disabling symptom which often co-exists with a decline in quality of life measures in these patients. Subjective estimation of somnolence in this patient group is often inaccurate[87] as the patients, overwhelmed by somnolence, lose their frame of reference for alertness. Such measures as the Stanford Sleepiness Scale (SSS) may therefore prove inaccurate (compared to objective measures eg. MSLT) in determining the magnitude of sleepiness in OSA. Of note, such subjective tests remain highly correlated with objective measures in normals[22, 88]. Thus, it is particularly important to assess the method used for measuring somnolence when looking for sleepiness in the OSA group.

In an early study of somnolence in OSA, Roth et al[36] performed MSLT on 10 patients with sleep disordered breathing and 10 normal controls. Sleep stages and respiratory events were scored according to R & K criteria. The mean number of apnoeas for the OSA group ranged from 28 - 91 per hour. Arousals were scored as shifts to Stage 1 sleep or as an "arousal subsequent to respiration" (ASR). The results of the MSLT reflected increased somnolence in the OSA group (2.6 minutes latency) versus normals (12.9 minutes latency). Of note, the OSA groups' subjective rating (using SSS) was the same as the normal group. This clearly demonstrates the discrepancy between subjective and measured somnolence, in a moderately severe patient group. Further analysis of the data demonstrated a correlation between the frequency of arousals and a decrease in sleep latency in normals, a relationship which was not similarly demonstrable in the OSA group. Indeed, the authors found no correlations between any of the measured sleep variables (TST, minutes with sat < 85%, no. of events below 85%, no. apnoeas per hour TST, length of apnoeas) and the sleep latency. The only association determined was that the greater the ASR, the shorter the latency to Stage 2 sleep.

In summary, they found that the brief arousals following the end of an apnoea correlated best with the latency to Stage 2 in the MSLT. In normals, shifts in stage of sleep to stage 1 correlated with both stage 1 and 2 latency in the MSLT. Thus, while apnoeic patients are measurably more somnolent, the exact cause of somnolence is ill-defined and the subjective tool of measurement, SSS, was insensitive. Additionally, there was a poor correlation between SSS and MSLT in this study.

Later work by Sink et al[89] examined EDS and measures of impaired respiration in an effort to define the relationship further. In a study of 37 elderly patients, they performed polysomnography and administered a battery of self assessed psychological variables (Beck Depression Inventory, Geriatric Depression Scale and SCL-90). They also used a non-standard questionnaire to measure somnolence. Of note, the authors found that the number of desaturations below both 90% and 80% were able to discriminate between the self reported 'somnolent' and 'non-somnolent' groups. They did not find any correlation between the RDI or the number of arousals per hour and measures of somnolence. The finding of a relationship between the degree of hypoxia and the self reporting of somnolence, is supported by the work of Timms et al[90] who calculated that the lowest SaO2 accounted for 22% of the variance in MWT in OSA. In this study, the RDI accounted for only 14% of the variance in MWT. It is important to note the discrepancy with the work of Roth when vigilance rather than sleep propensity is assessed with respiratory variables.

Work by Sangal et al[25] demonstrated that while the MSLT and MWT correlated (coefficient 0.41) this is not a simple relationship and accounted for less than 17% of the variance. In work by the same authors[26] there was no demonstrable difference in MSLT in 26 OSA patients when compared pre and post treatment. However, the same group showed improvements in MWT. Unfortunately, this work did not

include evaluation of sleep parameters to better define which features of sleep disordered breathing (SDB) correlated best with MWT or MSLT respectively. Furthermore, there was no analysis of the post treatment group to retrospectively analyse which improved parameters of respiration may possibly have contributed to the improvement in somnolence.

In a more recent article by Verstraeten[91] 26 apnoeics were compared to 22 insomniacs. Following PSG, morning alertness was assessed by the FCRTT (four choice reaction time test - a test of vigilance). The investigators performed forward stepwise multiple regression analysis to attempt to explain morning alertness in OSA. They found that the percentage of slow wave sleep and to a lesser extent REM sleep, contributed to morning alertness. The less the percentage of slow wave sleep and REM sleep, the lower the morning alertness.

Thus it would seem that both hypoxia and disruption of sleep architecture in OSA contribute to daytime somnolence. The insensitivity of the techniques for measuring sleepiness often hinder the process of analysis and much about the effects of treatment remains unanswered.

1.3.3 The role of OSA in the genesis of mood disturbance.

Early work by Kales et al[72] assessed personality scales (MMPI) in 48 OSA patients and a group of 80 sex and aged matched controls. The study demonstrated a predominance of the "somatic-neurotic" type traits with the highest scales for hypochondriasis, depression and conversion hysteria. The same groups were administered the SCL-90-R (a self reporting clinical rating scale for psychopathology). Similar findings of depression and somatisation were evident. No correlations between the severity of psychopathology and measures of hypoxia or arousal were assessed.

Cheshire[80] using the Hospital Anxiety and Depression Scale (HADS) found 7 of their 29 OSA patients met the criteria for clinical depression. A further 5 patients of the 29 were considered at risk for clinically significant levels of anxiety and depression. Although the high rate of mood disturbance confirmed the work of others[92, 93] no direct correlates with measures of hypoxia or arousal were examined.

In contrast to the aforementioned studies, Cassel[94] reported a study of 76 OSA patients and 30 matched controls who were assessed by Freidberger Personality Inventory (FPI-R). This is a self evaluation of 12 personality traits and of note only 2 of 138 items are embedded with sleepiness co-variables. The questionnaires were completed prior to polysomnography to avoid bias. There was no detectable difference between the patient and control groups. Even when a subgroup of severe OSA sufferers (AI > 40) were analysed, no difference was seen. It was the contention of this author that assessment of depression in patients with reduced alertness should include the contribution fatigue makes to the elevation of depression scores.

Further to this work, Gall et al[95] in a study of 42 males, referred for assessment of snoring, demonstrated that although many measures of psychological testing in mild apnoea (AHI 8.7 +/- 5.5) were abnormal, they were still within the normal range. Although, even at low levels of sleep apnoea, there were measured abnormalities of quality of life (QOL). The QOL changes were characterised by greater sickness-related behaviour impairment, poorer psychological adjustment to illness and lower functioning due to health. Again, although the authors suggest that these abnormalities are related to the primary sleep disorder, no specific mechanism is postulated.

Additional information from the Dan-MONICA II study[20] emphasised that it is the abnormalities of concentration and memory that are associated with the tendency to morning depression. This suggests that the relationship between sleep disordered breathing and changes in mood may not be direct and may reflect a measure of poorer self asessed function and therefore lower self esteem.

Finally, a recent study of Swedish obese subjects[96] sought to examine whether OSA had an independent effect on psychosocial morbidity, over and above that of obesity alone. Multivariable analysis between two groups of 'high' and 'low' likelihood OSA (on questionnaire data) were performed. The authors demonstrated that either OSA, or frequent sleepiness or both, were independent predictors of divorce rate, self-rated general health, amount of sick leave and impaired work performance. No relationship between the severity of OSA and the risk of psychosocial disruption was reported although it appeared to be accentuated in women with OSA.

In summary, many studies have found correlations between the presence of SDB and alterations in mood. Even at low levels of OSA there is demonstrably more self reporting of poor general health status. No clear causal relationship between this finding and measures of hypoxia, arousal or sleep architecture have to-date been demonstrated. Furthermore no dose-response data is available.

1.3.4 The effect of OSA on driving performance.

In 1988, Findley et al[97] compared the driving records of 29 OSA patients and 35 normals. The authors demonstrated a seven-fold increase in motor vehicle accidents (MVA) in the OSA group. The percentage of persons having one or more accidents, for which they were responsible, was also greater in the OSA group. 24% of the OSA patients reported falling asleep once per week while driving. This early study did not directly correlate severity of apnoea (hypoxia or arousal) or measures of

somnolence, with the rate of MVA's. Although descriptive, this study did herald the need for more research.

Findley et al[98] then proceeded to further unravel the relationship using a driving simulator in a laboratory controlled study. They compared 6 untreated severe OSA patients with 7 normal controls. Using the Doron Driving Simulator (film projector, simulator car and driving analyser) they demonstrated statistically more obstacle collisions in the apnoea group. There was also a statistically demonstrable improvement after nCPAP therapy. No correlations were reported for hypoxic variables, number of arousals, and the number of collisions.

A 1993 study by Flemons et al[99] using another driving simulator (Steer Clear) to examine for possible relationships between the magnitude of OSA and the number of collisions. In a study of 200 patients referred for assessment of possible apnoea, the patients underwent PSG, completed a symptom orientated questionnaire and were asked to perform the Steer Clear program. They demonstrated no relationship between Steer Clear and the Stanford Sleepiness Scale. Furthermore, there was no correlation between Steer Clear and habitual snorers or the number of reported accidents or near accidents over the preceding 10 years. The authors were unable to demonstrate a correlation between the percentage of hits, the apnoea hypopnoea index or severity of oxygen desaturation. Correlations were found between Steer Clear hits and 4 neuropsychological tests (including Benton Visual Retention, Trails B, Stroop Colours and Wechsler Memory Scales). There were also correlations between level of education, somnolence while driving and the number of hits. The authors concluded that the test could identify some patients with neurocognitive deficit in OSA but that the relationship was not dependent on the severity of the OSA. The data set was not normed prior to analysis to correct for age and level of education which may have confounded the results.

A more recent analysis by George et al[100] used yet another simulator, the DADT (Divided Attention Driving Test), in a study of driving performance in OSA. 21 male patients with OSA (AHI 73 +/- 29) underwent PSG followed by MSLT. Prior to each nap, they were asked to perform the DADT. OSA patients demonstrated substantially more tracking errors than a comparative normal group. However, AHI and MSLT explained less than 25% of the variance, making predictive statements about MVA in any OSA individual difficult, particularly if based on PSG and MSLT data alone.

To further explore sleepiness and driving, George et al[101] examined the outcome for DADT in a group of narcoleptics and OSA patients (EDS group) and a group of normals. Following the same experimental format as their previous data, the authors demonstrated increased sleepiness (MSLT) in the narcoleptic group versus the OSA group - both being sleepier than the normal controls. Tracking errors were again much worse in the EDS group versus controls, however half of the OSA and narcoleptic group performed as well as controls leaving only a weak relationship between tracking and MSLT. Thus, the degree of impairment in driving is difficult to predict from sleepiness alone.

To confirm the relationship between driving accidents and obstructive sleep apnoea, a number of epidemiological studies have been performed.

Early work by Stoohs et al[102] demonstrated that obesity and sleep disordered breathing with hypoxaemia were risk factors for accidents in long-haul truck drivers. Each variable, obesity or SDB, independently was associated with a two-fold increased accident rate per mile.

Hanning and Welsh[103] published data from a self reporting questionnaire mailed out to 5,000 drivers randomly selected from a group of motorists with a maximum 'no

claims bonus'. They found 'snorers' were more likely to report daytime sleepiness than 'non-snorers' and were more likely to have pulled off the road due to sleepiness. There was no overall increase in accident rate between 'snorers' and 'non-snorers' although the selection criteria probably excluded those with recent MVA.

More recently Wu et al[104] developed a routine survey instrument for all patients attending a Sleep Disorders Centre. The survey tool included data on self-reported MVA's. They found 31% of OSA patients reported at least one MVA compared to 15% of patients without OSA. The calculated odds ratio by multiple regression was 2.99. The data was adjusted for age, sex, shift work, daytime nap, alcohol, coffee intake and a history of neurological disease. Additionally, the authors described that falling asleep at inappropriate times and driving past destinations were good indicators for those at risk of MVA.

Thus, it is evident from both epidemiological data and laboratory studies, that OSA is associated with an increased potential for motor vehicle accidents. The exact mechanism is as yet not known although somnolence appears to be a co-variable. Of note, treatment with nasal CPAP has been shown in at least two studies[98, 105] to reduce the rate of accidents both on the road and in the laboratory.

1.3.5 The effect of treatment with nCPAP on cognitive dysfunction in OSA.

Nasal continuous positive airway pressure (nCPAP) is a documented treatment for OSA and has gained favour over uvulopalatopharyngoplasty and tracheostomy as the treatment of first choice. The effects of treatment have been documented with respect to control of desaturation and a reduction in sleep fragmentation. There has been more recent work looking at the possible benefits for the abnormalities in cognition, mood and sleepiness which have been reviewed in the previous chapters.

Ramos Platon et al[106] examined the effects of nCPAP in a group of 35 severe OSA patients (AHI ≥ 20). The group underwent initial psychological testing and were then retested 3 - 6 months, 7 - 10 months and final retesting was performed at 11 - 14 months. 24 control subjects were used. All subjects were tested by MMPI and a semi-structured questionnaire regarding somatic, neuropsychological and socioemotional disturbance. There is no evidence that compliance was measured or that any of the subjects underwent further PSG to ensure that control of apnoeic events was adequate. Furthermore, there was a significant number of non-attendances for follow up, and a drop out associated with incorrect CPAP application. In fact, of the 23 patients (from the pre-CPAP group) used for the comparative analysis, only 8 were retested at the first retest time. This number declined further to 5 and 5 at retest times two and three. If one includes the additional test data collected (the Adjustment Inventory) only 9 patients completed all tests in the pre-CPAP phase, and less than 50% (n = 4) completed the entire task to retest 3. Despite the obvious problems with study design and numbers, the investigators were still able to show that regular CPAP use is associated with a generalised improvement in psychosocial functioning.

In a more organised study of 20 moderate OSA patients, Montplaisir[107] examined vigilance (MSLT) and neuropsychological variables following PSG and at 6 months follow-up after CPAP. 10 normal matched controls were used. CPAP pressure was titrated to reduce the apnoea index to less than 5 per hour. No reference to measures of compliance are available. The authors found that while CPAP improved respiratory function during sleep, as well as sleepiness (MSLT) and alertness (FCRTT), MSLT values were still lower than normals in the treated OSA group. Furthermore, while most measures of intellectual function and verbal memory improved to levels comparable to those of the matched normals, executive function and manual dexterity remained impaired. The non-uniform recovery across the cognitive range suggested that some deficits are irreversible. Of note, these largely

correlated with the degree of hypoxaemia. These conclusions were reiterated in a later reworking of related data by the same group[108].

The first rigorous analysis of the effects of nCPAP was performed by Engleman et al[109]. This randomised, placebo-controlled crossover study sought to examined objective sleepiness (MSLT), cognitive function and mood in 32 OSA patients. The patient group ranged from mild (AHI = 7) to severe (AHI = 129). The placebo used was a tablet which the patients were informed might improve airway function. This was the first study to employ objective compliance measures which, of note, only averaged at 3.4 hours per night. Crossover occurred after four weeks of treatment. The major findings included improvements in mood and a lengthening of the sleep latency on MSLT, although values still remained below the expected normal range(as per the previous study of Montplaisir). Other findings included improved mental flexibility and coding speed. Furthermore, the authors contended that, unlike the previous studies of Charbonneau[110] and Bearpark[111] randomised crossover controlled for learning effects, a common bias for repetitively administered cognitive tasks. There is no data available correlating the severity of OSA (hypoxia or arousal indices) with the magnitude of improvement to indicate a possible treatment threshold. This theme was explored in a later body of work by the same authors[112].

The most recent work by Engleman and colleagues[112] examined the effects of treatment, again versus placebo, in 16 mild OSA patients (AHI 5 - 14.9 per hour). They demonstrated improvements in depression rating, symptom scores and mental flexibility with CPAP usage. Of note, this study group showed a lower CPAP compliance rate (2.8 hours per night) than the previous study. The best predictors of improved compliance were a higher AHI and a greater number of microarousals (ie those with greater sleep fragmentation) - although the authors did not indicate a point at which treatment compliance could be predicted by severity of OSA. The investigators found no improvement with either objective (MSLT) or subjective

(Epworth Sleepiness Scale) somnolence with treatment. Thus, the confounder of somnolence would not appear to be a co-variable for cognitive impairment, at least not in mild OSA. Additionally, mental flexibility (as measured by Trails B) was shown to improve. This finding was in contrast to the previous work which had suggested that reversal of cognitive impairment may not have been completely achievable. It is likely that, in mild OSA with a less profound hypoxic injury, an element of reversibility in cognitive dysfunction is achievable.

Thus, there is clear evidence from the data available that cognitive impairment can improve with nCPAP, although the severity of the insult and compliance may determine the magnitude of change. As yet, there is no definable treatment threshold despite evidence of improvement even in milder disease and evidence of sustained improvement over time. Finally, in a recent systematic review of the literature Wright et al[113] suggested while there is evidence of improvement in objective sleepiness with nCPAP, further studies are warranted. Furthermore, these authors argued that the relevance of OSA to public health has been exaggerated - this is debatable.

1.4 Proposed mechanisms for the development of cognitive dysfunction in OSA.

1.4.1 Evidence of altered control of ventilation in the presence of OSA, and the consequences for cerebral oxygenation.

Early work by Cooper et al[114] examined the effect of sleep loss on respiratory function in 15 normal subjects. All patients were subjected to 27 hours of total sleep deprivation, although there was no polysomnographic data to confirm that sleep had not occurred. The only abnormality detected was a small but significant decline in forced vital capacity and maximal voluntary ventilation. Additionally, there was a 20% decline in the hypercapnic ventilatory response curve. The authors proposed that the relationship between sleep loss and decline in CO2 drive may predispose hypersomnolent apnoeic patients to hypercapnoea.

In later work, Loeppky et al[115] examined the response of cerebral blood flow and resistance to changes in CO2 and O2 in a group of moderately severe OSA patients and a group of normals matched for all parameters except weight. Of note, the apnoeic group were significantly heavier. Cerebral blood flow was calculated by extrapolation of carotid blood flow, measured by Doppler, which does not necessarily reflect regional flow changes within the cortex. The major finding of the study was a detectable abnormality in the response to raising and lowering the PACO2 in apnoeic subjects. The usual increase in cerebral blood flow with rising PACO2 was attenuated. There was also a rise in carotid resistance which occurred in the apnoeic patients in comparison to the normals in whom resistance fell. There was no data regarding the effects of hypoxia on cerebral blood flow and although an abnormal cerebrovascular reponse to CO2 was demonstrated, no mechanism for this finding was reported. One interesting hypothesis proposed by the authors was that increases in intracranial pressure during apnoeas may alter cerebral blood flow, although all the data in this study were collected during wakefulness.

In a similar body of work, Loeppky et al[116] used similar non-invasive techniques to explore changes in cerebral blood flow in response to breath-holding and during sleep. The subjects included 5 OSA patients and 5 normals. While the technical aspects of measuring wave forms and calculating resistance indices were not precise, the findings were of some interest. To summarise, the previous findings of attenuated CO2 response and a concomitant paradoxical increase in carotid resistance during breath-holding were again demonstrated. Blood flow diminished significantly as a function of apnoeic duration while the resistance increased.

Work by Espinoza et al[117] revisited the role of altered sleep quality as a possible mechanism by which ventilatory control may become displaced. Using a model of sleep fragmentation, rather than sleep deprivation, they measured hypercapnic ventilatory response curves in 13 healthy male subjects before and after a night of sleep fragmentation (induced by auditory tone arousal). Contrary to the findings of Cooper, Espinoza could detect no significant change in CO2 responsiveness as a result of sleep fragmentation. While this finding suggests that the altered response to ventilation in OSA is likely to be primary rather than secondary to the sleep disruption, an incidental finding was the increase in apnoeas and hypnoeas in these normal individuals on night two of the fragmentation protocol. Indeed, progressive sleep disruption actually induced apnoea in these subjects. The authors explained this finding as follows: the induced arousal was followed by a brief period of hyperventilation which induced a brief central apnoea secondary to hypocapnoea. Although this hypothesis was tested by the authors and preliminary data appeared to be supportive, the final results remain unreported.

The most illuminating work to date is that of Sforza et al[118]. In a study of 38 non-consecutive patients with OSA, all subjects underwent an awake hypoxic and hypercapnic challenge prior to PSG. The ventilatory response to each stimulus was

then correlated to the measured variability of respiratory effort during apnoeas. They determined the effort to breathe using oesophageal manometry, defining the end point as the overall increase from the minimum to the maximum Pes (oesophageal pressure), the rate of increase of Pes during apnoeas and the maximal effort at apnoea termination. They examined non REM and REM sleep separately. They found correlations between all indices of respiratory effort during apnoea with the awake response to hypoxia and hypercapnoea in NREM sleep. Similar correlations in REM sleep were not detected. Of note, apnoea duration and the magnitude of desaturation did not contribute significantly to the degree of effort.

This study demonstrates several key abnormalities in OSA. Firstly, the chemical response to hypoxia appears to be one of the predictive factors influencing the magnitude of intrathoracic pressure during NREM apnoea. Secondly, the altered hypoxic and hypercapnic responsiveness accounts for observed changes in respiratory effort in NREM sleep although this does not hold true for REM sleep and accounts for only 15 - 19% of the variance.

In summary, it is clear that the cerebral blood flow responses OSA patients during wakefulness are abnormal when compared to a normal subject group (discussed in detail chapter 1.4.2). The relationship between these abnormalities and the drive to breath during sleep is of interest. Ideally, one would like to see data looking at the hypoxic and hypercapnic responses during sleep in apnoeic patients although this may well precipitate sleep disordered breathing in its own right and is an experiment which is as yet unreported. The ramifications for prolonging apnoeas and generating greater hypoxia is pertinent to the question of cognitive insult, but whether the ventilatory drive abnormality is primary or secondary remains largely unanswered.

1.4.2 Evidence of abnormal cerebral blood flow in OSA.

The earliest studies of cerebral blood flow (CBF) in OSA date back to the work of Meyer et al[119]. In a study comparing CBF in OSA patients and narcoleptics using Xenon 133, they demonstrated that brainstem functional activity was low in OSA in the awake state and became critically low during sleep culminating in apnoea - stimulated arousal. Unfortunately this agent and technique use relative uptake to the rest of the brain as a measure of the regional flow. Thus, relative hyperperfusion to the cortex may mean the data measured at the brainstem is misleading.

Using a non-invasive Doppler technique to calculate middle cerebral artery blood flow, Klingelhofer et al[120] demonstrated that there was an increase in mean flow velocity during apnoeic episodes (n=6). The authors also examined CO2 reactivity (calculated from measured end-tidal CO2), as well as blood pressure changes. They concluded that the elevation in cerebral blood flow was secondary to the increase in CO2 reactivity (which rose dramatically during apnoeas) as well as the increase in blood pressure. This study demonstrates, at least by non-invasive techniques, that crude fluctuations in cerebral blood flow in apnoea are present. Unfortunately, there is no data as to the regional displacement of this increased blood flow or what part autoregulatory processes in the smaller vessels may play in blood flow redistribution. In fact, an article by Fischer et al[121] only one month later demonstrated that flow velocities were reduced when measured by similar techniques. Of note the Fisher study used 12 severe OSA patients and included a normal control group (n = 11), but failed to report the intra-apnoea velocities. Thus it may be that global blood flow is reduced in OSA patients, even when awake, but may fluctuate during the apnoea. Indeed, a later study by Siebler[122] demonstrated an increase in the mean acceleration of cerebral blood flow velocity during apnoea.

Finally, Hajak et al[123] using the same Doppler techniques as previous workers confirmed the finding of Fisher, which was that there was a slight reduction in cerebral blood flow velocity in OSA subjects compared to normals when the analysis included controlling for sleep state, and that the general pattern of brain perfusion during normal sleep is maintained in OSA. They also confirmed the finding that cerebral blood flow velocity increased during REM and Stage 2 sleep in OSA probably reflecting dynamic change during apnoea.

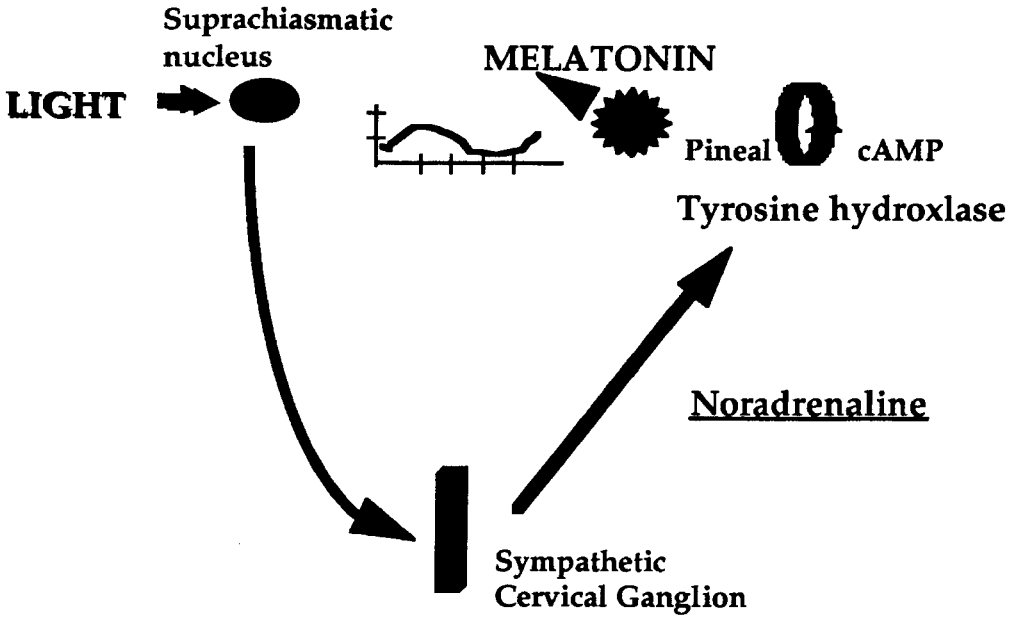
Despite the evidence of altered blood flow in OSA, there is little evidence of the downstream effects of changes in large vessel blood flow. In a small series of 8 men with moderate to severe OSA, Hayakawa et al[124] measured cerebral oxygenation using near-infrared spectroscopy, with polysomnography during sleep. They demonstrated correlations between changes in total haemoglobin (Thb) and the changes in oxyhaemoglobin (OxyHb) in both REM and NREM sleep. The authors proposed that the increase in flow (THb) was insufficient to compensate for the reduced arterial oxygen saturation (as measured by OxyHb). This of course has significant ramifications for brain metabolism and function.

In summary, there is evidence of altered cerebral blood flow and tissue perfusion in OSA. However, no real evidence of specific regional abnormalities has yet been published which would support the findings of selective cognitive deficits. It is hoped that newer techniques such as photon emission spectography (PET) may be of value in exploring the indirect findings of altered blood flow and regional cortical pathology.

1.5 Melatonin production and the genesis of excessive daytime somnolence in OSA.

1.5.1 The proposed mechanisms of melatonin production.

Melatonin has been demonstrated to be a sleep inducing hormone[125]. It is produced in the pineal gland and has been found to enhance the concentration of neurotransmitters such as serotonin and GABA in the hypothalamus[126]. Melatonin is released in a circadian fashion in response to a putative pacemaker thought to be located in the suprachiasmatic nucleus of the anterior hypothalamus[126]. The pineal is innervated by noradrenaline containing neurones from the superior cervical ganglion and has a high content of sympathetic nerve endings as well as a high content of noradrenaline and the enzymes involved in it's synthesis. Noradrenaline content and the activity of tyrosine hydroxylase in these nerve endings exhibit a diurnal rhythm. The synthesis of melatonin has been shown to be directly controlled by catecholamine levels from the superior cervical ganglion, using cyclic AMP as a second messenger, while animal studies have shown that melatonin is involved in suppression of sympathetic activity[127] possibly via negative feedback[128]. The production of melatonin is inhibited by light[129], and more recently, it has been shown that cervical sympathectomy (removing the pathway via which melatonin is controlled in its release) can ablate circadian melatonin rhythm in normal individuals[130]. A previous study by Birkland suggested melatonin may be also be secreted at night in response to arousals[131], possibly as result of transient rises in catecholamine levels, although no mechanism was established. The proposed mechanism for the release of melatonin can be diagramatically represented as follows:



The effect of exogenous oral melatonin has been studied by polysomnography. Dijk et al[132] in a placebo-controlled crossover study of 8 normal men, demonstrated that 5mg of oral melatonin administered immediately prior to a 4 hour sleep period (following 13-17 hours of partial sleep deprivation) did not significantly affect the duration of NREM or REM sleep stages. There were detectable changes to sleep micro-structure which included enhanced spectral frequency in NREM sleep in the range 13.75-14Hz i.e. within the spindle range for Stage 2 sleep. Within the first 2 hours low range frequencies (2.25-5hz i.e. the SWS frequencies) were reduced. These changes are similar to those seen with benzodiazepine hypnotics and similar to the spectral frequency of normally occurring nocturnal sleep. Thus, it can be said that melatonin is able to induce physiological sleep when given at supraphysiological doses and is possibly responsible for sleep onset at night.

Various clinical conditions of abnormal daytime sleepiness have been demonstrated to occur when the circadian rhythm of the pineal is disturbed for example, jet lag, delayed/advanced sleep phase insomnia and entrainment failure.

1.5.2 Excess sympathetic activity in OSA and the possible relationship to excessive melatonin production.

Obstructive sleep apnoea is associated with hypoxaemia and repetitive arousals. It is thought that the obstructive events and hypoxaemia commonly seen in OSA give rise to sympathetic stimulation with a consequent loss of diurnal variation in noradrenaline secretion[133]. This increase in noradrenaline predominantly appears to be due to hypoxia[134]. The question as to whether the hypersecretion of catecholamines and the arousals which occur in response to upper airway obstruction in OSA give rise to changes in the diurnal secretion of melatonin and its circadian rhythm is therefore important. To date there has been only one study which has measured melatonin in OSA. In a small study of 10 OSA patients and 10 controls Entzian et al[135] examined whether the circadian release of somnogenic cytokines (Interleukin-1 and tumour necrosis factor-alpha), pre or post treatment with nCPAP, were abnormal. They also examined overnight melatonin profiles which were reported as normal. They found however that TNF-alpha levels were elevated in OSA and did not normalise after treatment. The finding of a persistent daytime peak of TNF-alpha may well be important in explaining the anomaly of persistently short sleep latencies in OSA even after CPAP. However, given the key role of melatonin in the circadian cycle, further confirmation that melatonin secretion does not play a role directly or indirectly remains important.