

# **Obstructive Sleep Apnoea**

## **The Genesis Of Daytime Somnolence and Cognitive Impairment**

### **- Arousals, Hypoxia and Circadian Rhythm**

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## **STATEMENT**

The work described in this thesis was carried out in the Department of Respiratory Medicine of the Royal North Shore Hospital, University of Sydney, under the supervision of Professor Norbert Berend. Unless otherwise stated, it is the original work of the author and has neither been presented nor is it currently being presented for any other degree.

**David Joffe**

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## **DEDICATION**

I would like to dedicate this thesis to my darling wife Sara, and my two loving sons Adam and Benjamin. Thank you.

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## **ABBREVIATIONS AND DEFINITIONS**

|              |                                                                                                                                                                         |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>AI:</b>   | arousal index (definition: page 77 reference 166)                                                                                                                       |
| <b>CAL:</b>  | chronic airflow limitation (definition: physiologically determined reduction in airflow)                                                                                |
| <b>EDS:</b>  | excessive daytime sleepiness                                                                                                                                            |
| <b>MSLT:</b> | multiple sleep latency test (definition: average time to sleep onset determined over 5 naps at 2 hourly intervals according to the standard criteria for sleep scoring) |
| <b>MWT:</b>  | maintenance of wakefulness test (definition: measure of a subjects ability to resist sleep under neutral conditions)                                                    |
| <b>NREM:</b> | non- rapid eye movement sleep (definition: page 77 reference 166)                                                                                                       |
| <b>OSA:</b>  | obstructive sleep apnoea (definition: page 6)                                                                                                                           |
| <b>PLM:</b>  | periodic limb movement (definition: periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep)                                      |
| <b>RDI:</b>  | respiratory disturbance index (definition: page 76)                                                                                                                     |
| <b>REM:</b>  | rapid eye movement sleep (definition: page 77 reference 166)                                                                                                            |
| <b>SDB:</b>  | sleep disordered breathing                                                                                                                                              |
| <b>SWS:</b>  | slow wave sleep (definition: page 77 reference 166)                                                                                                                     |
| <b>STM:</b>  | short term memory                                                                                                                                                       |
| <b>S.C.:</b> | Steer Clear                                                                                                                                                             |

## **SUMMARY**

Obstructive Sleep Apnoea (OSA) is a disease characterised by repetitive upper airway obstructions which are manifest by desaturation and arousal from sleep. It has been known for many years that this interruption to the normal architecture of sleep may present to the clinician as excessive daytime somnolence often with a complaint of difficulties with concentration and short term memory. Previous work had demonstrated a relationship between variables of cognitive dysfunction in patients with obstructive sleep apnoea, however, little was known about which components of the syndrome contributed to this outcome and whether specific clinical thresholds of sleep disordered breathing could be defined for the development of cognitive dysfunction. In the context of this body of work cognitive dysfunction is defined as: a level of cognitive performance below normal derived values for a given cognitive test, when the subjects performance is controlled for age, sex, and level of education.

55 patients were randomly recruited from the Sleep Unit of the Royal North Shore Hospital. Routine polysomnography was performed. A carefully selected battery of neurocognitive tests were administered the following morning. Correlations between cognitive performance and variables of sleep disordered breathing (SDB) were then derived. The data demonstrated a significant relationship between increasing sleep fragmentation and both immediate and delayed short term memory decrement. This finding was demonstrated to be independent of other variables of SDB. Further analysis demonstrated a relationship between the respiratory disturbance index (RDI) in rapid eye movement (REM) sleep and a decline in information processing speed. Again, this finding was demonstrated to be independent of other sleep variables and indeed independent of the total time spent in REM sleep. A separate sub-analysis of the sleep arousals, defined by modified criteria, was performed against all cognitive outcomes. These analyses demonstrated a significant relationship between repetitive

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shifts in sleep to a lesser stage, arousals to wakefulness and decrements in working memory. This was a novel and unexpected finding.

The intention of this body of work was to clarify the role of hypoxia and arousals in altering cognitive function in patients with sleep apnoea . This work also sought to examine the relationship between these variables and somnolence, a common feature in obstructive sleep apnoea (OSA) patients. Finally, clinically significant thresholds for developing a given degree of cognitive decline were derived. It is believed these may have implications for the intention to treat in this condition.

A separate, but integral body of work, examined whether hypoxia and arousals may alter the secretion of melatonin (a sleep inducing hormone) in individuals with OSA, to explore the possibility that this may be contributing to daytime somnolence.

40 patients were randomly recruited from the Sleep Unit of the Royal North Shore Hospital. Polysomnography was performed and consecutive 12 hour urine samples were collected for 6-sulphatoxymelatonin analysis. This stable metabolite of melatonin was measured to gauge the total production of the hormone for analysis against variables of SDB. Despite the physiological evidence to support the hypothesis that abnormal secretion of this hormone may be present in OSA, no such relationship was able to be demonstrated.

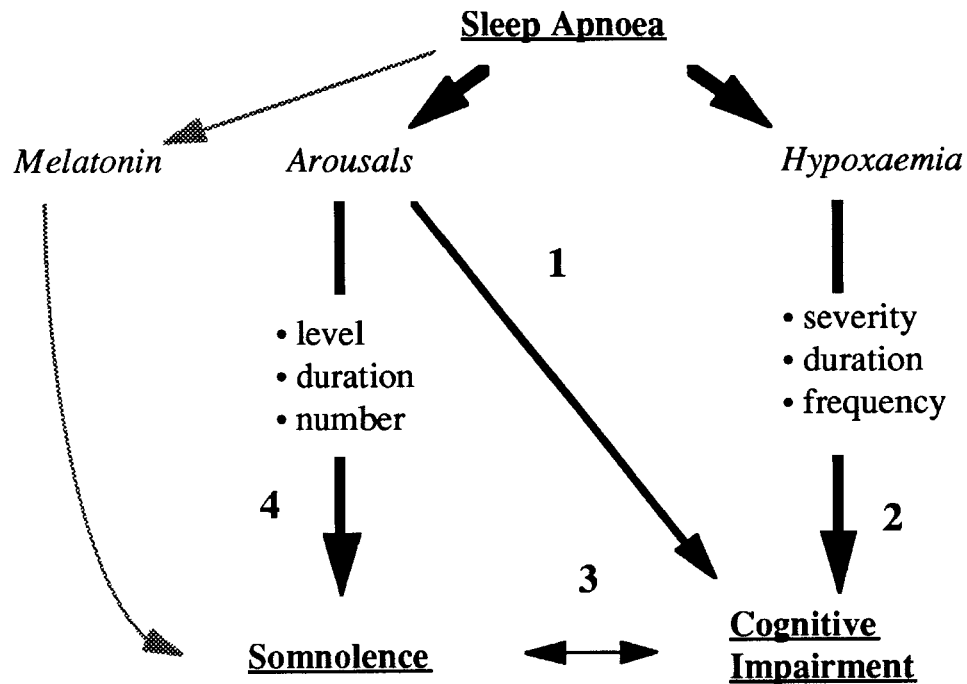
## **Hypotheses - Neurocognitive study**

- 1.** Arousals from sleep gives rise to measureable abnormalities of cognition as a result of sleep fragmentation and this relationship is independent of hypoxia.
- 2.** Repetitive hypoxia resulting from OSA gives rise to measureable abnormalities of cognition. This relationship is independent of sleep fragmentation.
- 3.** The effects of somnolence (impaired vigilance) acts as a co-variable in the genesis of cognitive dysfunction in OSA.
- 4.** Sleep fragmentation gives rise to excessive daytime sleepiness independent of the magnitude of other the variables of sleep disordered breathing.
- 5.** Different aspects of cognition may be affected by sleep disordered breathing depending on the type of insult i.e. hypoxic or fragmentational.
- 6.** Defineable risks for cognitive impairment can be derived from the magnitude of the hypoxic injury and the degree of sleep fragmentation.

## **Hypotheses - Melatonin study**

- 1.** Excessive sympathetic activity due to hypoxia and arousal in obstructive sleep apnoea gives rise to excessive secretion of melatonin.

This hypothetical construct is best represented by the diagram below. Each pathway will be later referenced in the Results Chapters as relevant findings are presented.



PATHWAY 1: Sleep fragmentation and cognitive impairment (hypothesis 1).

PATHWAY 2: Hypoxia and cognitive impairment (hypothesis 2).

PATHWAY 3: Somnolence and cognitive impairment (hypothesis 3).

PATHWAY 4: Sleep fragmentation and somnolence (hypothesis 4).

## **Aims - Neurocognitive study**

- 1.** To analyse the relationship between arousal, cognitive dysfunction and somnolence in patients with sleep disordered breathing (SDB).
- 2.** To analyse the relationship between hypoxic events (ie. duration, number, and severity), cognitive impairment and somnolence in SDB.
- 3.** To investigate the relationship between cognitive impairment and excessive daytime sleepiness (EDS).

## **Aims - Melatonin study**

- 1.** To examine whether total secretion of melatonin as measured by urinary excretion of the metabolite 6-sulphatoxymelatonin is abnormal in a group of moderate OSA patients compared to a matched group of non-apnoeic patients.
- 2.** To correlate the total excretion of 6-sulphatoxymelatonin with measures of hypoxia and arousal from sleep to examine the relationship between apnoea severity and melatonin production.

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## **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<sup>1</sup> 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<sup>2-4</sup> 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<sup>5</sup> and Siesjo<sup>6</sup>, 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<sub>2</sub> = 35mmHg).

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

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

In 1993, Noble<sup>9</sup> 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<sup>10</sup>. The patients in this amnesic group appeared orientated and did not confabulate, suggesting that the insult incurred differs from other forms of amnesic 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<sup>11</sup> 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<sup>12</sup> when oxygen was administered.

A matched control study of 203 COPD patients was carried out by Grant<sup>13</sup>. 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 PaO<sub>2</sub> 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<sup>14</sup> 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.

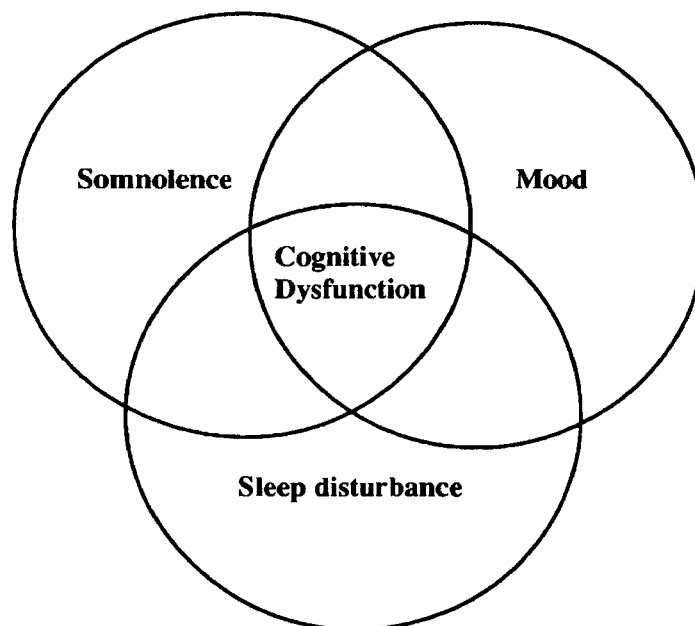
In reviewing the available data, Berry<sup>7</sup> drew together these studies to conclude that clearly tests of abstract reasoning and motor speed are “sensitive to the effects of cerebral hypoxia”. The level of chronic daytime hypoxia is similarly correlated with cognitive dysfunction although the 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.

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## **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 <sup>15</sup> 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<sup>16</sup> 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<sup>17</sup> in concert with Bonnet<sup>18</sup> 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<sup>19</sup> 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<sup>20</sup> 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<sup>21</sup> 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<sup>22</sup>. 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)<sup>23</sup>. 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<sup>24</sup> 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<sup>25</sup> 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 adjunctive test. In a related article<sup>26</sup> 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) <sup>27</sup>. 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 <sup>28</sup> and by factor analysis <sup>29</sup>. 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<sup>30</sup> 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 aforementioned 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<sup>31, 32</sup> and cerebral evoked potentials<sup>33</sup> 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<sup>34, 35</sup> 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<sup>36</sup> 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<sup>37</sup> 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<sup>38</sup>. 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<sup>39</sup> 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<sup>40</sup> 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.

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An experimental model of sleep fragmentation devised by Roehrs et al <sup>41</sup> 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<sup>21</sup> 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<sup>42</sup> 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<sup>34</sup> 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<sup>43</sup> 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<sup>44</sup> 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<sup>45</sup>. 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<sup>46</sup> and Foo<sup>47</sup> 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<sup>48</sup> 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<sup>49</sup> 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<sup>50</sup>. 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<sup>51</sup> 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<sup>52</sup> 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.

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#### **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<sup>16</sup> 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<sup>21</sup> demonstrated abnormalities in hedonic tone and energetic arousal scores in their subjects following the sleep fragmentation night.

Several studies<sup>53-58</sup> 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<sup>58</sup> makes the assessment of TST questionable. A recent paper by Richardson<sup>59</sup> 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.

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Indeed, Pilcher's<sup>50</sup> review demonstrated only 6 studies of partial sleep loss that were of sufficient calibre for analysis.

The meta-analysis by Pilcher<sup>50</sup> 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<sup>16</sup> 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 measurable 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<sup>60</sup> 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<sup>61</sup> 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<sup>62</sup>, 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<sup>63</sup> 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<sup>64-70</sup>.

Finally, Perlis et al<sup>71</sup> 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<sup>72</sup> and Yesavage<sup>73</sup>. 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<sup>74</sup> 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

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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<sup>75</sup>, and later by Greenberg et al<sup>76</sup>. 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<sup>77</sup> 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<sup>78</sup> 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<sup>79</sup> 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<sup>80</sup> 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<sup>81</sup> 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<sup>20</sup> 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<sup>82</sup> 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<sup>75</sup> 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<sup>77</sup> reported an abnormality in a spatial orientation test (Clock test) in habitual snorers. The authors concluding later<sup>81</sup> 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<sup>80</sup> used the conventional criteria of Rechtschaffen and Kales<sup>83</sup>. 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<sup>84</sup> 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<sup>75</sup> examined correlations between hypoxia and cognitive outcomes, comparing two groups both with nocturnal desaturation. One group demonstrated co-existing daytime hypoxia (PaO<sub>2</sub> 63 $\pm$ 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 $\pm$ 5 events per hour sleep and the 'hypoxic' group had 86 $\pm$ 14 events per hour sleep. The 'hypoxic' group were substantially heavier (BMI = 47 $\pm$ 4) and would most likely represent patients with concomitant Obesity Hypoventilation Syndrome. No control group was used. The authors demonstrated correlations between the median SaO<sub>2</sub> and awake PaO<sub>2</sub> 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<sup>76</sup> 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 possibly improve performance as the co-variable of sleepiness is diminished.

In 1991 Bedard et al<sup>79</sup> 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<sup>85</sup> 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<sup>80</sup> confirmed the relationship between the magnitude of hypoxia and cognitive impairment. Again, they used the lowest SaO<sub>2</sub> 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<sup>82</sup> 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”<sup>86</sup> 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<sup>87</sup> 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<sup>22, 88</sup>. 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<sup>36</sup> 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<sup>89</sup> 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<sup>90</sup> who calculated that the lowest SaO<sub>2</sub> 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<sup>25</sup> 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<sup>26</sup> 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<sup>91</sup> 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<sup>72</sup> 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<sup>80</sup> 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<sup>92, 93</sup> no direct correlates with measures of hypoxia or arousal were examined.

In contrast to the aforementioned studies, Cassel<sup>94</sup> 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<sup>95</sup> 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<sup>20</sup> 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 assessed function and therefore lower self esteem.

Finally, a recent study of Swedish obese subjects<sup>96</sup> 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<sup>97</sup> 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<sup>98</sup> 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<sup>99</sup> 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<sup>100</sup> 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<sup>101</sup> 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<sup>102</sup> 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<sup>103</sup> 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<sup>104</sup> 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<sup>98, 105</sup> 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<sup>106</sup> examined the effects of nCPAP in a group of 35 severe OSA patients ( $AHI \geq 20$ ). 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<sup>107</sup> 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<sup>108</sup>.

The first rigorous analysis of the effects of nCPAP was performed by Engleman et al<sup>109</sup>. This randomised, placebo-controlled crossover study sought to examine 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<sup>110</sup> and Bearpark<sup>111</sup> 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<sup>112</sup>.

The most recent work by Engleman and colleagues<sup>112</sup> 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<sup>113</sup> 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<sup>114</sup> 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 CO<sub>2</sub> drive may predispose hypersomnolent apnoeic patients to hypercapnoea.

In later work, Loeppky et al<sup>115</sup> examined the response of cerebral blood flow and resistance to changes in CO<sub>2</sub> and O<sub>2</sub> 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 PACO<sub>2</sub> in apnoeic subjects. The usual increase in cerebral blood flow with rising PACO<sub>2</sub> 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 response to CO<sub>2</sub> 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<sup>116</sup> 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 CO<sub>2</sub> 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<sup>117</sup> 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 CO<sub>2</sub> 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<sup>118</sup>. 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<sup>119</sup>. 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<sup>120</sup> demonstrated that there was an increase in mean flow velocity during apnoeic episodes (n=6). The authors also examined CO<sub>2</sub> reactivity (calculated from measured end-tidal CO<sub>2</sub>), as well as blood pressure changes. They concluded that the elevation in cerebral blood flow was secondary to the increase in CO<sub>2</sub> 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<sup>121</sup> 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<sup>122</sup> demonstrated an increase in the mean acceleration of cerebral blood flow velocity during apnoea.

Finally, Hajak et al<sup>123</sup> 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.

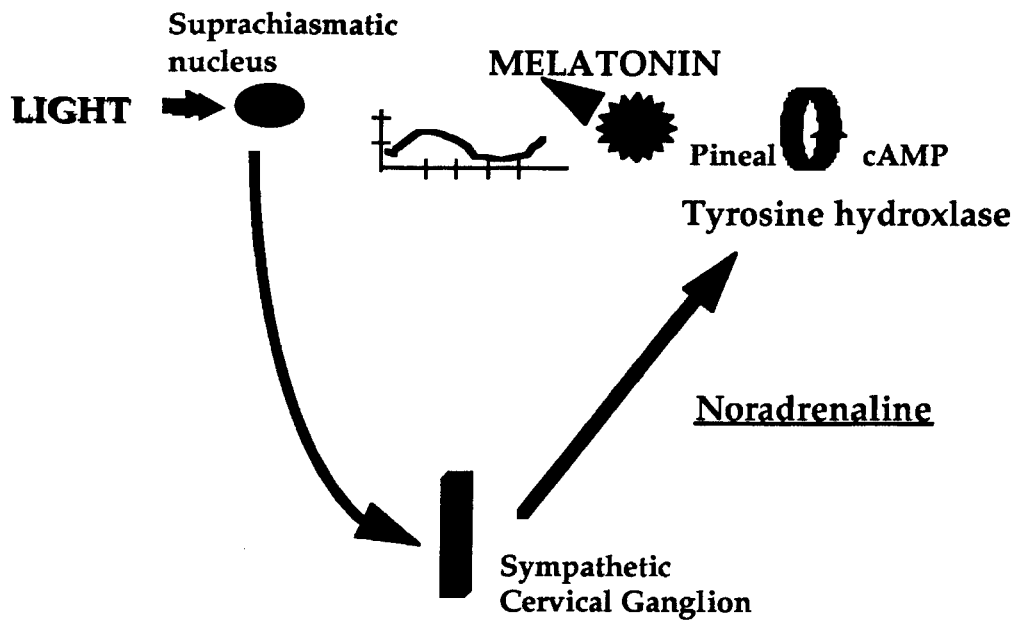
Despite the evidence of altered blood flow in OSA, there is little evidence of the downstream effects of changes in large vessel blood flow. In a small series of 8 men with moderate to severe OSA, Hayakawa et al<sup>124</sup> measured cerebral oxygenation using near-infrared spectroscopy, with polysomnography 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<sup>125</sup>. 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<sup>126</sup>. 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<sup>126</sup>. 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 its 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<sup>127</sup> possibly via negative feedback<sup>128</sup>. The production of melatonin is inhibited by light<sup>129</sup>, 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<sup>130</sup>. A previous study by Birkland suggested melatonin may also be secreted at night in response to arousals<sup>131</sup>, possibly as result of transient rises in catecholamine levels, although no mechanism was established. The proposed mechanism for the release of melatonin can be diagrammatically represented as follows:



The effect of exogenous oral melatonin has been studied by polysomnography. Dijk et al<sup>132</sup> 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<sup>133</sup>. This increase in noradrenaline predominantly appears to be due to hypoxia<sup>134</sup>. 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<sup>135</sup> 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.

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## **METHODS CHAPTER**

### **Introduction.**

The data with respect to neurocognitive dysfunction in OSA was collected from 55 patients over 18 months (June 1995 - November 1996). All melatonin samples were collected over the periods April-July 1994-1996 from a separate group of 40 subjects.

The following chapters will categorise the neurocognitive battery, the methods of administration, scoring and statistical analysis. Similar attention will be paid to the polysomnographic analyses. Furthermore, additional chapters will elucidate the melatonin sample collection methods and data analysis.

### **2.1 Overview of Cognitive Tests.**

For the sake of simplicity the test battery order is presented in List 1 (see Chapter 2.5). All tests were performed on the morning immediately following the sleep study. The test time ran from 0800 to 1100 hours. Further detail is presented in Chapter 2.5. In order to allow for the development of a clinical relationship between cognitive tests and the measured components of sleep disordered breathing, the tests have been compartmentalised into broad categories. The specifics of the tests within each category are discussed separately.

### **2.1.1 Tests Of Short Term Memory.**

- Logical memory passages I and II
- Benton Visual Retention Test
- Digitspan forwards

The logical memory passages of the Wechsler Memory Scale - Revised (WMS-R)<sup>136</sup> are two brief stories incorporating details such as names, places and numbers interspersed with contextual text. Each story is read in turn and the subject is required to recall as much detail as possible. Marks are accorded for correctness and accuracy allowing for a minor degree of interpretation. The standard scoring procedure and normative data have been well validated and published (Wechsler 1987). A score out of a possible best of 25 correct responses can be calculated and percentiles derived from age-matched controls. The candidate is then instructed to remember both story passages and delayed recall is then tested at 30 minutes. There is no re-reading of the passages prior to the delayed recall testing. Scoring of the re-testing procedure is as previous. All tests were performed with modified Australian content as described by Sullivan<sup>137</sup>.

The logical memory passages were chosen for ease of administration and have been demonstrated to show good internal validity<sup>138</sup>.

The Benton Visual Retention Test (BVRT) is a complex test of visual recall and reconstruction. Described by the author<sup>139</sup>, it is both complex in administration and scoring. Normative data<sup>140</sup> on 1,128 healthy normals has been validated demonstrating a positive association between education level and performance. The test comprises the presentation of geometric objects, squares, circles etc of increasing complexity. A 10 second presentation is followed by a period

whereby the subject is requested to reconstruct the picture they have been shown. The total score is derived from a complex scoring of the correct and erroneous reconstructions. The final outcome is measured by a calculation of the predicted score for age and level of education and the measured score. The test has been previously used in a study of snorers versus normals<sup>77</sup>.

Digitspan forward<sup>141</sup> of the WMS-R is a test of immediate numerical recall. The subject is given a series of numbers of increasing length (3 - 8 digits). They are required to retain the sequence and repeat it in exactly the same order. Two different sequences are presented at each length. The score is derived by the total correct (out of 12) and the test terminated once an incorrect sequence has been given at both presentations of a given digit length. Normative scoring for age is then calculated<sup>141</sup>.

The tests outlined above were selected in an effort to measure short term memory by three different presentation modes, numerical, visual and verbal, since selective memory dysfunction may occur in a given clinical setting.

### **2.1.2 Tests Of Information Processing**

- Symbol Digit (oral presentation)

The Symbol Digit Test<sup>142</sup> is a useful measure of cognitive processing speed. The subject is presented with a key of numbers (1 - 9) matched to symbols of a simple design. Below the key is a series of matching boxes (15 per line) with symbols presented above empty boxes. The oral performance of the test follows an untimed attempt to match the first 10 symbols by calling out the numbers from the key above. No psychomotor component is incorporated by this

technique. Following the trial, the subject is given 90 seconds to call out the numbers in sequence, corresponding to the symbols in each box. A score of all correct responses is then normed for age<sup>142</sup>.

The test as a measure of information processing speed has been validated both in normals <sup>143</sup> and patients with closed-head injury<sup>144</sup>.

### **2.1.3 Tests Of General Intellectual Ability / IQ.**

- Vocabulary component of the Shipley Institute of Living Scale (SILS)
- Abstraction component of SILS
- Estimated WAIS full scale IQ from SILS

The vocabulary component of the SILS is an untimed word matching test. The subject is given a key word and asked to find the appropriate synonym from four given choices. Forty words are presented and a score calculated from the total of correct answers. A t-score is then derived from the accompanying text manual<sup>145</sup> as corrected for age. Vocabulary as a fixed measure of intellectual ability is generally recognised to be unimpaired by cognitive insult, thus the derived Vt was used as a regression covariable to control for general intellectual ability across all other cognitive measures.

The abstraction component of the SILS is a 10 minute timed test of problem solving. The subject is given a series of words, letters or numbers followed by blank spaces. They are instructed to examine the pattern of the preceding series in order to complete the solution. A total of 20 puzzles are given with an instruction to attempt all problems in the time allocated. The total of correct answers is used to derive a t-score from normal tables for age matched controls.

A further subanalysis is possible using predicted values for the test based on the level of education and the Vt. This is used to derive the abstraction quotient again from the normed tabular data.

The WAIS full-scale IQ is calculated from the sum of the t-scores for vocabulary and abstraction using normal tables published with the manual for the test. The use of this test as a comparable measure of IQ has been validated by Dalton<sup>146</sup> particularly for grouped data.

The controlled oral word association test (COWAT) is predominately a test of verbal knowledge although unlike the SILS vocabulary component, it is a timed test requiring reasonable verbal agility. The subject is presented in turn with three consonants: F, A & S. They are given 60 seconds to call out as many words as possible starting with the given letter. Proper nouns, perseveration and words of like structure (eg eat, eats, eaten) are scored correctly for the initial word only.

A normative value is derived from age-matched totals for the sum of the three trials. The test has been demonstrated by Axelrod et al<sup>147</sup> to be unrelated to intellectual competence, educational experience or general health status of the subject, although there is age related decline. Furthermore verbal knowledge has been demonstrated to be a major contributor<sup>148</sup>.

#### **2.1.4 Tests Of Psychomotor Speed.**

- Grooved peg board
- Block design test
- Trails making tests parts A and B

The Grooved peg board<sup>149</sup> is a test of psychomotor speed and manual dexterity. The subject is instructed to place grooved metal pegs into randomly rotated matching grooved holes, set out in a 5 by 5 matrix. They are instructed to use the dominant hand first with subsequent non-dominant re-testing. The time to completion is measured and normal values derived from reference tables for each hand<sup>149</sup>. A subcalculation for dropped pegs can be included, although the time penalty for continuing the test is deemed equally satisfactory.

The block design test is a complex measure of psychomotor speed as well as visuospatial perception and construction. The subject is given a set of 4 red/white blocks identical in design. They are shown 5 consecutive patterns (2-dimensional) and are directed to recreate the pattern using the coloured blocks (3 dimensional). The time to completion is recorded, and a score for each trial is derived from 3 time intervals - higher marks accorded for faster performance. The same paradigm is then performed using 9 blocks over 4 trials, with longer time intervals being allowed for each test.

The total score for all tests is then calculated and normative data corrected for age is derived from known tables<sup>150</sup>. Indeed, while image segmentation processes remain constant with age, other processes become slower<sup>151</sup> such that age corrections become critical to analysis of data derived by this test.

Trails making tests part A and B are timed tests of visual tracking and sequencing.

Part A: The subject is instructed to join numbered circles in ascending order e.g. 1 to 2, 2 to 3 , 3 to 4 etc. The circles are spread across the page in random order, but in such a manner that no lines are ever crossed. Time from start to completion is recorded and normal values are derived from matched controls for age and level of education.

Part B: Follows a similar paradigm to the first part to the test but incorporates an added task of mental dexterity. The subject is required to join the circles in sequence, however they must simultaneously progress through a concurrent alphabetic process i.e. 1 to A, A to 2, 2 to B, B to 3 etc. Normal values are derived for age and level of education from tabular data<sup>142</sup>.

Trails B is deemed harder<sup>152</sup> since it demands greater levels of motor speed and visual search. Furthermore it is more closely associated with visual non - verbal intelligence than with attention information processing. For subjects of average or higher intelligence, test performance is independent of intellectual ability<sup>153</sup> and demonstrates good inter-rater variability<sup>154</sup>.

#### **2.1.5 Tests Of Visuospatial Perception and Construction.**

- Reye - Osterrieth Complex Figure Test

The Reye-Osterrieth Complex Figure Test (RCFT) is an untimed test of visuospatial perception and construction<sup>150</sup>.

The subject is shown a complex line diagram comprising several standard geometric patterns including squares, circles, oblongs and triangles. Within the construct are smaller additional details such as parallel lines and dots. There are, in total, 18 standard elements. The subject is asked to reproduce the figure as neatly and accurately as possible in a space on the paper below the template. No rubbers or rulers are allowed. A complex scoring algorithm is employed with marks out of a total of 36 being accorded. Deductions are made for incorrect placement, missing detail and poor spatial perspective. The scoring method has

been validated by Loring<sup>155</sup> who demonstrated that the criteria could be reliably applied by independent raters.

#### **2.1.6 Tests Of Working Memory.**

- Paced Auditory Serial Addition Task (PASAT 2.4 second presentation)
- Digitspan - reverse.

The PASAT<sup>150</sup> is a timed test of mental addition. The subject is presented with sequential single digit numbers read from an audio cassette at 2.4 second intervals. They are instructed to add the last two digits that have been presented. After each digit is presented they are asked to call out the answer from the calculation performed. Thus, there is both a timed addition task as well as a short term memory task for the retention of the previous number. The test has been demonstrated by Deary et al<sup>156</sup> to correlate with all WAIS-R subtests. No effect of education or race has been demonstrated<sup>157, 158</sup> although age and IQ have been shown to affect the PASAT test results and should therefore be controlled for in analysis.

The reverse presentation of digitspan<sup>141</sup> (description Chapter 2.1.1) is a test of numerical short term memory and attention. The subject is presented with a series of single digit numbers of progressively increasing length, ranging from 2 - 7 digits. They are required to remember the numbers as presented and call them back to the instructor in exactly the opposite order. For each digit length they are given two trials. The test is terminated when an incorrect answer is given for both trials of a given length. A total out of 12 is calculated and normal values derived from age-matched tables<sup>141</sup>.

The test has been demonstrated to be age sensitive in patients over 60 years, possibly due to a decreased flexibility in processing changes<sup>159</sup>. This needs to be considered when using the test in older patients.

#### **2.1.7 Tests Of Supraspan Learning.**

- Serial digit learning

Serial digit learning is a test of verbal memory which incorporates an element of learning strategy differentiating it from digitspan.

The subject is presented with a very long number either 8 or 9 digits depending on age and level of education. Subjects over 65 or with less than 12 years of schooling receive an 8 digit test, all others receive 9 digits. They are instructed in advance that they will be told a long number of a given length. The number is then read out at a regular speed and without pause. There are no repeated digits. The subject is advised to try and “learn” the first part of the number and add on numbers with subsequent attempts. They are given 12 opportunities to complete the task. The test is terminated when the correct sequence is given by the subject at two consecutive attempts. A maximum total of 24 is calculated for the number of correct answers ie 2 marks for each attempt with 1 mark being accorded for any attempt with only one error and none for any trials with greater than two errors. Normative results are derived from tables of age-education-matched normals<sup>160</sup>. The test has been demonstrated to correlate with attention-information processing rather than general memory<sup>161</sup> given the requirement for strategy development such as linking the 9 digit sequence into 3 blocks of 3.

### **2.1.8**

#### **Beck Depression Inventory (BDI).**

The BDI <sup>162</sup> is a self administered, untimed questionnaire of mood state. The subject is required to complete a 21 item inventory of subjective rating pertaining to symptoms and attitudes. The test has been designed to assess the severity of depression in adolescents and adults and has been validated for use in detecting possible depression in normal populations<sup>163</sup>. It has been demonstrated to correlate with other standard tests of mood such as POMS (Profile of Mood States)<sup>164</sup>. The test, like many self rating mood scales, includes embedded questions regarding sleep, weight and sexual interest which are likely to score abnormally in OSA patients. Unfortunately, more disease specific questionnaires are still undergoing validation and were not available for use in this study. Other, perhaps more sensitive tests, such as the Multiphasic Minnesota Personality Inventory were deemed to be inappropriately lengthy. Generic questionnaires such as Short Form 36 may have application in the setting of OSA but do not specifically reference depression in a measurable manner.

## **2.2 Overview of Objective and Subjective Tests of Somnolence.**

### **2.2.1 Epworth Sleepiness Scale.**

This self reporting 8 point questionnaire was developed as a simple and quick assessment of subjective sleepiness. The subject is asked to rate (from 1 - 3) the likelihood of falling asleep in circumstances of low stimulation (eg reading a book, passenger in a car). A total from 0 - 24 is then calculated, with greater scores correlating with increased somnolence. It has been validated against objective sleepiness scores, in particular the MSLT<sup>27</sup>. It has also been demonstrated to be an effective tool for measuring persistent daytime somnolence in adults<sup>29</sup>.

### **2.2.2 Steer Clear Driving Simulator.**

This relatively simple computerised test was initially designed to measure vigilance impairment<sup>30</sup>.

The subject is presented with a two-dimensional, 2 lane road intended to represent a monotonous highway drive. During a 30 minute study, 780 obstacles (Steers) are pseudo-randomly presented. The subject is instructed to hit the 'space bar' of the key board to shift the car from one lane to the other to avoid the oncoming obstacle.

There is no standardised data with respect to computer processor speed, screen size or speed of presentation of the obstacles. For the work presented here, the test (version B) was run on a 486 NEC computer with 13 inch colour screen at the default setting of 70.

Steer Clear has been demonstrated to correlate with a higher rate of automobile accidents in OSA patients who have been shown by comparison to normals to perform more poorly on this driving simulator.

A total number of 'hits' is calculated by the software and z-scores derived from age-sex-matched normative data<sup>165</sup>.

The sensitivity of Steer Clear for predicting automobile accidents remains unknown. Furthermore, no studies to date have sought to correlate the test with subjective somnolence (see results). Despite these flaws, it remains a simple and useful tool for objectively measuring vigilance. It was selected for use in this study given its value in determining vigilance decrement in OSA, as has been demonstrated by Engleman et al<sup>109</sup> who showed improvement post CPAP treatment.

## **2.3**                      **Enrollment.**

### **2.3.1**                      **Neurocognitive Data Set.**

#### **PATIENTS**

55 male volunteers were randomly recruited through the Sleep Unit of the Royal North Shore Hospital. All patients were undergoing polysomnography for investigation of possible sleep disordered breathing. The primary investigators had no prior knowledge of the magnitude of sleep disturbance at the time of administration of the test battery. Consent was obtained prior to test administration and in accordance with the Ethics Committee of the institution. All subjects were asked to refrain from taking caffeinated beverages on the morning of testing.

## EXCLUSION CRITERIA

Patients older than 70 years or with a past history of excessive alcohol, epilepsy, previous head injury, or past history of stroke were excluded from the study. Patients were allowed to use their regular medications. Patients taking benzodiazepines or anti-depressants were not enrolled.

### **2.3.2 Melatonin Data Set.**

## PATIENTS

40 randomly selected males aged between 18-65 were asked to participate. Patients were enrolled from the Sleep Investigation Unit of the Royal North Shore Hospital. All patients completed a consent form under the guidelines of the Ethics Committee of the Institution.

## EXCLUSION CRITERIA

Patients with a history of severe underlying respiratory or cardiac failure, the presence of right or left heart failure on physical examination, documented or clinically evident thyroid or adrenal disease were excluded. Patients on oral steroids or those using tricyclic antidepressant or benzodiazepine medications were excluded so as not to interfere with assay techniques. Female patients were excluded to avoid menstrual hormonal fluctuation which could alter melatonin levels.

## **2.4                      Polysomnographic Data for the Neurocognitive Data Set.**

### **2.4.1                      Collection of Data.**

All studies were performed using standard 21 channel computerised polysomnography (Compumedics - Melbourne).

Collected data included:

- EEG (Single channel C3, A1/C4,A2)
- Submental EMG
- EOG
- Thoracic and abdominal movement by inductive plethysmography
- Airflow by pressure transducer
- Finger oximetry
- Tibialis EMG

### **2.4.2                      Analysis and scoring of respiratory events, sleep stages and arousals.**

Apnoeas and hypopnoeas were defined as a greater than 10 second obstructive apnoea (complete cessation of airflow) or obstructive hypopnoea (50% or greater reduction in tidal volume). All respiratory events required a  $\geq 4\%$  desaturation to be included in the analysis. The total apnoeas and hypopnoeas for REM and NREM sleep were derived separately. An average across the night score was calculated to derive the total RDI.

All polysomnographs were scored by one of two full time sleep technologists. Previous (unpublished) inter-rater reliability for the laboratory has been

calculated at > 90%. This process was performed as part of ongoing laboratory quality assurance.

Sleep stages were scored according to R & K criteria, defined as:

- 1: Low voltage mixed frequency with or without slow rolling eye movements.
- 2: Presence of spindles or K-complexes.  
The absence of the above excluded epochs from Stage II.
- 3: Presence of  $\geq 20\%$  and  $<50\%$  delta waves per epoch.
- 4: Presence of  $\geq 50\%$  delta waves per epoch.

**REM:** Low voltage mixed frequency.

Presence of spindle or K complexes in the first half of any epoch was rescored as Stage II.

Reduction in chin EMG signal was required and fast eye movements on the EOG needed to be present.

Arousals were scored according to the Atlas Task Force of the American Sleep Disorders Association<sup>166</sup>. In summary, arousals were defined as a  $\geq 3$  second change in EEG sleep state with increase in chin EMG irrespective of the cause of the arousal.

## **2.4.2 Subanalysis of Arousals. A Modified Scoring System.**

### **2.4.2.1 Rationale for Development of a Four Level Scoring System.**

Previous data by Stepanski et al<sup>38</sup> demonstrated that when arousals were subclassified by duration and magnitude, that a strong correlation existed between sleepiness and arousals of shorter duration. Furthermore, there was an additional correlation between sleepiness and the frequency of these brief arousals. This work was later confirmed by Roehrs et al<sup>41</sup> in a sleep fragmentation model. More recently, Martin et al<sup>21</sup> demonstrated both increased sleepiness and cognitive decrement after one night of sleep fragmentation by auditory tone (using a  $\geq 3$  second change in EEG to define an arousal).

Based upon the findings of these previous authors, a modified version of Stepanski's criteria was evolved in an effort to define whether the outcomes of this study correlated with arousals of a specific duration or magnitude. It was hoped that the presence of a larger sample size and use of a more expansive neurocognitive battery than the previous studies would generate greater sensitivity and specificity in detecting arousal driven cognitive decrement.

The arousal scoring system was developed by combining the IA and IB, IVA and IVB definitions of Stepanski. This was in accordance with the finding of Stepanski that no extra information was forthcoming with the use of further sub-classification. The follow criteria were applied:

| <b>LEVEL</b> | <b>CRITERIA</b>                                                 |
|--------------|-----------------------------------------------------------------|
| <b>I</b>     | Increase in EEG frequency and increase in chin EMG 3-10 seconds |
| <b>II</b>    | Alpha burst in EEG of 10-29sec.                                 |
| <b>III</b>   | A stage shift to a lesser stage (eg. 2 to 1)                    |
| <b>IV</b>    | An awakening from any stage of sleep (1-4 and REM)              |

An awakening was defined as 30sec. of wakefulness in the EEG with/without eyes open.

#### **2.4.2.2 Method of Scoring Arousals by Modified Criteria.**

All studies were independently scored by one of two sleep technologists according to the standard criteria of the Atlas Task Force and the R & K criteria. All studies were then copied to optical media and held by the primary investigator. At study termination, all PSG results were relabeled by the sleep technologists with deletion of all names and dates from the original studies and a randomised coding applied. All studies were then rescored by the primary investigator having been blinded to the coding procedure. All original arousals were rescored according to the modified Stepanski criteria and assigned to one of the four levels outlined in Chapter 2.4.2.1.

#### **2.4.2.3 Validation Procedure for Modified Arousal Scoring.**

A random series of 8 studies were similarly presented to another physician (neurologist) for rescoring according to the modified criteria. Inter-rater variability was determined by simple linear regression and paired t-testing. For details of the statistical methods of validation see Chapter 2.6.4.

Eight studies were rescored by the primary investigator and similar analysis of variance derived for intra-rater variability. Having determined good inter and intra-rater concordance, the total number of each arousal type was then subjected to analysis against cognitive and somnolence outcomes.

#### **2.4.3 Analysis of Measures of Hypoxia.**

The following variables were extracted from the computerised polysomnograph:

- Lowest saturation in NREM.
- Lowest saturation in REM.
- Average desaturation for the entire night.
- Total time (minutes) with a saturation below 90%.

All values were derived by the software of the sleep system. The total time with a saturation below 90% was later logarithmically transformed to normalise the data given the spread of values.

Previous authors such as Bedard<sup>79</sup> defined the magnitude of hypoxia at an arbitrary level below 80%. This cut-off would define more severe OSA and was not considered suitable for this study. Furthermore, a saturation of 90% is at the steepest part of the oxygen saturation curve and standard practice accepts that tissue hypoxia is likely to occur below this physiological threshold. Hence, a saturation cut-off at 90% was deemed to be clinically appropriate.

Findley<sup>75</sup> determined a correlation existed between the median nocturnal saturation and the cognitive outcomes. As the total area under the curve may be more representative than a specific point of greatest frequency on the curve itself, it was felt that total time may be more reflective of the magnitude of the hypoxic injury.

## **2.5**

### **Neurocognitive Battery Administration.**

The following list defines the sequence of the test battery.

#### **Order and timing of the test battery**

Epworth Sleepiness Scale

Steer Clear Driving Test

**5 minute break.**

Digitspan forward and reverse

Trails A and Trails B

Digit Symbol substitution (oral)

Controlled Oral Word Association Test

Reye-Osterrieth Complex Figure Test

Serial digit learning

Grooved Peg Board (dominant then non-dominant hands)

Beck Depression Inventory

Shipley Institute of Living Scale (verbal untimed, then timed abstraction)

**10-15 minute break.**

*The following tests were performed by Mr. Geoffrey Marshall, neuropsychologist, Royal North Shore Hospital.*

Logical Memory Passages I

Benton Visual Retention Test

Block Design

PASAT (Paced Auditory Serial Addition Task - 2.4 second)

Logical Memory Passages II

All patients were requested to refrain from ingestion of caffeinated beverages on the morning of testing. Polysomnography was terminated at 0600 hours and the patients woken to attend to personal hygiene and to allow time for a light breakfast. Testing commenced at 0800 hours and was completed by 1100 hours. There were two brief breaks during the battery testing period.

The battery was developed in consultation with Mr Geoffrey Marshall (Clinical Neuropsychologist, Royal North Shore Hospital) after extensive review of the previous literature. Several of the tests chosen for this study have been used in prior studies, although some are unique to this data. The exact order was determined to minimise any possible learning effect being carried over between tests.

The primary investigator was instructed in the administration of all tests and a standard instruction set was developed in order that all subjects be given the battery in a uniform manner. The final five tests were administered by Mr Marshall given their added complexity. The primary investigator acted as observer in the second sequence.

The absence of any pre-existing knowledge of the magnitude of sleep disordered breathing was felt to be crucial to the blinding of the investigators in an effort to avoid administration bias. Furthermore, the selection of several short tests of various complexity immediately following PSG was determined to be the construct most likely to avoid the pitfalls of night to night variability of unmeasured domiciliary sleep quality. Finally, the use of short tests was employed to minimise the subjective potential for inattention secondary to repetition.

## **2.6                      Statistical Methods for Analysis of Neurocognitive Outcomes.**

### **2.6.1                      Simple Regression Modelling.**

All neurocognitive outcomes were normed according to the techniques discussed in Chapters 2.1.1 - 2.1.8. The t-scores, z-scores or percentiles were then used for the analysis of the data by simple regression. The outcomes for arousal indices and hypoxic variables were considered in turn.

All cognitive tests were separately entered as dependent variables. The various parameters of sleep disturbance were entered as independent variables and all derived p values < 0.05 were considered statistically significant and are presented in the results.

### **2.6.2                      Stepwise and Multiple Regression Techniques.**

Having defined the relationships of statistical significance by simple linear regression, stepwise regression was then performed between each of the cognitive outcomes, about which there were a priori hypotheses, and all measures of sleep disordered breathing in order to ascertain which of the relationships were statistically independent.

From the stepwise regression analysis, several independent interrelationships between cognitive and sleep variables were able to be demonstrated. In order to ensure that no important explanatory variable was omitted from the final analysis, further multiple regression was performed. Each defined cognitive variable was entered as the dependent variable. Independent variables of sleep disordered breathing identified in the stepwise regression, were forced into the multiple regression model and omitted variables entered individually to

determine their effect over and above variables identified from the preceding stepwise regression. The SILS Vt was forced into each equation to control for the effect of general intellectual ability. All steps of the regression modelling are presented in the results.

### **2.6.3 Secondary Analysis of the Data.**

Secondary analyses of clinically relevant outcomes, derived by stepwise and multiple regression, were performed by stratifying the normed cognitive data into quartiles of performance. Similarly, each relevant measure of sleep disordered breathing was stratified into quartiles. The cut-offs for determining percentile decrements in performance, for a given degree of sleep disturbance, were determined by calculation of the sensitivity and specificity curves at each interval. The actual value for each measure of SDB was derived by inspection of the quartile ranges. The odds ratios and confidence intervals for determining the risks of impairment at a given respiratory / arousal index were calculated from the logit transformed probability scale using the asymptotic standard error.

### **2.6.4 Validation Procedure for the Modified Arousal Scoring Method.**

Having re-scored the arousals according to the modified criteria, inter and intra rater variability was determined by paired t-testing of the total number of arousals within each category. A statistically non-significant difference was considered evidence of satisfactory inter-rater agreement. A satisfactory level of concordance was considered to have been achieved for both intra and inter-rater scoring at an r-value of  $> 0.95$ . This was derived by linear regression of the total number of each arousal type between the eight rescored studies of the primary investigator and the eight studies which were rescored by the second observer.

The blinding code was then broken, and the individual totals for each arousal type were assigned to the subjects in the study. All previous steps of analysis from single linear to stepwise and multiple regression were performed using the modified arousal index (AI-M) of interest as the dependent variable and all cognitive outcomes as independent variables. All outcomes of analysis are presented in the results.

## **2.7                      Melatonin Samples.**

### **2.7.1                      Sample Collection Methods.**

All samples were collected by the chief investigator. Following enrollment, all subjects were given two 4 litre urine sample bottles. One teaspoon of boracic acid was added to each sample bottle to reduce odour and to act as a preservative. Subjects were asked to empty their bladders at 7pm on the night of polysomnography. All urine produced overnight through to 0700 the following morning was collected. They were then furnished with a second sample bottle for daytime collection and instructed to return the bottle to the Sleep Unit at the completion of the study i.e. 7pm that evening. Each of the two consecutive 12 hour samples were weighed to measure volume and 10mls stored at minus 70°C for subsequent analysis. Calculation of serum creatinine was performed on the night of PSG and urinary creatinine was determined from each sample. Body mass index was calculated in the standard fashion from measurements performed on the study night.

### **2.7.2                      Analysis Methods.**

#### **2.7.2.1                      Urinary 6 Sulphatoxymelatonin Analysis (6-SM).**

All samples were analysed by radioimmunoassay<sup>167</sup> in the laboratory of Dr David Kennaway (Department of Obstetrics and Gynaecology Adelaide University). The night time samples were diluted prior to the running of the assay. All samples were run in duplicate. Three samples were lost to analysis as a result of unreturned daytime collection.

Total 12 hour urinary 6-SM was calculated by multiplying the measured 6-SM (nmols/L) by the calculated urinary volume (L). To calculate the urine volume,

the Siersbaek-Nielsen<sup>168</sup> nomogram was used. The nomogram determines the urinary output based upon the urinary creatinine, serum creatinine and the body mass index. This step was deemed necessary to control for the possibility of missed samples during the course of collection.

#### **2.7.2.2 Polysomnographic Analysis of Hypoxia and Arousal.**

All sleep studies were scored according to R & K <sup>83</sup> criteria. Measures of hypoxia including minimum saturation in REM and NREM, RDI in REM and NREM, the total RDI and the arousal index were extracted in the same manner as those described in Chapter 2.4.2 for the cognitive data set.

#### **2.7.3 Statistical Analysis of Data.**

The diurnal and nocturnal results were separately analysed. All values were correlated by simple linear regression against the variables of sleep disordered breathing. A p-value of < 0.05 was used to determine relationships of statistical significance.

A subanalysis was also performed to compare subjects without significant OSA (RDI < 5) and those with moderate OSA (RDI > 20). Unpaired t-testing of the subjects within each group was performed to examine whether an intergroup relationship existed external to the simple linear correlation. Results are presented in the subsequent chapter.

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## **RESULTS CHAPTER**

### **3.1 Patient demographics for melatonin data analysis.**

|                        |               |
|------------------------|---------------|
| Age                    | 49 +/- 10.3   |
| BMI                    | 29 +/- 5.2    |
| Total RDI              | 14 +/- 22.4   |
| RDI NREM               | 15.0 +/- 25.0 |
| RDI REM                | 19.7 +/- 22.4 |
| Min sat% NREM          | 86.4 +/- 14.9 |
| Min sat% REM           | 86. +/- 8.7   |
| Total arousal index/hr | 29.3 +/- 22.7 |

All data is expressed as mean +/- standard deviation.

The demographic data demonstrates a satisfactory spread of ages. The spread of values for the parameters of sleep disordered breathing suggest that an adequate patient sample was obtained for data analysis.

### **3.2 Melatonin Data Analysis.**

#### **3.2.1 Simple linear regression of urinary production of 6-sulphatoxymelatonin versus variables of sleep disordered breathing.**

Both diurnal and nocturnal urinary metabolite levels were analysed by simple linear regression against NREM and REM RDI as well as total RDI and the arousal index. Analysis was also performed in the same fashion against parameters of hypoxia including the lowest saturation in REM and NREM sleep. The data for all variables is presented in table form below.

### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI REM

|                    |        |
|--------------------|--------|
| Count              | 39     |
| Num. Missing       | 1      |
| R                  | .102   |
| R Squared          | .010   |
| Adjusted R Squared | •      |
| RMS Residual       | 14.010 |

### ANOVA Table

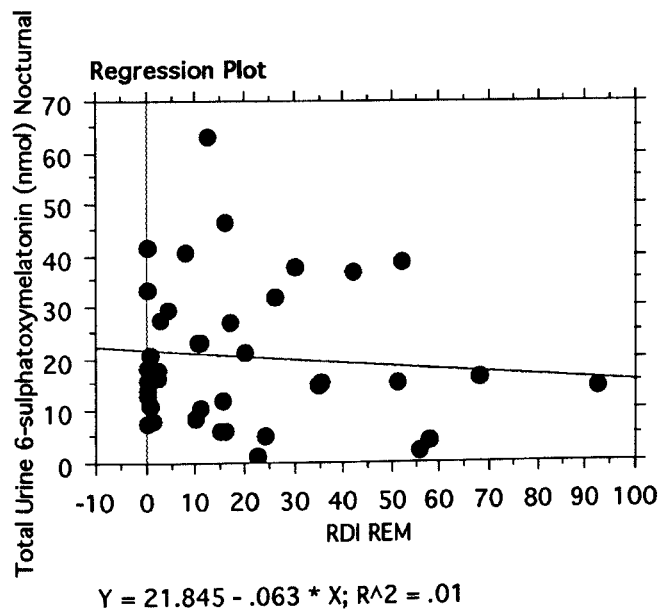
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI REM

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 76.487         | 76.487      | .390    | .5363   |
| Residual   | 37 | 7262.516       | 196.284     |         |         |
| Total      | 38 | 7339.003       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI REM

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 21.845      | 3.006      | 21.845      | 7.266   | <.0001  |
| RDI REM   | -.063       | .102       | -.102       | -.624   | .5363   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI NREM

|                    |        |
|--------------------|--------|
| Count              | 40     |
| Num. Missing       | 0      |
| R                  | .030   |
| R Squared          | .001   |
| Adjusted R Squared | •      |
| RMS Residual       | 13.928 |

### ANOVA Table

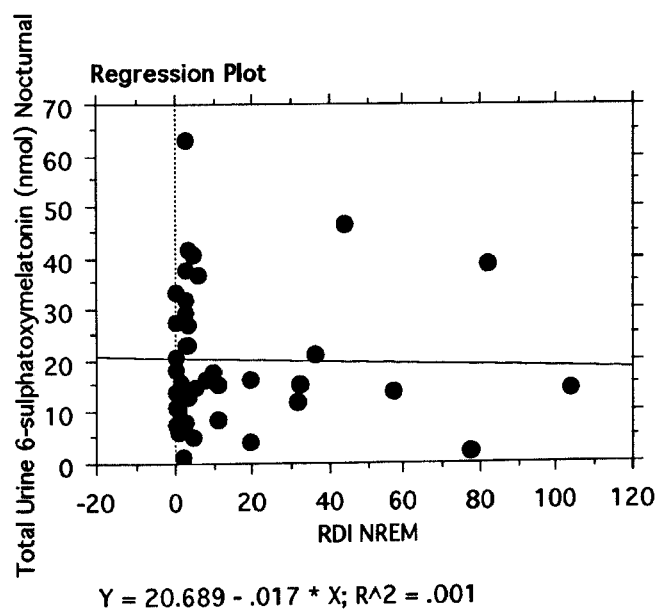
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI NREM

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 6.835          | 6.835       | .035    | .8521   |
| Residual   | 38 | 7371.293       | 193.981     |         |         |
| Total      | 39 | 7378.129       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI NREM

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 20.689      | 2.577      | 20.689      | 8.027   | <.0001  |
| RDI NREM  | -.017       | .089       | -.030       | -.188   | .8521   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(REM)

|                    |        |
|--------------------|--------|
| Count              | 38     |
| Num. Missing       | 2      |
| R                  | .172   |
| R Squared          | .030   |
| Adjusted R Squared | .003   |
| RMS Residual       | 14.065 |

### ANOVA Table

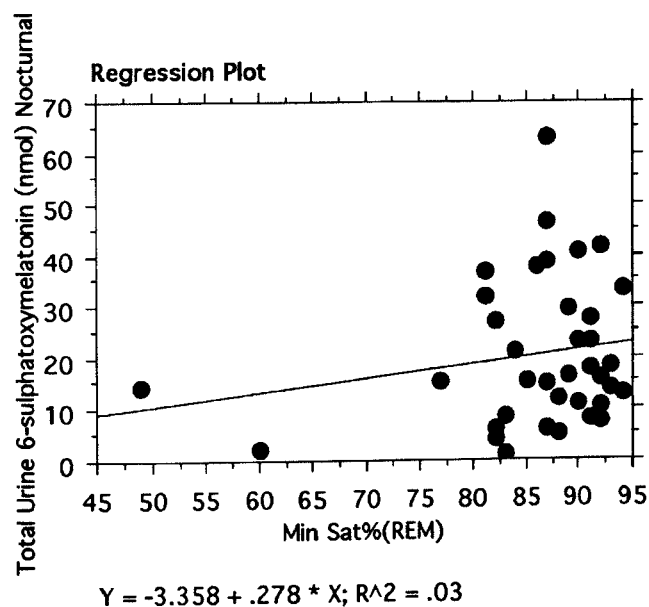
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(REM)

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 217.346        | 217.346     | 1.099   | .3015   |
| Residual   | 36 | 7121.577       | 197.822     |         |         |
| Total      | 37 | 7338.923       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(REM)

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | -3.358      | 22.959     | -3.358      | -.146   | .8845   |
| Min Sat%(REM) | .278        | .266       | .172        | 1.048   | .3015   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(NREM)

|                    |          |
|--------------------|----------|
| Count              | 38       |
| Num. Missing       | 2        |
| R                  | .002     |
| R Squared          | 2.741E-6 |
| Adjusted R Squared | •        |
| RMS Residual       | 14.210   |

### ANOVA Table

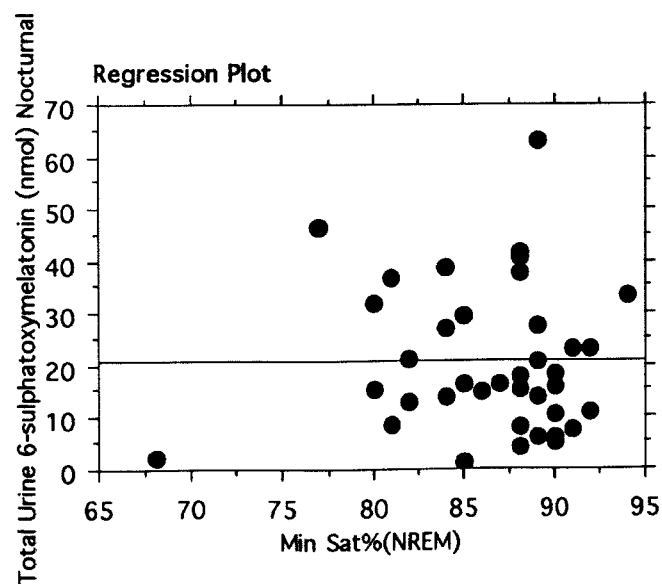
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(NREM)

|            | DF | Sum of Squares | Mean Square | F-Value  | P-Value |
|------------|----|----------------|-------------|----------|---------|
| Regression | 1  | .020           | .020        | 9.867E-5 | .9921   |
| Residual   | 36 | 7268.968       | 201.916     |          |         |
| Total      | 37 | 7268.988       |             |          |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. Min Sat%(NREM)

|                | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|----------------|-------------|------------|-------------|---------|---------|
| Intercept      | 21.214      | 40.775     | 21.214      | .520    | .6061   |
| Min Sat%(NREM) | -.005       | .471       | -.002       | -.010   | .9921   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI

|                    |        |
|--------------------|--------|
| Count              | 40     |
| Num. Missing       | 0      |
| R                  | .098   |
| R Squared          | .010   |
| Adjusted R Squared | •      |
| RMS Residual       | 13.867 |

### ANOVA Table

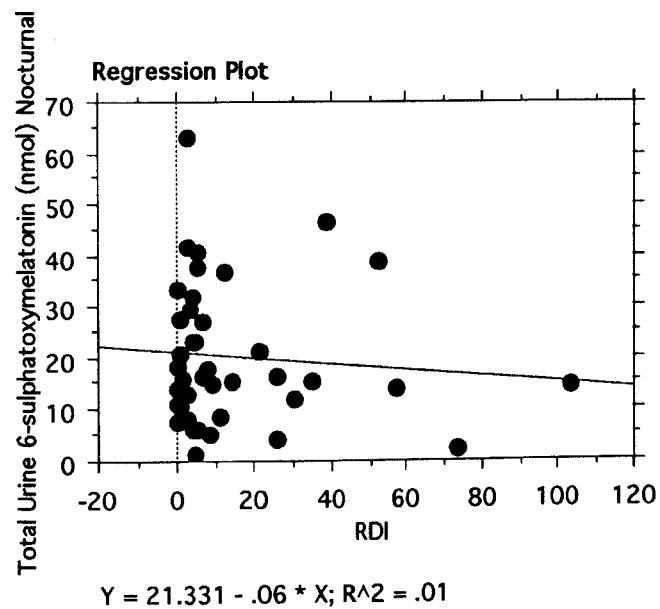
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 70.810         | 70.810      | .368    | .5476   |
| Residual   | 38 | 7307.319       | 192.298     |         |         |
| Total      | 39 | 7378.129       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. RDI

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 21.331      | 2.641      | 21.331      | 8.076   | <.0001  |
| RDI       | -.060       | .099       | -.098       | -.607   | .5476   |



# Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. AI

|                    |        |
|--------------------|--------|
| Count              | 40     |
| Num. Missing       | 0      |
| R                  | .046   |
| R Squared          | .002   |
| Adjusted R Squared | •      |
| RMS Residual       | 13.920 |

# ANOVA Table

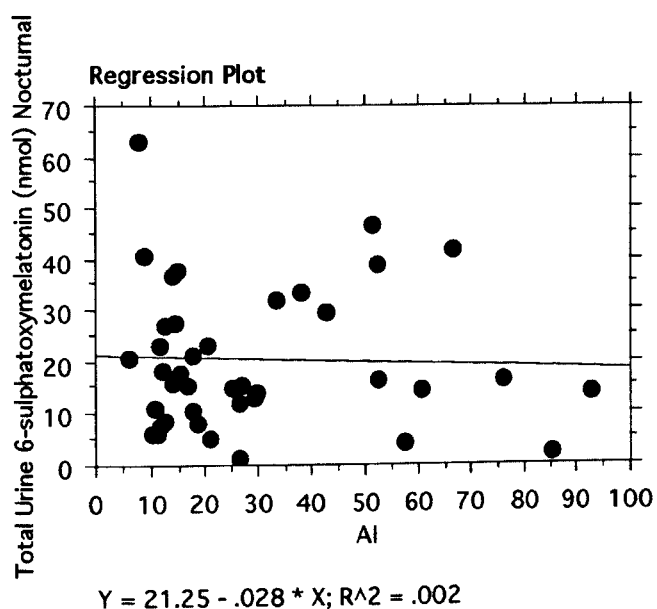
Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. AI

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 15.525         | 15.525      | .080    | .7787   |
| Residual   | 38 | 7362.604       | 193.753     |         |         |
| Total      | 39 | 7378.129       |             |         |         |

# Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Nocturnal vs. AI

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 21.250      | 3.617      | 21.250      | 5.876   | <.0001  |
| AI        | -.028       | .098       | -.046       | -.283   | .7787   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI REM

|                    |       |
|--------------------|-------|
| Count              | 36    |
| Num. Missing       | 4     |
| R                  | .186  |
| R Squared          | .035  |
| Adjusted R Squared | .006  |
| RMS Residual       | 7.173 |

### ANOVA Table

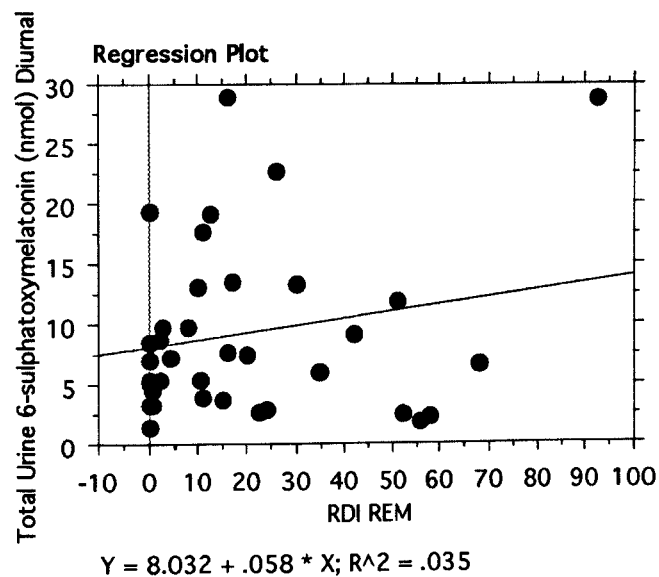
Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI REM

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 62.809         | 62.809      | 1.221   | .2769   |
| Residual   | 34 | 1749.177       | 51.446      |         |         |
| Total      | 35 | 1811.987       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI REM

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 8.032       | 1.592      | 8.032       | 5.044   | <.0001  |
| RDI REM   | .058        | .053       | .186        | 1.105   | .2769   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI NREM

|                    |       |
|--------------------|-------|
| Count              | 37    |
| Num. Missing       | 3     |
| R                  | .237  |
| R Squared          | .056  |
| Adjusted R Squared | .029  |
| RMS Residual       | 8.230 |

### ANOVA Table

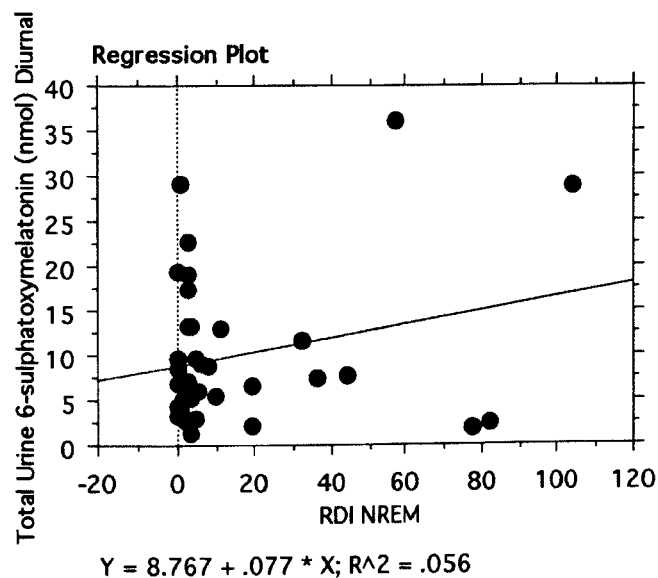
Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI NREM

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 141.448        | 141.448     | 2.088   | .1573   |
| Residual   | 35 | 2370.546       | 67.730      |         |         |
| Total      | 36 | 2511.994       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI NREM

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 8.767       | 1.570      | 8.767       | 5.583   | <.0001  |
| RDI NREM  | .077        | .053       | .237        | 1.445   | .1573   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(REM)

|                    |       |
|--------------------|-------|
| Count              | 35    |
| Num. Missing       | 5     |
| R                  | .334  |
| R Squared          | .111  |
| Adjusted R Squared | .085  |
| RMS Residual       | 6.941 |

### ANOVA Table

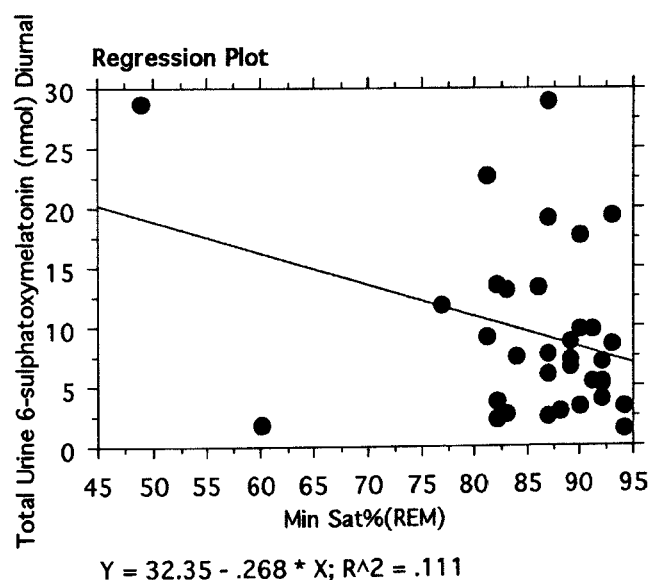
Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(REM)

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 199.461        | 199.461     | 4.140   | .0500   |
| Residual   | 33 | 1589.964       | 48.181      |         |         |
| Total      | 34 | 1789.425       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(REM)

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 32.350      | 11.375     | 32.350      | 2.844   | .0076   |
| Min Sat%(REM) | -.268       | .132       | -.334       | -2.035  | .0500   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(NREM)

|                    |       |
|--------------------|-------|
| Count              | 36    |
| Num. Missing       | 4     |
| R                  | .028  |
| R Squared          | .001  |
| Adjusted R Squared | •     |
| RMS Residual       | 7.943 |

### ANOVA Table

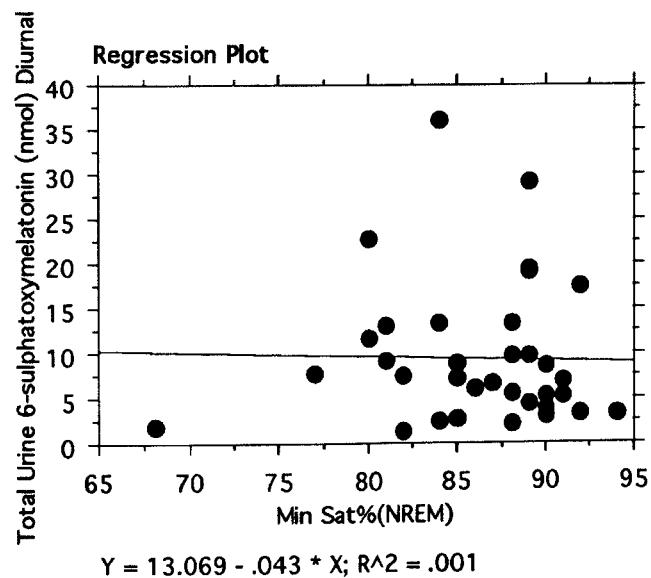
Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(NREM)

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1.637          | 1.637       | .026    | .8730   |
| Residual   | 34 | 2145.223       | 63.095      |         |         |
| Total      | 35 | 2146.859       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. Min Sat%(NREM)

|                | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|----------------|-------------|------------|-------------|---------|---------|
| Intercept      | 13.069      | 22.842     | 13.069      | .572    | .5710   |
| Min Sat%(NREM) | -.043       | .264       | -.028       | -.161   | .8730   |



### Regression Summary

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI

|                    |       |
|--------------------|-------|
| Count              | 37    |
| Num. Missing       | 3     |
| R                  | .299  |
| R Squared          | .089  |
| Adjusted R Squared | .063  |
| RMS Residual       | 8.085 |

### ANOVA Table

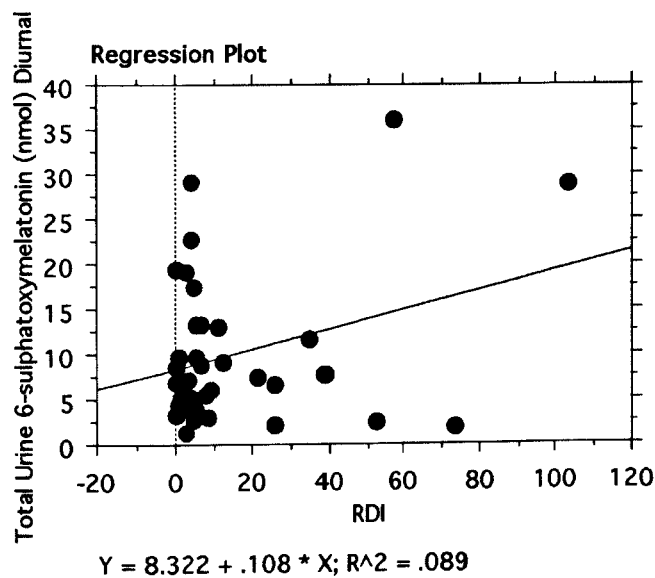
Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 224.335        | 224.335     | 3.432   | .0724   |
| Residual   | 35 | 2287.659       | 65.362      |         |         |
| Total      | 36 | 2511.994       |             |         |         |

### Regression Coefficients

Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. RDI

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 8.322       | 1.584      | 8.322       | 5.252   | <.0001  |
| RDI       | .108        | .058       | .299        | 1.853   | .0724   |



#### Regression Summary

##### Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. AI

|                    |       |
|--------------------|-------|
| Count              | 37    |
| Num. Missing       | 3     |
| R                  | .147  |
| R Squared          | .022  |
| Adjusted R Squared | •     |
| RMS Residual       | 8.380 |

#### ANOVA Table

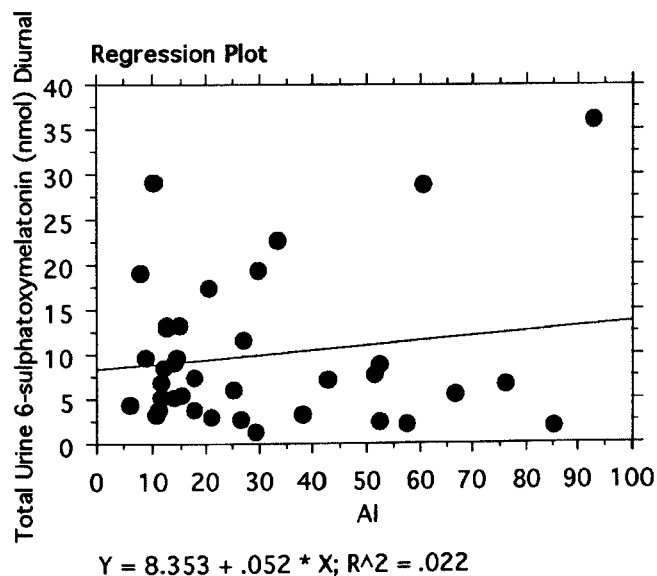
##### Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. AI

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 54.241         | 54.241      | .772    | .3855   |
| Residual   | 35 | 2457.753       | 70.222      |         |         |
| Total      | 36 | 2511.994       |             |         |         |

#### Regression Coefficients

##### Total Urine 6-sulphatoxymelatonin (nmol) Diurnal vs. AI

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 8.353       | 2.252      | 8.353       | 3.708   | .0007   |
| AI        | .052        | .060       | .147        | .879    | .3855   |

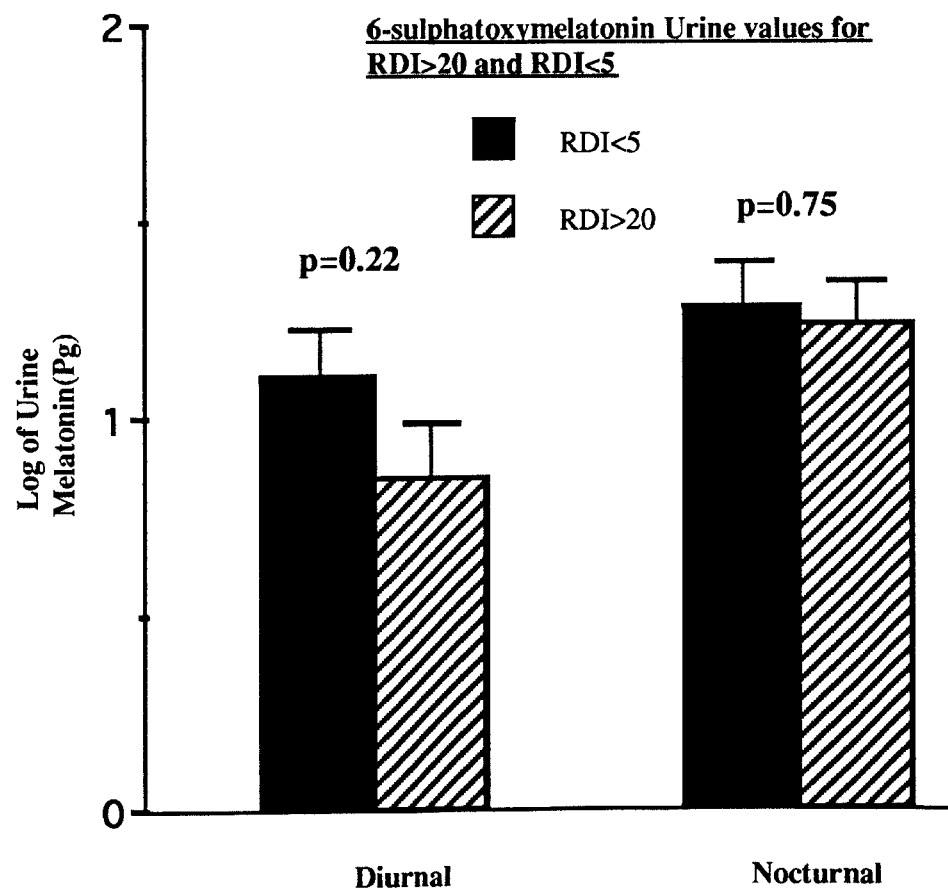


The results demonstrate that no relationship exists between the diurnal or nocturnal production of melatonin, as measured by urinary metabolite and the magnitude of sleep disordered breathing as defined by standard criteria.

### 3.2.2

#### Unpaired t-testing of apnoeic (RDI>20) versus non-apnoeic (RDI<5) patient groups.

Despite the lack of a direct correlation between the magnitude of SDB, a subsequent analysis between subjects with moderate to severe OSA (RDI>20) and those within the clinical normal range (RDI<5) was performed to explore the possibility of a relationship existing between the severity of OSA and melatonin production which was not evident from the linear regression data. The graph below demonstrates there is no difference between nocturnal or diurnal melatonin production between these two groups by unpaired t-testing. The urinary values have been logged for presentation purposes to overcome the large differences between daytime and night time production of the hormone.



## **SUMMARY OF MELATONIN DATA**

The findings of this arm of the study do not support the hypothesis that abnormal production of melatonin occurs as a result of sleep disordered breathing, and is thus unlikely to play a key role in the genesis of daytime somnolence in this condition.

### **3.3**

#### **Patient demographics for cognitive data analysis.**

|                                           |                |
|-------------------------------------------|----------------|
| Age                                       | 51 +/- 12      |
| Level of education (years)                | 15 +/- 3       |
| BMI                                       | 29.1 +/- 4.4   |
| Total RDI                                 | 14. +/- 19.1   |
| RDI NREM                                  | 12.5 +/- 19.2  |
| RDI REM                                   | 22.9 +/- 24    |
| Min sat % NREM                            | 86.2 +/- 5.4   |
| Min sat % REM                             | 84.4 +/- 6.8   |
| Total Sleep time(min)                     | 307.9 +/- 56.4 |
| Total arousal index/hr                    | 29.3 +/- 14.5  |
| Estimated WAIS Full Scale IQ from Shipley | 114 +/- 12     |

All data is expressed as mean +/- standard deviation

The majority of patients had received education up to high school (10 - 12 years) although the mean IQ suggests they were an above average group for intelligence. The data with respect to NREM and REM RDI as well as arousal index demonstrates a spread of values ranging between severe OSA and patients without clinical sleep disordered breathing and suggests that a suitable range of subjects was enrolled for the study.

### **3.4**

#### **Simple regression analysis of cognitive variables versus variables of hypoxia.**

For ease of presentation, and in light of the large number of regression analyses only those correlations which reached statistically significant values ( $P < 0.05$ ) are presented in of the following chapters. Remaining correlations are presented in Appendix 1 The major findings are presented in the following table including those for Chapter 3.5.1 (total arousal index versus cognitive outcomes). Correlation matrices for each relationship are discussed in detail in each sub-chapter.

### Simple regression correlates

| Cognitive test    | Variable of sleep<br>disordered<br>breathing | p<br>value | r<br>squared | correl<br>-ation |
|-------------------|----------------------------------------------|------------|--------------|------------------|
| Logical memory I  | Arousal index                                | 0.05       | 0.13         | -                |
| Logical memory II | Arousal index                                | 0.05       | 0.15         | -                |
| Logical memory I  | NREM RDI                                     | 0.02       | 0.09         | -                |
| Logical memory II | NREM RDI                                     | 0.01       | 0.10         | -                |
| Logical memory I  | Log desat% <90                               | 0.05       | 0.09         | -                |
| Logical memory II | Log desat% <90                               | 0.01       | 0.14         | -                |
| Logical memory II | Total RDI                                    | 0.04       | 0.08         | -                |
| Symbol digit      | Total RDI                                    | 0.03       | 0.08         | -                |
| Symbol digit      | RDI REM                                      | 0.05       | 0.15         | -                |
| PASAT             | Total RDI                                    | 0.02       | 0.10         | -                |
| PASAT             | NREM RDI                                     | 0.02       | 0.11         | -                |
| PASAT             | Min. sat% NREM                               | 0.02       | 0.11         | -                |
| PASAT             | Min. sat% REM                                | 0.03       | 0.10         | -                |
| Digitspan reverse | Log desat% <90                               | 0.05       | 0.09         | -                |
| Epworth scale     | Arousal index                                | 0.03       | 0.09         | -                |
| Steer Clear       | Log desat% <90                               | 0.04       | 0.10         | -                |
| COWA              | Arousal Index                                | 0.03       | 0.08         | +                |

The table demonstrates 17 statistically significant results by simple linear regression out of 147 performed. This is in excess of that which would be likely to occur by chance for the given number of variables suggesting they cannot readily be put down to Type I error. All of the associations in the above table have clinical explanations with the exception of COWA versus AI. This final relationship is counter intuitive and therefore thought to be spurious.

### 3.4.1

### Cognitive outcomes versus NREM RDI.

#### Regression Summary

##### RDI NREM vs. Logical MP 1

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .282   |
| R Squared          | .079   |
| Adjusted R Squared | .062   |
| RMS Residual       | 18.564 |

#### ANOVA Table

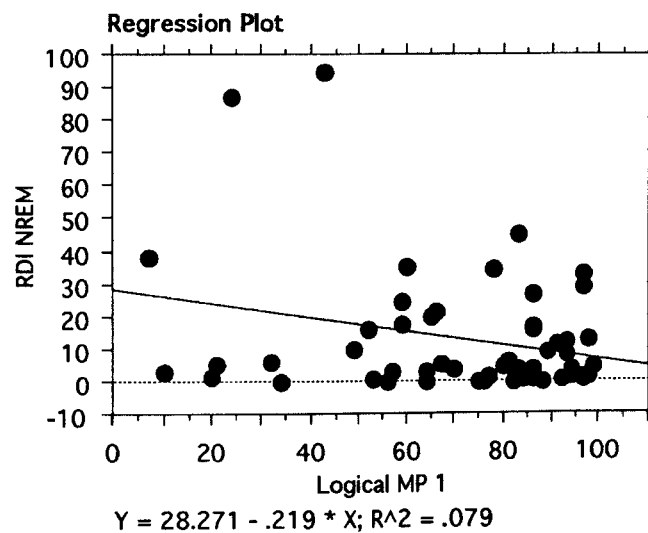
##### RDI NREM vs. Logical MP 1

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1574.437       | 1574.437    | 4.568   | .0372   |
| Residual   | 53 | 18265.508      | 344.632     |         |         |
| Total      | 54 | 19839.945      |             |         |         |

#### Regression Coefficients

##### RDI NREM vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 28.271      | 7.788      | 28.271      | 3.630   | .0006   |
| Logical MP 1 | -.219       | .103       | -.282       | -2.137  | .0372   |



### Regression Summary

RDI NREM vs. Logical MP 2

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .317   |
| R Squared          | .100   |
| Adjusted R Squared | .083   |
| RMS Residual       | 18.351 |

### ANOVA Table

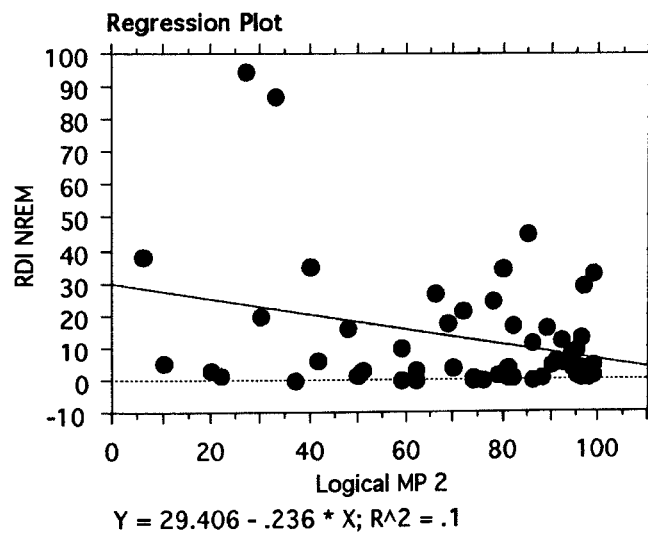
RDI NREM vs. Logical MP 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1992.571       | 1992.571    | 5.917   | .0184   |
| Residual   | 53 | 17847.375      | 336.743     |         |         |
| Total      | 54 | 19839.945      |             |         |         |

### Regression Coefficients

RDI NREM vs. Logical MP 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 29.406      | 7.374      | 29.406      | 3.988   | .0002   |
| Logical MP 2 | -.236       | .097       | -.317       | -2.433  | .0184   |



**Regression Summary**  
**RDI NREM vs. PASAT**

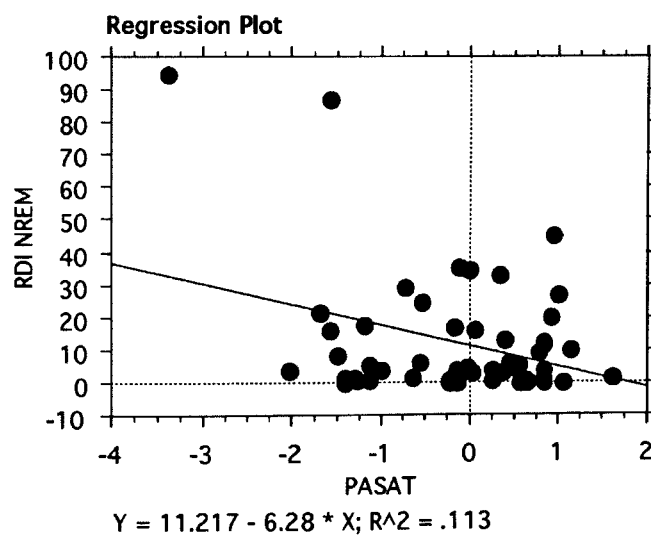
|                    |        |
|--------------------|--------|
| Count              | 52     |
| Num. Missing       | 3      |
| R                  | .336   |
| R Squared          | .113   |
| Adjusted R Squared | .095   |
| RMS Residual       | 18.329 |

**ANOVA Table**  
**RDI NREM vs. PASAT**

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 2139.522       | 2139.522    | 6.369   | .0148   |
| Residual   | 50 | 16796.932      | 335.939     |         |         |
| Total      | 51 | 18936.454      |             |         |         |

**Regression Coefficients**  
**RDI NREM vs. PASAT**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 11.217      | 2.586      | 11.217      | 4.338   | <.0001  |
| PASAT     | -6.280      | 2.488      | -.336       | -2.524  | .0148   |



The above matrices demonstrate that both immediate and delayed short term memory are adversely effected by increasing respiratory events in NREM sleep. Furthermore, there is an adverse relationship between working memory, as measured by PASAT and this sleep variable. The relationship between the NREM RDI and both logical memory I and II is best explained by the strength of the relationship between arousal and STM decrement. By multiple regression, the correlation between NREM RDI and LM1 and 2 becomes non-significant when the arousal index is forced into the equation. This is explained by the power of the correlation between the arousal index and these two cognitive outcomes. More detail with respect to these findings are presented in Chapters 3.5.1 and 3.7.

### 3.4.2

### Cognitive outcomes versus REM RDI.

#### Regression Summary

##### RDI REM vs. Symbol digit

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .385   |
| R Squared          | .148   |
| Adjusted R Squared | .132   |
| RMS Residual       | 22.322 |

#### ANOVA Table

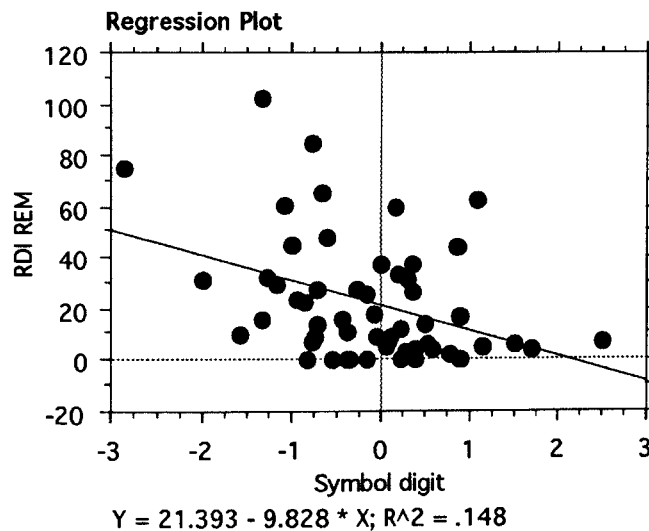
##### RDI REM vs. Symbol digit

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 4590.969       | 4590.969    | 9.214   | .0037   |
| Residual   | 53 | 26408.548      | 498.274     |         |         |
| Total      | 54 | 30999.517      |             |         |         |

#### Regression Coefficients

##### RDI REM vs. Symbol digit

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 21.393      | 3.048      | 21.393      | 7.019   | <.0001  |
| Symbol digit | -9.828      | 3.238      | -.385       | -3.035  | .0037   |



This correlation demonstrates a novel relationship between increasing severity of OSA in REM sleep and a decrement in information processing speed. This finding is discussed in greater detail in Chapters 2.7 - 2.8, particularly with respect to the inability of other sleep variables to account for the strength of this observation.

### 3.4.3 Cognitive outcomes versus minimum saturation in NREM sleep.

#### Regression Summary

##### Min desat% NREM vs. PASAT

|                    |       |
|--------------------|-------|
| Count              | 52    |
| Num. Missing       | 3     |
| R                  | .334  |
| R Squared          | .112  |
| Adjusted R Squared | .094  |
| RMS Residual       | 4.952 |

#### ANOVA Table

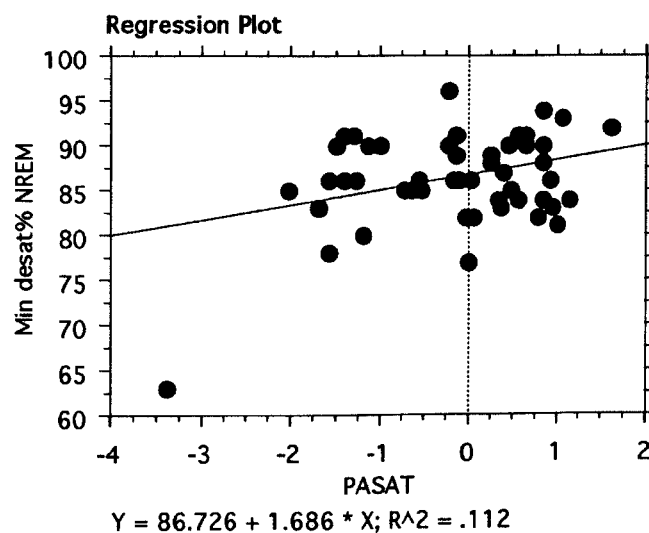
##### Min desat% NREM vs. PASAT

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 154.212        | 154.212     | 6.288   | .0155   |
| Residual   | 50 | 1226.307       | 24.526      |         |         |
| Total      | 51 | 1380.519       |             |         |         |

#### Regression Coefficients

##### Min desat% NREM vs. PASAT

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 86.726      | .699       | 86.726      | 124.125 | <.0001  |
| PASAT     | 1.686       | .672       | .334        | 2.508   | .0155   |



The correlation above demonstrates a relationship between a decline in working memory in association with more severe hypoxia in NREM sleep. It may well account for the findings in Chapter 3.4.1 which demonstrated a similar negative correlation between PASAT and NREM RDI. Indeed, by multiple regression when PASAT is entered as the dependent variable and the NREM RDI is entered as the independent variable, if the minimum saturation in NREM is forced into the equation, the relationship between the NREM RDI and PASAT fails to reach significance. Entering the data with the minimum saturation as an independent variable and forcing the NREM RDI into the equation yields the same non-significant result as demonstrated in the tables below:

**Regression Coefficients  
PASAT vs. 2 Independents**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | -3.222      | 3.741      | -3.222      | -.861   | .3933   |
| RDI NREM        | -.010       | .011       | -.193       | -.911   | .3668   |
| Min desat% NREM | .037        | .042       | .184        | .871    | .3882   |

**Regression Coefficients  
PASAT vs. 2 Independents**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | -3.222      | 3.741      | -3.222      | -.861   | .3933   |
| Min desat% NREM | .037        | .042       | .184        | .871    | .3882   |
| RDI NREM        | -.010       | .011       | -.193       | -.911   | .3668   |

This suggests that the finding of a relationship between working memory and the magnitude of the hypoxic insult in NREM sleep is not a separate finding but relates to the magnitude of OSA in NREM generally.

### 3.4.4

### Cognitive outcomes versus minimum saturation in REM sleep.

#### Regression Summary

Min desat% REM vs. Symbol digit

|                    |       |
|--------------------|-------|
| Count              | 54    |
| Num. Missing       | 1     |
| R                  | .286  |
| R Squared          | .082  |
| Adjusted R Squared | .064  |
| RMS Residual       | 6.582 |

#### ANOVA Table

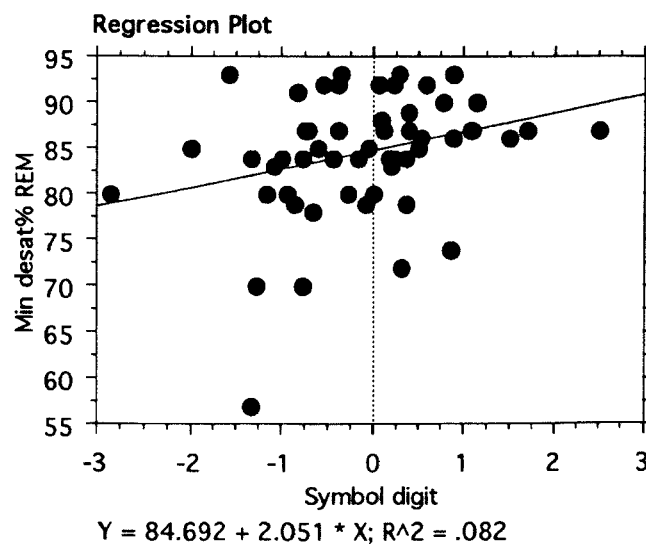
Min desat% REM vs. Symbol digit

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 199.936        | 199.936     | 4.615   | .0364   |
| Residual   | 52 | 2252.898       | 43.325      |         |         |
| Total      | 53 | 2452.833       |             |         |         |

#### Regression Coefficients

Min desat% REM vs. Symbol digit

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 84.692      | .907       | 84.692      | 93.400  | <.0001  |
| Symbol digit | 2.051       | .955       | .286        | 2.148   | .0364   |



### Regression Summary

Min desat% REM vs. PASAT

|                    |       |
|--------------------|-------|
| Count              | 51    |
| Num. Missing       | 4     |
| R                  | .308  |
| R Squared          | .095  |
| Adjusted R Squared | .076  |
| RMS Residual       | 6.624 |

### ANOVA Table

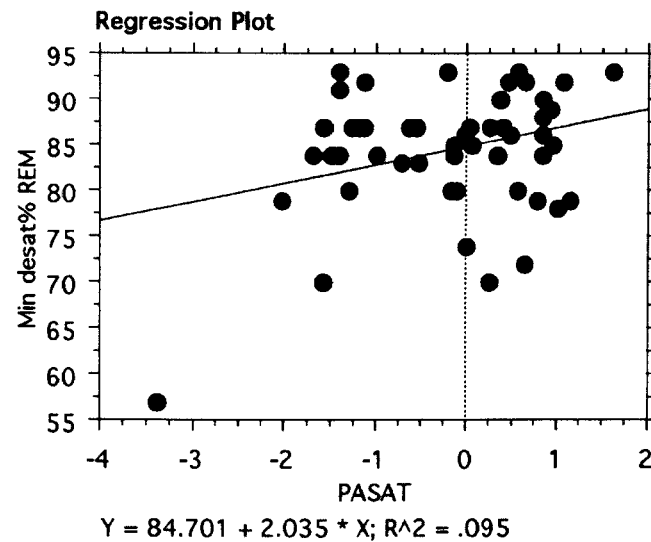
Min desat% REM vs. PASAT

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 224.664        | 224.664     | 5.120   | .0281   |
| Residual   | 49 | 2150.316       | 43.884      |         |         |
| Total      | 50 | 2374.980       |             |         |         |

### Regression Coefficients

Min desat% REM vs. PASAT

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 84.701      | .943       | 84.701      | 89.793  | <.0001  |
| PASAT     | 2.035       | .899       | .308        | 2.263   | .0281   |



The finding of a relationship between the minimum saturation in REM sleep and a decline in information processing is not surprising given the strength of the simple regression analysis of the REM RDI and symbol digit. Indeed, using the same multiple regression as that discussed with respect to NREM minimum sat%, RDI and PASAT, it is evident that while the forcing of the REM minimum sat% variable diminishes the statistical power of the REM RDI versus symbol digit correlation it remains significant. Inversely forcing the REM RDI variable into the model where the REM minimum sat% is the independent variable the relationship becomes non-significant. This multiple regression is presented in the tables below:

**Regression Coefficients  
Symbol digit vs. 2 Independents**

|                | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|----------------|-------------|------------|-------------|---------|---------|
| Intercept      | .356        | 2.422      | .356        | .147    | .8838   |
| Min desat% REM | -.002       | .027       | -.012       | -.061   | .9520   |
| RDI REM        | -.016       | .008       | -.398       | -2.046  | .0459   |

**Regression Coefficients  
Symbol digit vs. 2 Independents**

|                | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|----------------|-------------|------------|-------------|---------|---------|
| Intercept      | .356        | 2.422      | .356        | .147    | .8838   |
| RDI REM        | -.016       | .008       | -.398       | -2.046  | .0459   |
| Min desat% REM | -.002       | .027       | -.012       | -.061   | .9520   |

Thus the finding of a statistically significant correlation between the minimum saturation in REM and the speed of information processing is largely determined by the strength of the relationship between REM RDI and symbol digit.

The demonstrated correlation between a decline in working memory, as measured by PASAT and the minimum saturation in REM sleep is of interest. Given the findings in Chapter 3.4.3 of a relationship between the minimum saturation in NREM sleep and working memory, this corroborative correlation lends force to the suggestion that a decrement in working memory is determined by the magnitude of the hypoxic injury.

### 3.4.5 Cognitive outcomes versus log of the time with a saturation <90% versus cognitive outcomes.

#### Regression Summary

##### Log Desat <90% vs. Logical MP 1

|                    |       |
|--------------------|-------|
| Count              | 43    |
| Num. Missing       | 12    |
| R                  | .307  |
| R Squared          | .094  |
| Adjusted R Squared | .072  |
| RMS Residual       | 1.014 |

#### ANOVA Table

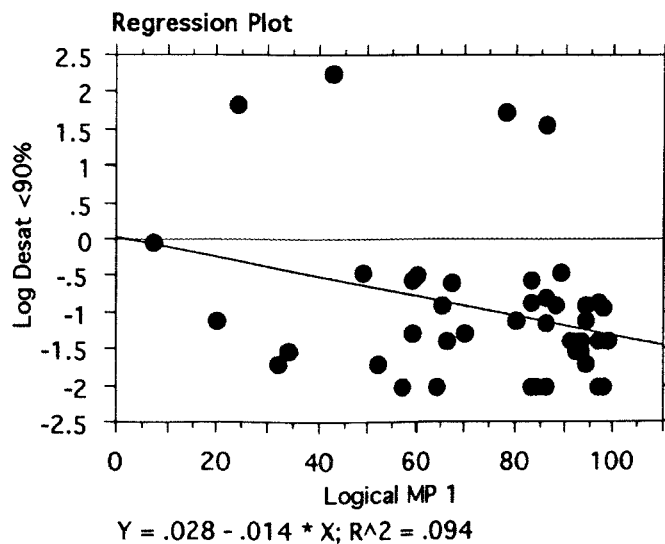
##### Log Desat <90% vs. Logical MP 1

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 4.381          | 4.381       | 4.261   | .0454   |
| Residual   | 41 | 42.158         | 1.028       |         |         |
| Total      | 42 | 46.539         |             |         |         |

#### Regression Coefficients

##### Log Desat <90% vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | .028        | .506       | .028        | .056    | .9557   |
| Logical MP 1 | -.014       | .007       | -.307       | -2.064  | .0454   |



### Regression Summary

Log Desat <90% vs. Logical MP 2

|                    |      |
|--------------------|------|
| Count              | 43   |
| Num. Missing       | 12   |
| R                  | .375 |
| R Squared          | .140 |
| Adjusted R Squared | .119 |
| RMS Residual       | .988 |

### ANOVA Table

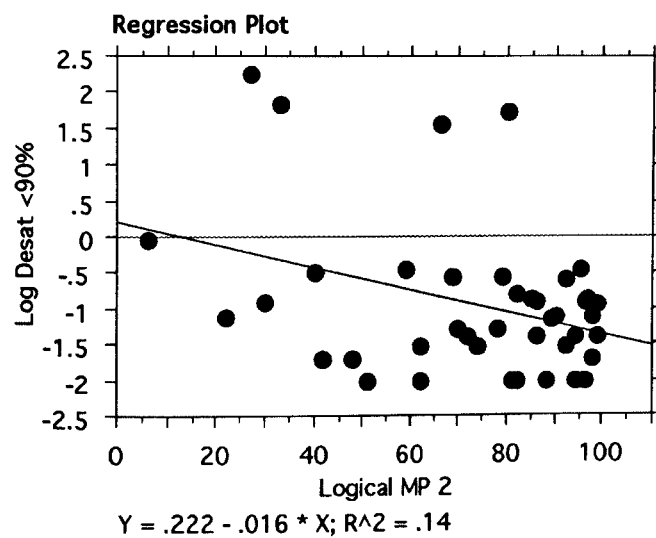
Log Desat <90% vs. Logical MP 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 6.531          | 6.531       | 6.693   | .0133   |
| Residual   | 41 | 40.008         | .976        |         |         |
| Total      | 42 | 46.539         |             |         |         |

### Regression Coefficients

Log Desat <90% vs. Logical MP 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | .222        | .483       | .222        | .460    | .6482   |
| Logical MP 2 | -.016       | .006       | -.375       | -2.587  | .0133   |



### Regression Summary

Log Desat <90% vs. Digitspan reverse

|                    |       |
|--------------------|-------|
| Count              | 43    |
| Num. Missing       | 12    |
| R                  | .302  |
| R Squared          | .091  |
| Adjusted R Squared | .069  |
| RMS Residual       | 1.016 |

### ANOVA Table

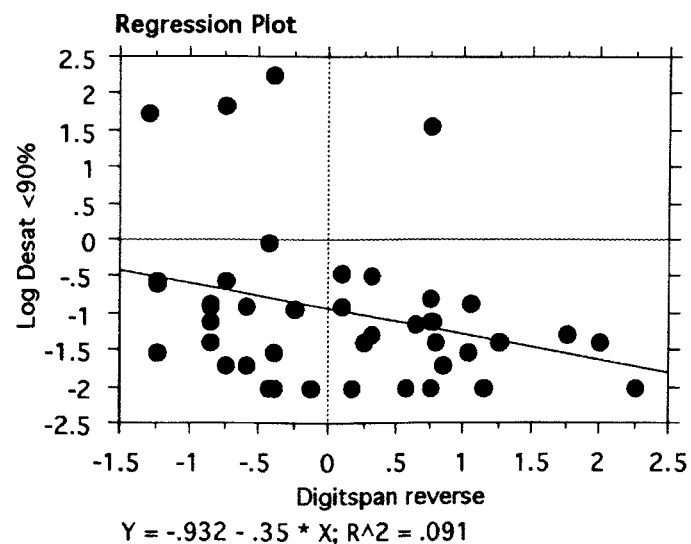
Log Desat <90% vs. Digitspan reverse

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 4.245          | 4.245       | 4.115   | .0490   |
| Residual   | 41 | 42.294         | 1.032       |         |         |
| Total      | 42 | 46.539         |             |         |         |

### Regression Coefficients

Log Desat <90% vs. Digitspan reverse

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | -.932       | .156       | -.932       | -5.980  | <.0001  |
| Digitspan reverse | -.350       | .173       | -.302       | -2.029  | .0490   |



### Regression Summary

Log Desat <90% vs. Z scores for S.C.

|                    |       |
|--------------------|-------|
| Count              | 43    |
| Num. Missing       | 12    |
| R                  | .318  |
| R Squared          | .101  |
| Adjusted R Squared | .079  |
| RMS Residual       | 1.010 |

### ANOVA Table

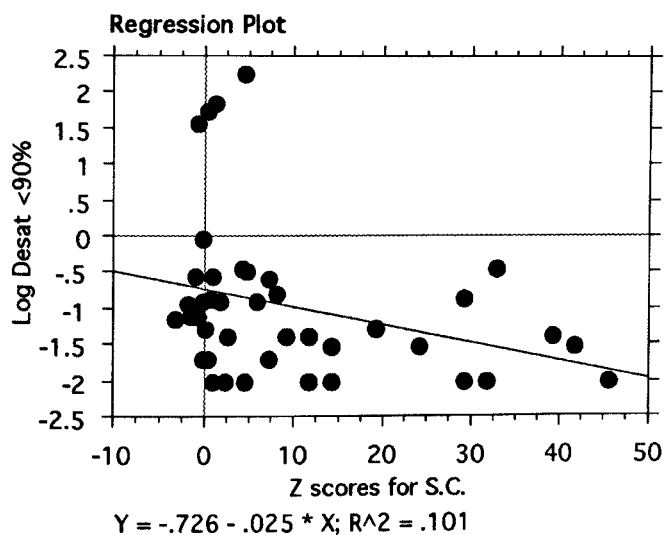
Log Desat <90% vs. Z scores for S.C.

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 4.698          | 4.698       | 4.603   | .0379   |
| Residual   | 41 | 41.841         | 1.021       |         |         |
| Total      | 42 | 46.539         |             |         |         |

### Regression Coefficients

Log Desat <90% vs. Z scores for S.C.

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | -.726       | .190       | -.726       | -3.813  | .0005   |
| Z scores for S.C. | -.025       | .012       | -.318       | -2.145  | .0379   |



The correlation between the log of the desat% <90 (LD<90%) and a decline in both immediate and delayed short term memory is interesting, although it is difficult to interpret the independent worth of this finding given the strong internal correlation between the NREM RDI and the LD<90% ( $r^2 = 0.57$ ). Furthermore there is a strong internal correlation between the arousal index and the LD<90% ( $r^2 = 0.40$ ). It is therefore most likely a consequence of the relationship between the arousal index, the NREM RDI and these tests of memory function which has produced this finding. To substantiate that the magnitude of the hypoxic insult independent of either of these parameters of sleep disordered breathing was related to the decrement on short term memory alone is beyond the power of this study and is unlikely to be clinical pertinent for OSA.

The correlation between the magnitude of the hypoxic insult and the digit span reverse demonstrates further the inter-relationship between working memory and hypoxia. As a alternate type of working memory test (i.e. in contrast to PASAT) it may be more sensitive to total hypoxia than to the minimum saturation in either REM or NREM.

The finding of a relationship between the z-score for Steer Clear and the total hypoxic insult may be of some clinical significance. This is a novel finding which for the first time demonstrates a correlation between vigilance (and possibly motor vehicle accidents) and a specific measureable dimension of sleep disordered breathing. The importance of this finding and its relationship to the other measures of SDB are discussed in Chapter 3.7.

### **3.5 Simple regression analysis of cognitive variables versus arousals.**

#### **3.5.1 Cognitive outcomes versus total arousal index.**

### Regression Summary

#### Arousal Index vs. Logical MP 1

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .365   |
| R Squared          | .133   |
| Adjusted R Squared | .117   |
| RMS Residual       | 13.650 |

### ANOVA Table

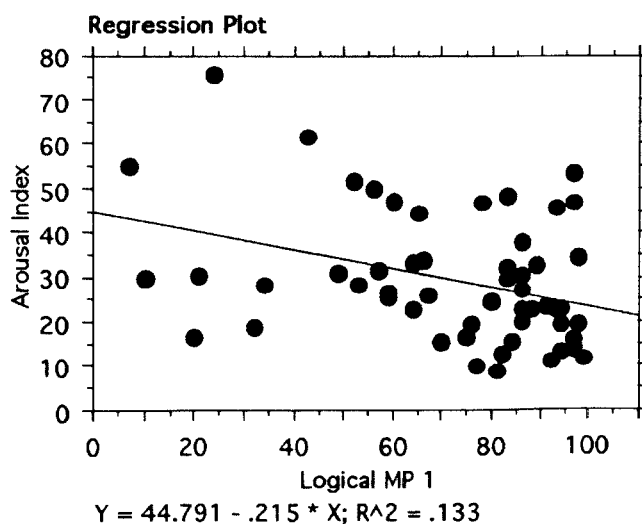
#### Arousal Index vs. Logical MP 1

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1516.979       | 1516.979    | 8.142   | .0062   |
| Residual   | 53 | 9874.909       | 186.319     |         |         |
| Total      | 54 | 11391.888      |             |         |         |

### Regression Coefficients

#### Arousal Index vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 44.791      | 5.726      | 44.791      | 7.822   | <.0001  |
| Logical MP 1 | -.215       | .075       | -.365       | -2.853  | .0062   |



**Regression Summary****Arousal Index vs. Logical MP 2**

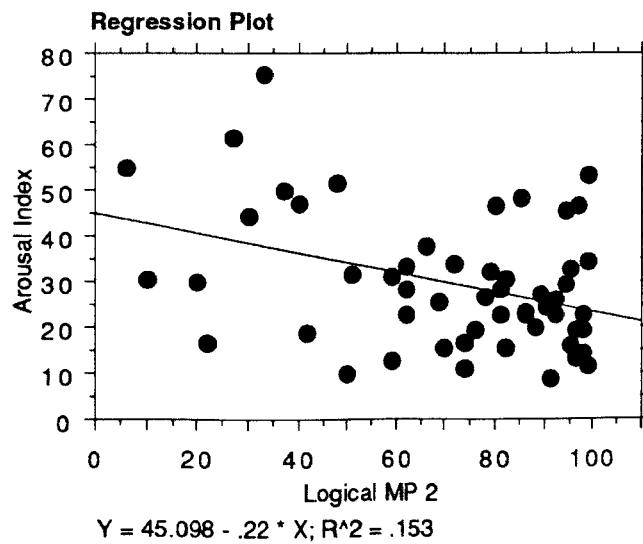
|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .391   |
| R Squared          | .153   |
| Adjusted R Squared | .137   |
| RMS Residual       | 13.497 |

**ANOVA Table****Arousal Index vs. Logical MP 2**

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1737.429       | 1737.429    | 9.538   | .0032   |
| Residual   | 53 | 9654.459       | 182.160     |         |         |
| Total      | 54 | 11391.888      |             |         |         |

**Regression Coefficients****Arousal Index vs. Logical MP 2**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 45.098      | 5.423      | 45.098      | 8.316   | <.0001  |
| Logical MP 2 | -.220       | .071       | -.391       | -3.088  | .0032   |



**Regression Summary****Arousal Index vs. Epworth SS**

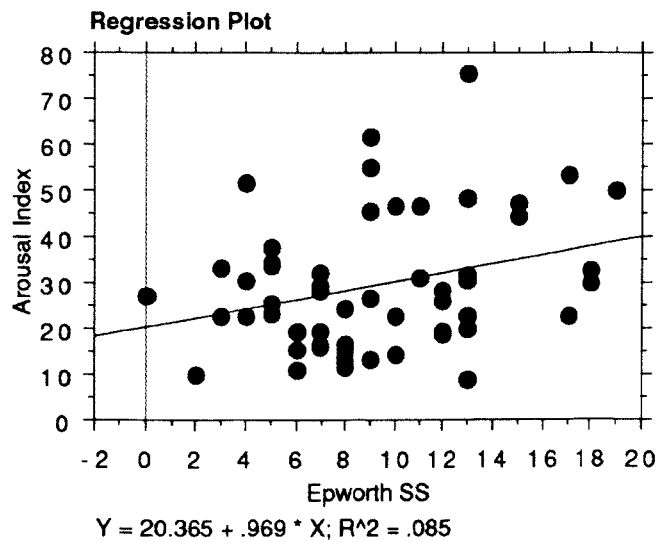
|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .292   |
| R Squared          | .085   |
| Adjusted R Squared | .068   |
| RMS Residual       | 14.023 |

**ANOVA Table****Arousal Index vs. Epworth SS**

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 969.914        | 969.914     | 4.932   | .0307   |
| Residual   | 53 | 10421.974      | 196.641     |         |         |
| Total      | 54 | 11391.888      |             |         |         |

**Regression Coefficients****Arousal Index vs. Epworth SS**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 20.365      | 4.453      | 20.365      | 4.573   | <.0001  |
| Epworth SS | .969        | .437       | .292        | 2.221   | .0307   |



The above correlations demonstrate a negative relationship between the severity of sleep disruption and the magnitude of the decline in both immediate and delayed short term memory. This finding is discussed in greater detail in Chapters 3.7 - 3.8 and is demonstrated to be independent of the respiratory disturbance index in both NREM and REM sleep. The correlation demonstrating a relationship between the magnitude of sleep fragmentation and subjective reporting of sleepiness makes intuitive sense but has not previously been demonstrated in this manner. Examination of the regression summary demonstrates that approximately 30% of subjective somnolence can be accounted for by the degree of sleep fragmentation suggesting that other factors may be important. The lack of a demonstrable relationship between other parameters of SDB and the Epworth Sleepiness Scale (ESS) does not discount their importance to the genesis of excessive daytime sleepiness and may be the result of inherent weaknesses in the ESS and its ability to detect subtle levels of somnolence.

A separate finding from this study was an internal correlation between Steer Clear and ESS (see below).

### Regression Summary

Z scores for S.C. vs. Epworth SS

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .298   |
| R Squared          | .089   |
| Adjusted R Squared | .072   |
| RMS Residual       | 12.450 |

### ANOVA Table

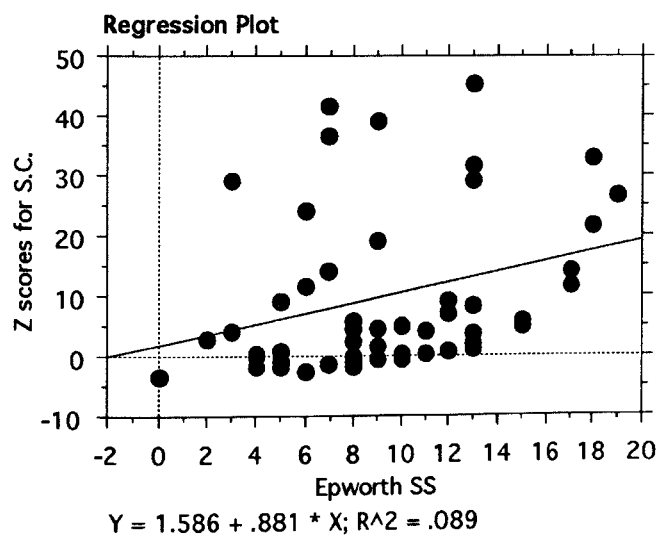
Z scores for S.C. vs. Epworth SS

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 801.609        | 801.609     | 5.172   | .0270   |
| Residual   | 53 | 8214.888       | 154.998     |         |         |
| Total      | 54 | 9016.496       |             |         |         |

### Regression Coefficients

Z scores for S.C. vs. Epworth SS

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 1.586       | 3.954      | 1.586       | .401    | .6899   |
| Epworth SS | .881        | .388       | .298        | 2.274   | .0270   |



This demonstrates that subjective and objective measures of somnolence have internal validity. One possible explanation therefore would be that the arousals of SDB define the magnitude of subjective sleepiness while the magnitude of the associated hypoxia defines the decrement in objective vigilance (Steer Clear). The strong correlation between the LD <90% and the arousal index ( $r^2 = 0.4$ ) would support this hypothesis, and suggests that a component of daytime somnolence in SDB relates to a decrement in vigilance. It is likely that both Steer Clear and ESS are insufficiently sensitive tools to be able to clearly delimit a causal association between elements of SDB and daytime sleepiness or indeed that EDS is multifactorial and no single test is likely to be predictive of sleepiness in OSA.

### **3.5.2 Cognitive outcomes versus modified arousal criteria.**

All 55 polysomnograms were rescored utilising the modified criteria specified in Chapter 2.4.2. Each arousal sub-type was tallied using the sleep scoring software and the raw total for each type was analysed by simple linear regression against the cognitive battery. The major positive findings are presented and discussed in the following Chapters 3.5.2.1 - 3.5.2.4.

### 3.5.2.1 Level I arousals versus cognitive outcomes.

#### Regression Summary

##### Arousal type 1 vs. Epworth SS

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .272   |
| R Squared          | .074   |
| Adjusted R Squared | .057   |
| RMS Residual       | 55.870 |

#### ANOVA Table

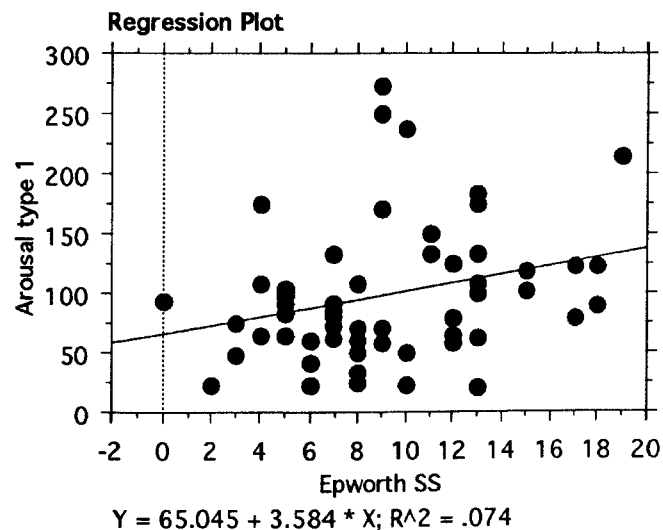
##### Arousal type 1 vs. Epworth SS

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 13252.882      | 13252.882   | 4.246   | .0443   |
| Residual   | 53 | 165439.954     | 3121.509    |         |         |
| Total      | 54 | 178692.836     |             |         |         |

#### Regression Coefficients

##### Arousal type 1 vs. Epworth SS

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 65.045      | 17.743     | 65.045      | 3.666   | .0006   |
| Epworth SS | 3.584       | 1.739      | .272        | 2.061   | .0443   |



The correlation above demonstrates a relationship between increasing brief arousals of less than 10 seconds with increasing subjective somnolence. The relationship between the overall arousal index and sleepiness has already been demonstrated and in the absence of any other correlations between sub-types of arousals and ESS it suggests that the lesser arousals (which make up a large component of the total arousal index) are likely to be responsible for the previously demonstrated findings.

### 3.5.2.2 Level II arousals versus cognitive outcomes.

#### Regression Summary

##### Arousal type 2 vs. Logical MP 1

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .272   |
| R Squared          | .074   |
| Adjusted R Squared | .056   |
| RMS Residual       | 25.361 |

#### ANOVA Table

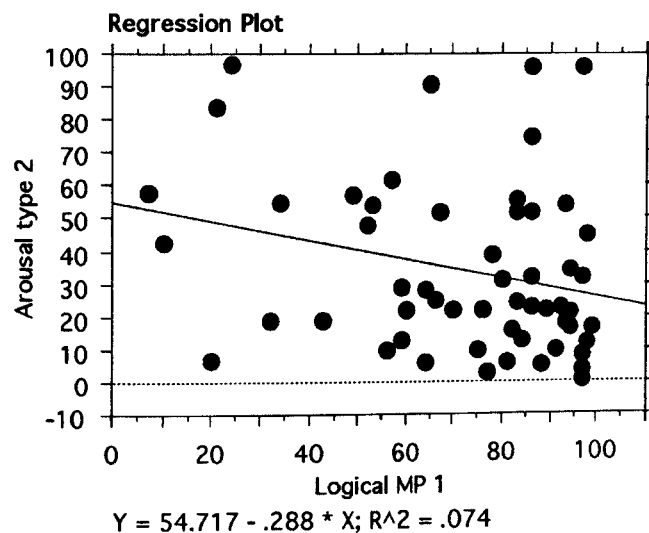
##### Arousal type 2 vs. Logical MP 1

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 2719.990       | 2719.990    | 4.229   | .0447   |
| Residual   | 53 | 34088.010      | 643.170     |         |         |
| Total      | 54 | 36808.000      |             |         |         |

#### Regression Coefficients

##### Arousal type 2 vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 54.717      | 10.639     | 54.717      | 5.143   | <.0001  |
| Logical MP 1 | -.288       | .140       | -.272       | -2.056  | .0447   |



### Regression Summary

#### Arousal type 2 vs. Logical MP 2

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .228   |
| R Squared          | .052   |
| Adjusted R Squared | .034   |
| RMS Residual       | 25.658 |

### ANOVA Table

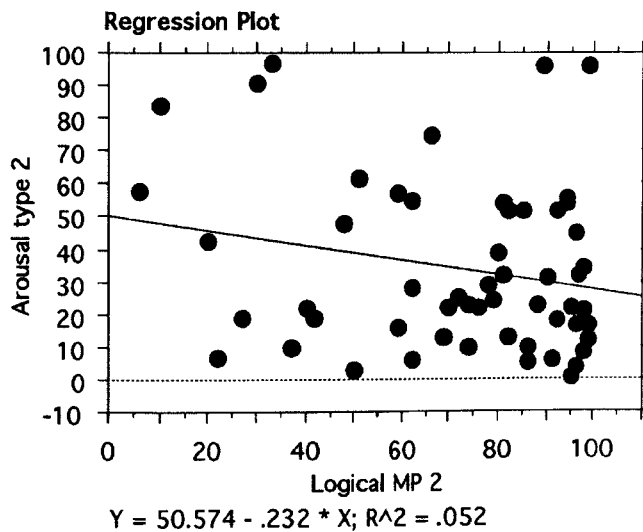
#### Arousal type 2 vs. Logical MP 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 1917.107       | 1917.107    | 2.912   | .0938   |
| Residual   | 53 | 34890.893      | 658.319     |         |         |
| Total      | 54 | 36808.000      |             |         |         |

### Regression Coefficients

#### Arousal type 2 vs. Logical MP 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 50.574      | 10.310     | 50.574      | 4.905   | <.0001  |
| Logical MP 2 | -.232       | .136       | -.228       | -1.706  | .0938   |



Analysis of type II arousals (i.e. those of 10-29 second duration) showed very few positive outcomes. Indeed, while a relationship to immediate short term memory was present it is substantially less statistically powerful than that demonstrated between total AI and short term memory decrement, both immediate and delayed. Furthermore, the previously significant relationship between total AI and delayed STM is not detectable at all. While the above correlation implies that arousals of longer duration may impact upon immediate STM function, the finding is overwhelmed by the previous data with respect to total AI and is likely therefore to be of research interest only and not of clinical significance.

### 3.5.2.3 Level III arousals versus cognitive outcomes.

#### Regression Summary

##### Arousal type 3 vs. PASAT

|                    |        |
|--------------------|--------|
| Count              | 52     |
| Num. Missing       | 3      |
| R                  | .371   |
| R Squared          | .138   |
| Adjusted R Squared | .120   |
| RMS Residual       | 10.555 |

#### ANOVA Table

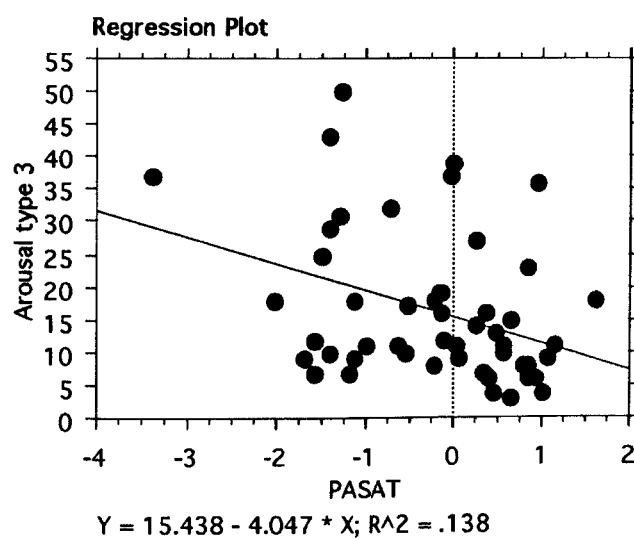
##### Arousal type 3 vs. PASAT

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 888.315        | 888.315     | 7.974   | .0068   |
| Residual   | 50 | 5570.358       | 111.407     |         |         |
| Total      | 51 | 6458.673       |             |         |         |

#### Regression Coefficients

##### Arousal type 3 vs. PASAT

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 15.438      | 1.489      | 15.438      | 10.367  | <.0001  |
| PASAT     | -4.047      | 1.433      | -.371       | -2.824  | .0068   |



### Regression Summary

#### Arousal type 3 vs. Digitspan reverse

|                    |        |
|--------------------|--------|
| Count              | 55     |
| Num. Missing       | 0      |
| R                  | .283   |
| R Squared          | .080   |
| Adjusted R Squared | .063   |
| RMS Residual       | 10.713 |

### ANOVA Table

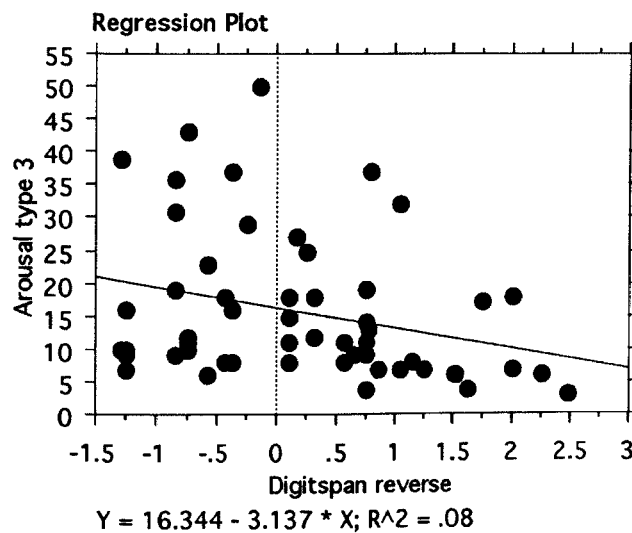
#### Arousal type 3 vs. Digitspan reverse

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 529.466        | 529.466     | 4.613   | .0363   |
| Residual   | 53 | 6082.716       | 114.768     |         |         |
| Total      | 54 | 6612.182       |             |         |         |

### Regression Coefficients

#### Arousal type 3 vs. Digitspan reverse

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 16.344      | 1.465      | 16.344      | 11.155  | <.0001  |
| Digitspan reverse | -3.137      | 1.460      | -.283       | -2.148  | .0363   |



The above relationship between type III arousals (i.e. changes in sleep stage to a lesser stage of sleep without wakefulness) and a decrement in working memory as measured by both PASAT and digit span reverse may be of considerable importance and somewhat unexpected. The previous analysis of total AI and these cognitive tests failed to demonstrate any relationship. However, the sub-analysis reveals a significant correlation between working memory and shifts in sleep stage. The findings above suggest that increasing sleep fragmentation when measured by shifting sleep stages may play a role in working memory decrement. This arousal scoring method would not be included in the total arousal score as it is not included in the R&K criteria, and is therefore a separate and important finding. Indeed, by multiple regression, the relationship between PASAT and type III arousals is demonstrably independent of the total AI, LD<90%, and the total RDI (see output below). These findings are still present when Vt (a general measure of intellectual ability) is entered into the regression analyses.

**Regression Coefficients**  
**Arousal type 3 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 23.851      | 11.291     | 23.851      | 2.113   | .0416   |
| Log Desat <90%   | .515        | 1.694      | .049        | .304    | .7628   |
| Shipley Vt score | -.119       | .190       | -.098       | -.624   | .5366   |
| PASAT            | -3.536      | 1.718      | -.326       | -2.058  | .0469   |

**Regression Coefficients**  
**Arousal type 3 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 21.281      | 10.624     | 21.281      | 2.003   | .0508   |
| RDI total        | .017        | .082       | .029        | .208    | .8359   |
| Shipley Vt score | -.103       | .176       | -.078       | -.583   | .5627   |
| PASAT            | -3.898      | 1.539      | -.357       | -2.532  | .0147   |

**Regression Coefficients**  
**Arousal type 3 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 22.374      | 10.724     | 22.374      | 2.086   | .0423   |
| Arousal Index    | -.037       | .108       | -.047       | -.344   | .7322   |
| Shipley Vt score | -.099       | .176       | -.076       | -.564   | .5757   |
| PASAT            | -4.114      | 1.495      | -.377       | -2.753  | .0083   |

### 3.5.2.4 Level IV arousals versus cognitive outcomes.

#### Regression Summary

##### Arousal type 4 vs. Serial digit percentiles

|                    |       |
|--------------------|-------|
| Count              | 55    |
| Num. Missing       | 0     |
| R                  | .343  |
| R Squared          | .117  |
| Adjusted R Squared | .101  |
| RMS Residual       | 7.975 |

#### ANOVA Table

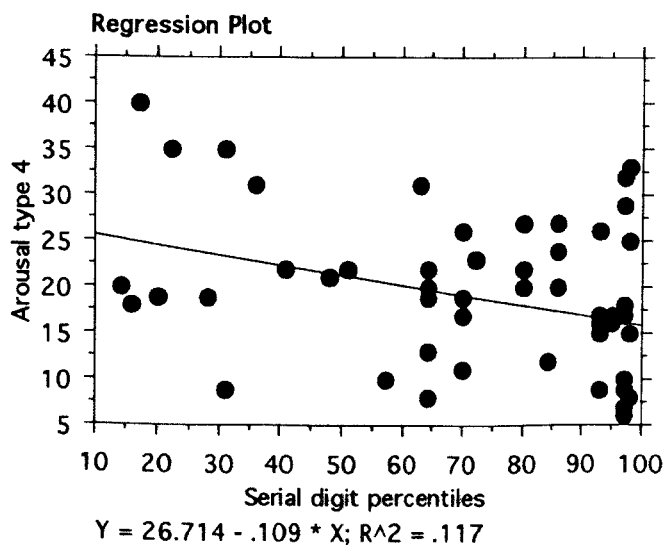
##### Arousal type 4 vs. Serial digit percentiles

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 448.352        | 448.352     | 7.049   | .0105   |
| Residual   | 53 | 3371.176       | 63.607      |         |         |
| Total      | 54 | 3819.527       |             |         |         |

#### Regression Coefficients

##### Arousal type 4 vs. Serial digit percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 26.714      | 3.156      | 26.714      | 8.464   | <.0001  |
| Serial digit percentiles | -.109       | .041       | -.343       | -2.655  | .0105   |



### Regression Summary

#### Arousal type 4 vs. Digitspan reverse

|                    |       |
|--------------------|-------|
| Count              | 55    |
| Num. Missing       | 0     |
| R                  | .404  |
| R Squared          | .163  |
| Adjusted R Squared | .148  |
| RMS Residual       | 7.765 |

### ANOVA Table

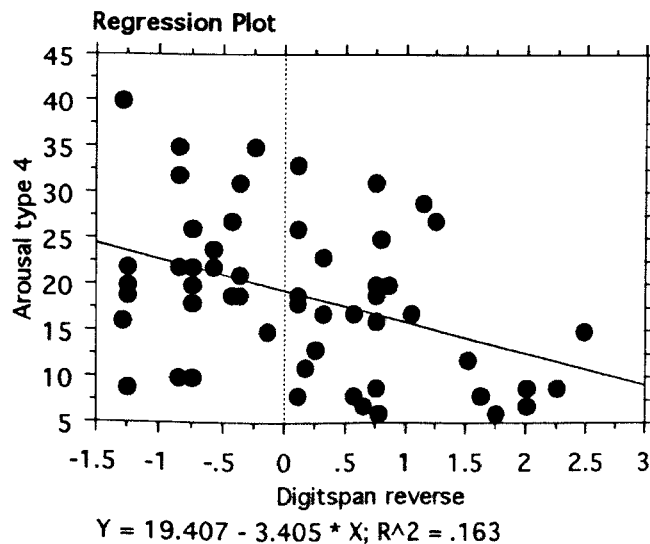
#### Arousal type 4 vs. Digitspan reverse

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 623.878        | 623.878     | 10.347  | .0022   |
| Residual   | 53 | 3195.649       | 60.295      |         |         |
| Total      | 54 | 3819.527       |             |         |         |

### Regression Coefficients

#### Arousal type 4 vs. Digitspan reverse

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 19.407      | 1.062      | 19.407      | 18.275  | <.0001  |
| Digitspan reverse | -3.405      | 1.059      | -.404       | -3.217  | .0022   |



The above correlations demonstrate a strong relationship between type IV arousals (i.e. those to full wakefulness) and digit span reverse, a measure of working memory. Indeed, as with type III arousals and PASAT the relationship between type IV arousals and digit span remains significant over and above the effects of the total AI, the total RDI or the LD<90% by multiple regression analyses (see below). Again, the effect of controlling for general intellectual ability ( by entering Vt into the regression) did not alter the outcome of the analyses. The finding of a correlation between the serial digit test (supraspan learning/working memory) further corroborates the evidence of a relationship between increasing episodes of wakefulness and working memory decrement. This effect combined with the findings in the previous chapter support the hypothesis that shifting sleep states and arousal to wakefulness impair working memory despite the absence of a similar finding when the data is scored according to standard criteria.

**Regression Coefficients**  
**Arousal type 4 vs. 3 Independents**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 16.865      | 7.694      | 16.865      | 2.192   | .0330   |
| RDI total         | .029        | .056       | .066        | .515    | .6086   |
| Shipley Vt score  | .036        | .129       | .037        | .281    | .7798   |
| Digitspan reverse | -3.412      | 1.106      | -.405       | -3.086  | .0033   |

**Regression Coefficients**  
**Arousal type 4 vs. 3 Independents**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 14.102      | 7.160      | 14.102      | 1.970   | .0543   |
| Arousal Index     | .206        | .070       | .356        | 2.946   | .0048   |
| Shipley Vt score  | -.014       | .121       | -.014       | -.114   | .9093   |
| Digitspan reverse | -2.938      | 1.035      | -.349       | -2.837  | .0065   |

**Regression Coefficients**  
**Arousal type 4 vs. 3 Independents**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 18.496      | 8.681      | 18.496      | 2.131   | .0395   |
| Log Desat <90%    | .242        | 1.273      | .030        | .190    | .8499   |
| Shipley Vt score  | .022        | .146       | .024        | .153    | .8793   |
| Digitspan reverse | -3.261      | 1.549      | -.348       | -2.105  | .0418   |

### **3.6**

#### **Simple regression analysis of cognitive variables versus somnolence measures.**

Simple linear regression of all cognitive variables versus the scores for the Epworth Sleepiness Scale failed to demonstrate any statistically significant correlations. The z-scores for Steer Clear were similarly correlated against all measures of cognition. While the analysis revealed a relationship between S.C. and the Rey Complex Figure Test ( $p < 0.05$ ,  $r^2 = 0.08$ ), this was clearly a weak relationship and possibly represents a type I error resulting from the large number of regression analyses performed. Furthermore, the finding of a decrement in untimed visuo-spatial construction and a test of vigilance is unlikely to be of clinical significance.

The findings of these analyses failed to demonstrate a relationship between the measures of somnolence and a decrement in cognition, and therefore do not support the pathway 3 hypothesis. This suggests that somnolence, at least as measured by ESS and S.C., does not contribute to the cognitive decline demonstrated elsewhere in this work.

### **3.7**

### **Validation of modified arousal scoring criteria.**

#### **3.7.1**

#### **Paired t-testing.**

##### **3.7.1.1**

##### **Intra-observer scoring.**

###### **Paired t-test**

**Hypothesized Difference = 0**

|                            | Mean Diff. | DF | t-Value | P-Value |
|----------------------------|------------|----|---------|---------|
| AI-1 score 1, AI-1 score 2 | 1.750      | 7  | 1.313   | .2306   |

###### **Paired t-test**

**Hypothesized Difference = 0**

|                            | Mean Diff. | DF | t-Value | P-Value |
|----------------------------|------------|----|---------|---------|
| AI-2 score 1, AI-2 score 2 | -2.000     | 7  | -1.482  | .1819   |

###### **Paired t-test**

**Hypothesized Difference = 0**

|                            | Mean Diff. | DF | t-Value | P-Value |
|----------------------------|------------|----|---------|---------|
| AI-3 score 1, AI-3 score 2 | -.500      | 7  | -.935   | .3807   |

###### **Paired t-test**

**Hypothesized Difference = 0**

|                            | Mean Diff. | DF | t-Value | P-Value |
|----------------------------|------------|----|---------|---------|
| AI-4 score 1, AI-4 score 2 | -.750      | 7  | -1.342  | .2216   |

Paired t-testing of all four arousal sub-types by the same primary observer demonstrates no statistically significant differences. This demonstrates that the scoring procedure was reproducible and the data derived was valid for analysis.

### 3.7.1.2

#### Inter-observer scoring.

##### Paired t-test

Hypothesized Difference = 0

|                               | Mean Diff. | DF | t-Value | P-Value |
|-------------------------------|------------|----|---------|---------|
| Mean inter count AI-1, AI-... | .875       | 7  | 1.433   | .1949   |

##### Paired t-test

Hypothesized Difference = 0

|                               | Mean Diff. | DF | t-Value | P-Value |
|-------------------------------|------------|----|---------|---------|
| Mean inter count AI-2, AI-... | 1.375      | 7  | 1.562   | .1622   |

##### Paired t-test

Hypothesized Difference = 0

|                               | Mean Diff. | DF | t-Value | P-Value |
|-------------------------------|------------|----|---------|---------|
| Mean inter count AI-3, AI-... | .500       | 7  | 1.155   | .2861   |

##### Paired t-test

Hypothesized Difference = 0

|                               | Mean Diff. | DF | t-Value | P-Value |
|-------------------------------|------------|----|---------|---------|
| Mean inter count AI-4, AI-... | 1.125      | 7  | 2.220   | .0618   |

Paired t-testing of the mean of both scores of the primary investigator versus the total of each of the arousal sub-types of the secondary scorer demonstrates no statistically significant differences. This demonstrates that the scoring procedure was reproducible and the data derived was valid for analysis.

### 3.7.2

### Linear regression.

#### 3.7.2.1

#### Intra-observer scoring.

##### Regression Summary

##### AI-1 score 1 vs. AI-1 score 2

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .997  |
| R Squared          | .995  |
| Adjusted R Squared | .994  |
| RMS Residual       | 3.807 |

##### ANOVA Table

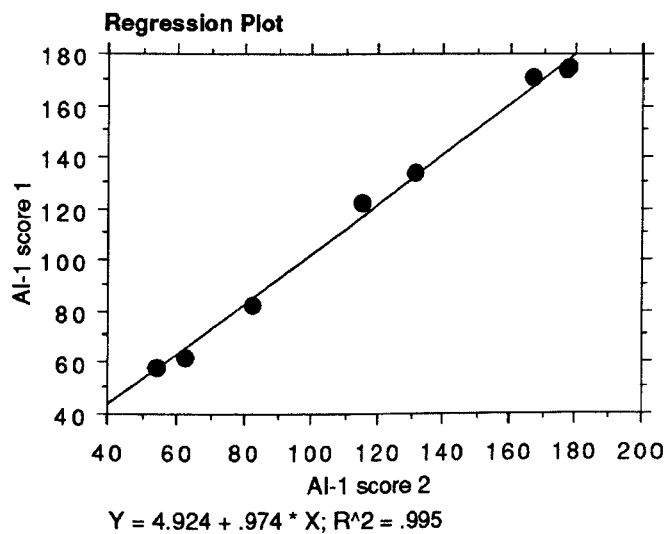
##### AI-1 score 1 vs. AI-1 score 2

|            | DF | Sum of Squares | Mean Square | F-Value  | P-Value |
|------------|----|----------------|-------------|----------|---------|
| Regression | 1  | 17187.025      | 17187.025   | 1185.657 | <.0001  |
| Residual   | 6  | 86.975         | 14.496      |          |         |
| Total      | 7  | 17274.000      |             |          |         |

##### Regression Coefficients

##### AI-1 score 1 vs. AI-1 score 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 4.924       | 3.670      | 4.924       | 1.342   | .2283   |
| AI-1 score 2 | .974        | .028       | .997        | 34.433  | <.0001  |



### Regression Summary

#### AI-2 score 1 vs. AI-2 score 2

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .992  |
| R Squared          | .983  |
| Adjusted R Squared | .981  |
| RMS Residual       | 3.524 |

### ANOVA Table

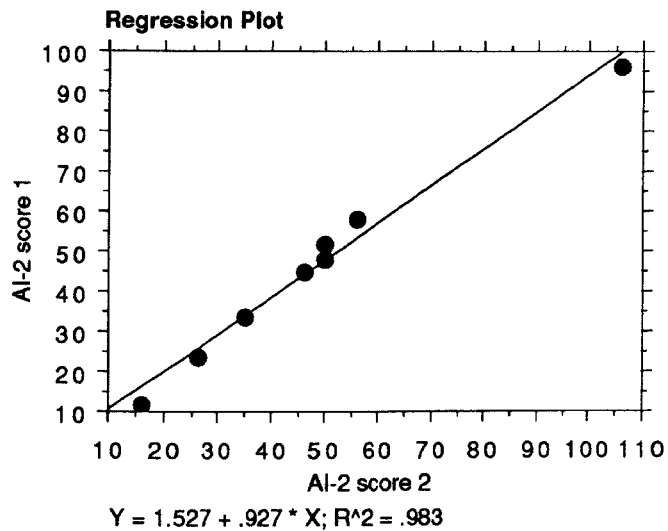
#### AI-2 score 1 vs. AI-2 score 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 4394.358       | 4394.358    | 353.825 | <.0001  |
| Residual   | 6  | 74.517         | 12.420      |         |         |
| Total      | 7  | 4468.875       |             |         |         |

### Regression Coefficients

#### AI-2 score 1 vs. AI-2 score 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 1.527       | 2.678      | 1.527       | .570    | .5893   |
| AI-2 score 2 | .927        | .049       | .992        | 18.810  | <.0001  |



### Regression Summary

#### AI-3 score 1 vs. AI-3 score 2

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .993  |
| R Squared          | .986  |
| Adjusted R Squared | .983  |
| RMS Residual       | 1.460 |

### ANOVA Table

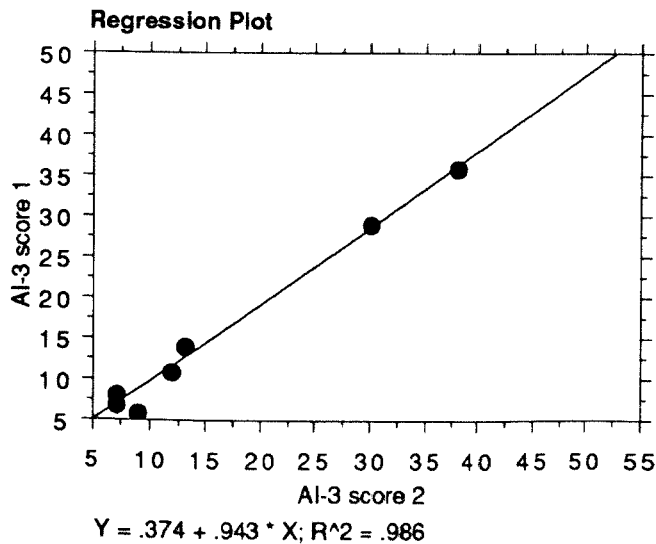
#### AI-3 score 1 vs. AI-3 score 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 884.087        | 884.087     | 414.802 | <.0001  |
| Residual   | 6  | 12.788         | 2.131       |         |         |
| Total      | 7  | 896.875        |             |         |         |

### Regression Coefficients

#### AI-3 score 1 vs. AI-3 score 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | .374        | .879       | .374        | .425    | .6854   |
| AI-3 score 2 | .943        | .046       | .993        | 20.367  | <.0001  |



### Regression Summary

#### AI-4 score 1 vs. AI-4 score 2

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .987  |
| R Squared          | .975  |
| Adjusted R Squared | .971  |
| RMS Residual       | 1.404 |

### ANOVA Table

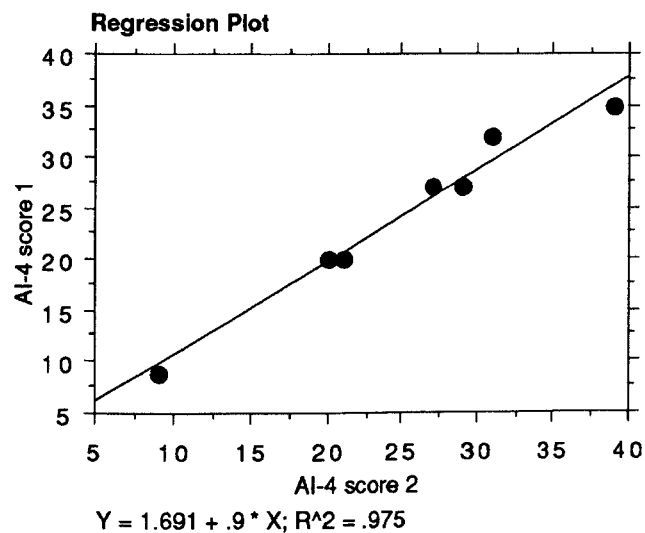
#### AI-4 score 1 vs. AI-4 score 2

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 463.680        | 463.680     | 235.372 | <.0001  |
| Residual   | 6  | 11.820         | 1.970       |         |         |
| Total      | 7  | 475.500        |             |         |         |

### Regression Coefficients

#### AI-4 score 1 vs. AI-4 score 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 1.691       | 1.521      | 1.691       | 1.112   | .3087   |
| AI-4 score 2 | .900        | .059       | .987        | 15.342  | <.0001  |



The results above demonstrate a very close correlation between scores 1 and 2 for all arousal types with less than 2% variance detected. An approximate line of best fit at 45 degrees demonstrates that there is little skew of the data even with large numbers of arousals being considered.

### 3.7.2.2

### Inter-observer scoring.

#### Regression Summary

##### AI-1 GK vs. Mean inter count AI-1

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .999  |
| R Squared          | .999  |
| Adjusted R Squared | .999  |
| RMS Residual       | 1.858 |

#### ANOVA Table

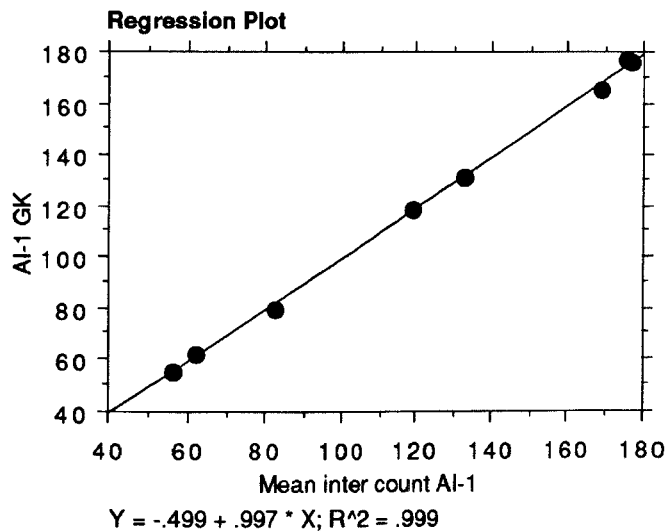
##### AI-1 GK vs. Mean inter count AI-1

|            | DF | Sum of Squares | Mean Square | F-Value  | P-Value |
|------------|----|----------------|-------------|----------|---------|
| Regression | 1  | 17566.794      | 17566.794   | 5090.302 | <.0001  |
| Residual   | 6  | 20.706         | 3.451       |          |         |
| Total      | 7  | 17587.500      |             |          |         |

#### Regression Coefficients

##### AI-1 GK vs. Mean inter count AI-1

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | -.499       | 1.822      | -.499       | -.274   | .7933   |
| Mean inter count AI-1 | .997        | .014       | .999        | 71.346  | <.0001  |



### Regression Summary

#### AI-2 GK vs. Mean inter count AI-2

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .997  |
| R Squared          | .995  |
| Adjusted R Squared | .994  |
| RMS Residual       | 1.865 |

### ANOVA Table

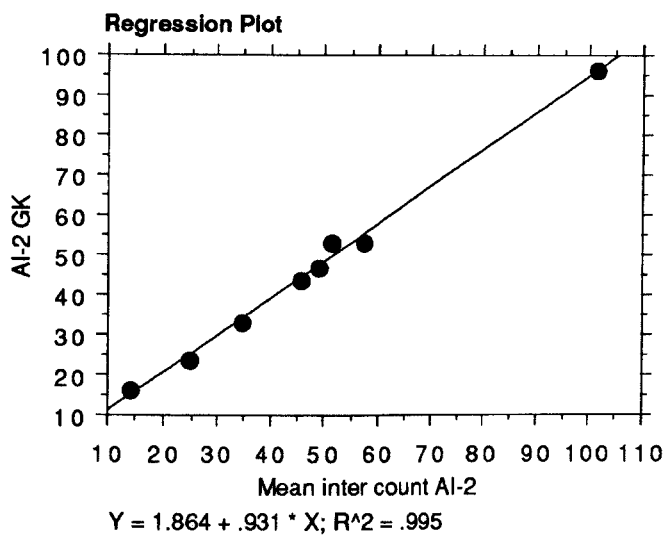
#### AI-2 GK vs. Mean inter count AI-2

|            | DF | Sum of Squares | Mean Square | F-Value  | P-Value |
|------------|----|----------------|-------------|----------|---------|
| Regression | 1  | 4134.640       | 4134.640    | 1189.262 | <.0001  |
| Residual   | 6  | 20.860         | 3.477       |          |         |
| Total      | 7  | 4155.500       |             |          |         |

### Regression Coefficients

#### AI-2 GK vs. Mean inter count AI-2

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 1.864       | 1.433      | 1.864       | 1.300   | .2412   |
| Mean inter count AI-2 | .931        | .027       | .997        | 34.486  | <.0001  |



### Regression Summary

#### AI-3 GK vs. Mean inter count AI-3

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .995  |
| R Squared          | .991  |
| Adjusted R Squared | .989  |
| RMS Residual       | 1.151 |

### ANOVA Table

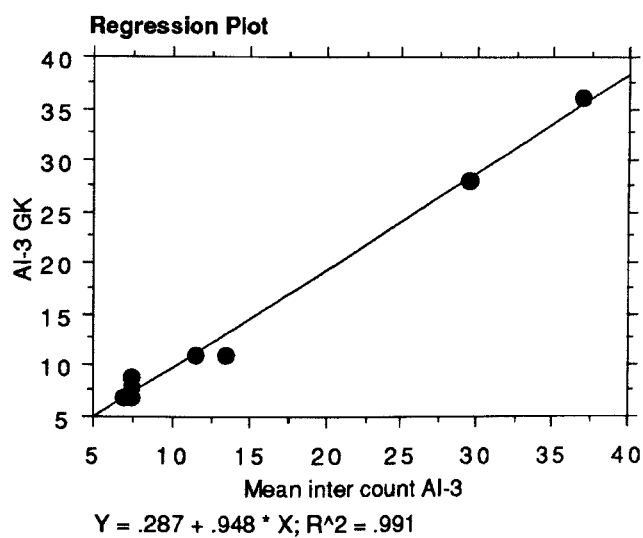
#### AI-3 GK vs. Mean inter count AI-3

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 845.926        | 845.926     | 638.476 | <.0001  |
| Residual   | 6  | 7.949          | 1.325       |         |         |
| Total      | 7  | 853.875        |             |         |         |

### Regression Coefficients

#### AI-3 GK vs. Mean inter count AI-3

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | .287        | .698       | .287        | .411    | .6951   |
| Mean inter count AI-3 | .948        | .038       | .995        | 25.268  | <.0001  |



### Regression Summary

#### AI-4 GK vs. Mean inter count AI-4

|                    |       |
|--------------------|-------|
| Count              | 8     |
| Num. Missing       | 0     |
| R                  | .991  |
| R Squared          | .983  |
| Adjusted R Squared | .980  |
| RMS Residual       | 1.080 |

### ANOVA Table

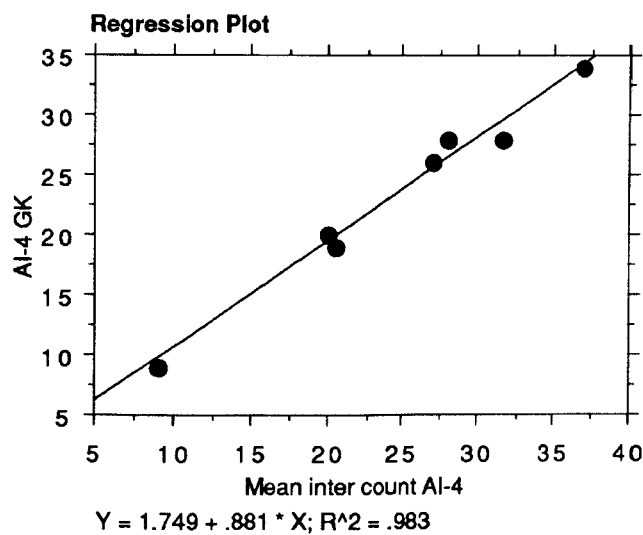
#### AI-4 GK vs. Mean inter count AI-4

|            | DF | Sum of Squares | Mean Square | F-Value | P-Value |
|------------|----|----------------|-------------|---------|---------|
| Regression | 1  | 402.996        | 402.996     | 345.247 | <.0001  |
| Residual   | 6  | 7.004          | 1.167       |         |         |
| Total      | 7  | 410.000        |             |         |         |

### Regression Coefficients

#### AI-4 GK vs. Mean inter count AI-4

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 1.749       | 1.206      | 1.749       | 1.451   | .1971   |
| Mean inter count AI-4 | .881        | .047       | .991        | 18.581  | <.0001  |



For all analyses GK refers to the initials of the secondary scorer. Mean inter count refers to the mean total of each arousal type derived from the primary scorer. The analyses above demonstrate a good correlation for each arousal subtype between the primary investigator and the secondary scorer. All  $r^2$  values are >95%. Having demonstrated good concordance the outcomes for arousal scoring by modified criteria were deemed satisfactory for the subsequent analyses.

### **3.8**

### **Stepwise regression analysis.**

Stepwise regression was performed between each cognitive outcome and all measures of sleep disordered breathing, in order to ascertain which of the relationships were statistically independent. The following analyses comprise this step. Only statistically significant outcomes are reported. Remaining regressions are presented in Appendix 2.

#### **Logical Memory I versus all sleep variables**

| <b>Stepwise Regression Summary</b>     |         |
|----------------------------------------|---------|
| <b>Logical MP 1 vs. 7 Independents</b> |         |
| F-to-Enter                             | 4.000   |
| F-to-Remove                            | 3.996   |
| Number of Steps                        | 1       |
| Variables Entered                      | 1       |
| Variables Forced                       | 0       |
| Stepwise Procedure                     | Forward |

#### **Variables In Model**

**Logical MP 1 vs. 7 Independents**  
**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 73.558      | 3.646      | 73.558      | 406.983     |

#### **Variables Not In Model**

**Logical MP 1 vs. 7 Independents**  
**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.383        | 7.063      |
| RDI REM         | -.179        | 1.359      |
| Arousal Index   | -.373        | 6.626      |
| Min desat% NREM | .318         | 4.628      |
| Min desat% REM  | .227         | 2.221      |
| RDI total       | -.365        | 6.310      |
| Log Desat <90%  | -.307        | 4.261      |

**Variables In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 80.458      | 4.285      | 80.458      | 352.619     |
| RDI NREM  | -.443       | .167       | -.383       | 7.063       |

**Variables Not In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .180         | 1.336      |
| Arousal Index   | -.110        | .488       |
| Min desat% NREM | .038         | .059       |
| Min desat% REM  | -.023        | .022       |
| RDI total       | .099         | .396       |
| Log Desat <90%  | -.027        | .030       |

The regression above demonstrates that the NREM RDI over and above the other sleep variables most strongly correlates with immediate short term memory decrement. Despite this, multiple regression (see Chapter 3.9) confirms that the relationship between sleep fragmentation as measured by the total arousal index and the decrement in immediate short term memory is independent of the both the total RDI and the RDI in NREM sleep when the data is corrected for general intellectual ability.

### Logical Memory II versus all sleep variables

#### Variables In Model

Logical MP 2 vs. 7 Independents

Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 74.047      | 3.750      | 74.047      | 389.878     |

#### Variables Not In Model

Logical MP 2 vs. 7 Independents

Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.457        | 10.816     |
| RDI REM         | -.141        | .831       |
| Arousal Index   | -.439        | 9.772      |
| Min desat% NREM | .380         | 6.914      |
| Min desat% REM  | .245         | 2.624      |
| RDI total       | -.417        | 8.625      |
| Log Desat <90%  | -.375        | 6.693      |

#### Variables In Model

Logical MP 2 vs. 7 Independents

Step: 1

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 82.504      | 4.244      | 82.504      | 377.908     |
| RDI NREM  | -.543       | .165       | -.457       | 10.816      |

#### Variables Not In Model

Logical MP 2 vs. 7 Independents

Step: 1

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .346         | 5.452      |
| Arousal Index   | -.124        | .627       |
| Min desat% NREM | .048         | .093       |
| Min desat% REM  | -.065        | .171       |
| RDI total       | .260         | 2.895      |
| Log Desat <90%  | -.049        | .096       |

**Variables In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 2**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 75.595      | 5.000      | 75.595      | 228.553     |
| RDI NREM  | -.962       | .238       | -.809       | 16.302      |
| RDI REM   | .473        | .203       | .468        | 5.452       |

**Variables Not In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 2**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| Arousal Index   | -.080        | .251       |
| Min desat% NREM | .038         | .058       |
| Min desat% REM  | .088         | .301       |
| RDI total       | -.148        | .869       |
| Log Desat <90%  | -.119        | .559       |

The regression above demonstrates that both the NREM and REM RDI over and above the other sleep variables most strongly correlates with delayed short term memory decrement. Again, despite this, multiple regression (see Chapter 3.9) confirms that the relationship between sleep fragmentation as measured by the total arousal index and the decrement in immediate short term memory is independent of the both the total RDI and the RDI in NREM and REM sleep when the data is corrected for general intellectual ability. The most probable explanation is the very strong internal correlation between the arousal index and the RDI in either sleep state.

**Symbol digit versus all sleep variables.**

**Stepwise Regression Summary**  
**Symbol digit vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**

**Symbol digit vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.170       | .151       | -.170       | 1.270       |

**Variables Not In Model**

**Symbol digit vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.262        | 3.015      |
| RDI REM         | -.436        | 9.636      |
| Arousal Index   | -.139        | .813       |
| Min desat% NREM | .184         | 1.436      |
| Min desat% REM  | .348         | 5.648      |
| RDI total       | -.316        | 4.563      |
| Log Desat <90%  | -.199        | 1.692      |

**Variables In Model****Symbol digit vs. 7 Independents****Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .334        | .213       | .334        | 2.463       |
| RDI REM   | -.018       | .006       | -.436       | 9.636       |

**Variables Not In Model****Symbol digit vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .112         | .511       |
| Arousal Index   | .144         | .848       |
| Min desat% NREM | -.085        | .290       |
| Min desat% REM  | .076         | .229       |
| RDI total       | .096         | .372       |
| Log Desat <90%  | .120         | .585       |

The regression above demonstrates the relationship between a decrement in information processing speed and the RDI in REM, and that no other variable of sleep disordered breathing had an effect over and above it. This is explored in greater depth in Chapters 3.9 - 3.10.

## PASAT versus all sleep variables

### Stepwise Regression Summary

#### PASAT vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

### Variables In Model

#### PASAT vs. 7 Independents

##### Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.268       | .165       | -.268       | 2.643       |

### Variables Not In Model

#### PASAT vs. 7 Independents

##### Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.346        | 5.154      |
| RDI REM         | -.201        | 1.601      |
| Arousal Index   | -.244        | 2.415      |
| Min desat% NREM | .333         | 4.749      |
| Min desat% REM  | .311         | 4.069      |
| RDI total       | -.330        | 4.632      |
| Log Desat <90%  | -.190        | 1.416      |

**Variables In Model**  
**PASAT vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .002        | .197       | .002        | 1.116E-4    |
| RDI NREM  | -.017       | .008       | -.348       | 5.154       |

**Variables Not In Model**  
**PASAT vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .100         | .376       |
| Arousal Index   | .075         | .207       |
| Min desat% NREM | .110         | .456       |
| Min desat% REM  | .128         | .612       |
| RDI total       | .090         | .301       |
| Log Desat <90%  | .111         | .459       |

The above regression demonstrates a significant relationship between working memory, as measured by PASAT, and the RDI in NREM sleep, and that no other variable of sleep disordered breathing had an effect over and above it.

# Digit span reverse versus all sleep variables

## Stepwise Regression Summary

Digitspan reverse vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 2       |
| Variables Entered  | 2       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

## Variables in Model

Digitspan reverse vs. 7 Independents

Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .097        | .138       | .097        | .488        |

## Variables Not in Model

Digitspan reverse vs. 7 Independents

Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.087        | .310       |
| RDI REM         | .068         | .189       |
| Arousal Index   | -.099        | .407       |
| Min desat% NREM | .208         | 1.854      |
| Min desat% REM  | .108         | .482       |
| RDI total       | -.074        | .227       |
| Log Desat <90%  | -.302        | 4.115      |

**Variables In Model****Digitspan reverse vs. 7 Independents****Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | -.155       | .182       | -.155       | .721        |
| Log Desat <90% | -.260       | .128       | -.302       | 4.115       |

**Variables Not In Model****Digitspan reverse vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .228         | 2.203      |
| RDI REM         | .361         | 5.989      |
| Arousal Index   | .125         | .634       |
| Min desat% NREM | -.023        | .021       |
| Min desat% REM  | -.198        | 1.634      |
| RDI total       | .267         | 3.068      |

**Variables In Model****Digitspan reverse vs. 7 Independents****Step: 2**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | -.874       | .341       | -.874       | 6.586       |
| RDI REM        | .017        | .007       | .450        | 5.989       |
| Log Desat <90% | -.511       | .159       | -.593       | 10.372      |

**Variables Not In Model****Digitspan reverse vs. 7 Independents****Step: 2**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .048         | .089       |
| Arousal Index   | .033         | .043       |
| Min desat% NREM | .044         | .075       |
| Min desat% REM  | -.067        | .178       |
| RDI total       | .025         | .025       |

The demonstrated finding of a relationship between the magnitude of the hypoxic insult and working memory is corroborated by the previously demonstrated correlation by simple linear regression. The findings of a relationship between REM RDI and digitspan reverse, when the log desat% < 90 is held constant, has no reasonable clinical explanation and was not further pursued.

### Steer Clear versus all sleep variables

#### Stepwise Regression Summary

##### Z scores for S.C. vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

#### Variables In Model

##### Z scores for S.C. vs. 7 Independents

###### Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 9.507       | 2.023      | 9.507       | 22.087      |

#### Variables Not In Model

##### Z scores for S.C. vs. 7 Independents

###### Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.145        | .879       |
| RDI REM         | -.179        | 1.354      |
| Arousal Index   | -.018        | .013       |
| Min desat% NREM | .227         | 2.229      |
| Min desat% REM  | .277         | 3.405      |
| RDI total       | -.162        | 1.108      |
| Log Desat <90%  | -.318        | 4.603      |

**Variables In Model****Z scores for S.C. vs. 7 Independents****Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | 5.642       | 2.649      | 5.642       | 4.538       |
| Log Desat <90% | -4.004      | 1.866      | -.318       | 4.603       |

**Variables Not In Model****Z scores for S.C. vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .155         | .982       |
| RDI REM         | .036         | .053       |
| Arousal Index   | .250         | 2.663      |
| Min desat% NREM | -.011        | .005       |
| Min desat% REM  | .057         | .129       |
| RDI total       | .141         | .816       |

The finding of a significant relationship between Steer Clear and the magnitude of the hypoxic insult over and above other sleep variables is a novel finding and will be discussed in greater detail in Chapter 3.8.

### Epworth Sleepiness Scale versus all sleep variables

#### Stepwise Regression Summary Epworth SS vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

#### Variables In Model Epworth SS vs. 7 Independents Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 9.279       | .621       | 9.279       | 223.209     |

#### Variables Not In Model Epworth SS vs. 7 Independents Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .225         | 2.192      |
| RDI REM         | .237         | 2.439      |
| Arousal Index   | .264         | 3.078      |
| Min desat% NREM | -.010        | .004       |
| Min desat% REM  | -.133        | .737       |
| RDI total       | .228         | 2.240      |
| Log Desat <90%  | .104         | .449       |

Although simple linear regression demonstrates a correlation between the ESS and the total arousal index, forward stepwise regression does not demonstrate this finding to be significant over and above the other variables of sleep disordered breathing. The simple regression supports hypothesis pathway 4, but suggests that this pathway is not independent of the hypoxic pathway.

## **SUMMARY OF FINDINGS:**

Thus the major findings of the stepwise forward regression analyses can be summarised as follows:

|                         |                                    |
|-------------------------|------------------------------------|
| Logical memory I and II | NREM RDI                           |
| Symbol digit            | REM RDI                            |
| PASAT                   | NREM RDI                           |
| Digit span reverse      | Log of time with a saturation <90% |
| Steer Clear             | Log of time with a saturation <90% |

### **3.9            Multiple regression analysis.**

Based upon the findings of the simple linear and stepwise regressions, further analysis of the data set was performed in an effort to examine whether the relationships demonstrated were likely to prove of clinical significance and indeed whether the various overlapping components of sleep disordered breathing could be separated and used to determine specific cognitive decrements.

#### **3.9.1            Logical Memory I and II versus arousal index, NREM and total RDI.**

To test the strength of the relationship between sleep fragmentation (arousals) and the measured decline in short term memory, multiple regression was performed using the arousal index as the independent variable. General intellectual ability was controlled by forcing Vt (t-score of the Shipley Living Institute of Living Scale) into the model. This did not diminish the significance of the relationship ( $p = 0.0013$  for LM1,  $p = 0.0007$  for LM2). Having already determined that the total RDI, the NREM RDI and the arousal index were strongly correlated (for total RDI  $p < 0.0001$ ,  $r^2 = 0.56$ , for NREM RDI  $p < 0.0001$ ,  $r^2 = 0.60$ ), the total RDI and the NREM RDI were separately forced into the previous model. While the  $p$  value, as expected due to the strong internal correlations, were diminished, they remained statistically significant (see below)

**Regression Coefficients  
Logical MP 1 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 57.957      | 22.340     | 57.957      | 2.594   | .0123   |
| Shipley Vt score | .580        | .375       | .200        | 1.546   | .1283   |
| RDI NREM         | .060        | .260       | .047        | .232    | .8177   |
| Arousal Index    | -.714       | .345       | -.421       | -2.068  | .0437   |

**Regression Coefficients****Logical MP 1 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 57.598      | 22.266     | 57.598      | 2.587   | .0126   |
| Shipley Vt score | .599        | .377       | .207        | 1.589   | .1182   |
| RDI total        | .117        | .252       | .091        | .464    | .6447   |
| Arousal Index    | -.769       | .333       | -.454       | -2.310  | .0250   |

**Regression Coefficients****Logical MP 2 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 63.451      | 23.251     | 63.451      | 2.729   | .0087   |
| Shipley Vt score | .499        | .391       | .165        | 1.277   | .2076   |
| RDI NREM         | .001        | .271       | 4.388E-4    | .002    | .9983   |
| Arousal Index    | -.722       | .359       | -.408       | -2.009  | .0499   |

**Regression Coefficients****Logical MP 2 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 63.391      | 23.161     | 63.391      | 2.737   | .0085   |
| Shipley Vt score | .531        | .392       | .175        | 1.356   | .1810   |
| RDI total        | .122        | .262       | .091        | .465    | .6440   |
| Arousal Index    | -.844       | .346       | -.476       | -2.436  | .0184   |

Thus, increasing sleep fragmentation independent of the total respiratory disturbance index and the NREM RDI correlates with a decrements in both immediate and delayed short term memory, despite the fact that many of the arousals may have been respiratory in origin. This finding supports hypothesis pathway 1.

Given the above finding, in addition to the stepwise analysis suggesting a significant relationship between the NREM RDI and Logical memory I and II, the same multiple regression model was applied to the correlation between memory deficits and the NREM RDI. Again, the Vt did not significantly alter the outcome. However, when the arousal index is forced into the equation where

NREM RDI is the independent variable, the p value fails to reach statistical levels for both Logical memory I and II (see below).

**Regression Coefficients**  
**Logical MP 1 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 57.957      | 22.340     | 57.957      | 2.594   | .0123   |
| Shipley Vt score | .580        | .375       | .200        | 1.546   | .1283   |
| Arousal Index    | -.714       | .345       | -.421       | -2.068  | .0437   |
| RDI NREM         | .060        | .260       | .047        | .232    | .8177   |

**Regression Coefficients**  
**Logical MP 2 vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 63.451      | 23.251     | 63.451      | 2.729   | .0087   |
| Shipley Vt score | .499        | .391       | .165        | 1.277   | .2076   |
| Arousal Index    | -.722       | .359       | -.408       | -2.009  | .0499   |
| RDI NREM         | .001        | .271       | 4.388E-4    | .002    | .9983   |

Thus, it appears that much of the of the relationship between short term memory deficit and the NREM RDI is related to the strength of the relationship between arousals and memory decrement rather than being an important separate finding.

### 3.9.2 Symbol digit versus REM RDI.

Using the same technique described above, symbol digit was regressed against the REM RDI using the Vt as a forced variable to control for general intellectual ability. Subsequently, the total AI was separately entered to examine their contribution to the relationship.

**Regression Coefficients**  
**Symbol digit vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | -.639       | .855       | -.639       | -.748   | .4581   |
| Shipley Vt score | .011        | .014       | .096        | .740    | .4625   |
| Arousal Index    | .009        | .010       | .147        | .951    | .3462   |
| RDI REM          | -.018       | .006       | -.458       | -2.965  | .0046   |

Thus the relationship between a decline in information processing speed and the increasing REM RDI is independent of the overall degree of sleep fragmentation. Given that the total RDI also correlated with a decline in the normed score of the Symbol Digit test, the same analytical method was applied to this relationship.

**Regression Coefficients**  
**Symbol digit vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | -.965       | .873       | -.965       | -1.106  | .2740   |
| ShIPLEY Vt score | .011        | .015       | .104        | .777    | .4405   |
| Arousal Index    | .016        | .013       | .246        | 1.217   | .2292   |
| RDI total        | -.023       | .010       | -.469       | -2.330  | .0238   |

Again, there is no demonstrable effect when controlling for general intellect by Vt. Forcing the arousal index into this model does not alter the relationship (prior to forcing AI  $p = 0.04$ , post forcing AI  $p = 0.02$ ) although the strength of the correlation is not as powerful as that of REM RDI and SD. Of note, when performing the same regression forcing the NREM RDI as an independent variable, no correlation with a decline in information processing was demonstrated. Thus it seems that a decline in information processing speed correlates with increasing REM apnoea. The relationship is independent of NREM apnoea and the impact of sleep fragmentation. The fact that the total RDI is similarly (but more weakly) correlated is most likely due to the strong internal correlation between total RDI and REM RDI ( $p = 0.0005$ ,  $r^2 = 0.73$ ).

To ensure that the effect was not related to the total amount of REM sleep, further analyses were performed. The total number of respiratory events in REM was calculated by multiplying the REM RDI by the total REM sleep time. The same multiple regression analyses were performed using the total REM arousals as the independent variable and symbol digit as the dependent variable. The total RDI, arousal index and log desat <90% were then forced into the equation and Vt entered to control for general intellectual ability (see below).

**Regression Coefficients**  
**Symbol digit vs. 3 Independents**

|                        | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------------|-------------|------------|-------------|---------|---------|
| Intercept              | -.388       | .866       | -.388       | -.449   | .6555   |
| Shipley Vt score       | .008        | .014       | .075        | .575    | .5681   |
| Arousal Index          | .002        | .009       | .038        | .280    | .7810   |
| Total REM resp. events | -.017       | .006       | -.420       | -3.050  | .0036   |

**Regression Coefficients**  
**Symbol digit vs. 3 Independents**

|                        | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------------|-------------|------------|-------------|---------|---------|
| Intercept              | -.377       | .863       | -.377       | -.437   | .6641   |
| Shipley Vt score       | .009        | .014       | .084        | .652    | .5174   |
| RDI total              | -.002       | .008       | -.045       | -.272   | .7868   |
| Total REM resp. events | -.015       | .007       | -.377       | -2.254  | .0285   |

**Regression Coefficients**  
**Symbol digit vs. 3 Independents**

|                        | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------------|-------------|------------|-------------|---------|---------|
| Intercept              | -.366       | .951       | -.366       | -.385   | .7021   |
| Shipley Vt score       | .013        | .015       | .121        | .857    | .3968   |
| Log Desat <90%         | .084        | .155       | .090        | .542    | .5907   |
| Total REM resp. events | -.021       | .007       | -.508       | -3.049  | .0041   |

The analyses demonstrate that respiratory events, of sufficient magnitude to contribute to the RDI in REM, correlate with a decline in speed of information processing independent of the total amount of REM sleep present or other variables of sleep disordered breathing. This supports hypothesis pathway 2, and demonstrates that specific components of sleep disordered breathing may contribute to a decrement in performance in certain areas of the test battery.

### 3.9.3 PASAT and Digit span reverse versus NREM RDI and log of the desat % < 90.

To further examine the relationship between PASAT and Digitspan (reverse), as measures of working memory, and the variables NREM RDI and log desat%<90, both were entered as dependent variables into multiple regression matrices. Forcing Vt into the equations did not alter the p values significantly. However, when AI was forced into each equation the relationships became statistically non significant, despite the fact that AI has no correlation with either PASAT ( $p = 0.12$ ) or Digitspan reverse ( $p = 0.28$ ) by simple linear regression.

**Regression Coefficients  
PASAT vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | -.344       | 1.001      | -.344       | -.343   | .7328   |
| ShIPLEY Vt score | .004        | .017       | .032        | .234    | .8162   |
| Arousal Index    | .007        | .015       | .092        | .431    | .6685   |
| RDI NREM         | -.022       | .011       | -.405       | -1.902  | .0631   |

**Regression Coefficients  
Digitspan reverse vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | -1.921      | .896       | -1.921      | -2.146  | .0382   |
| ShIPLEY Vt score | .027        | .015       | .278        | 1.859   | .0706   |
| Arousal Index    | .005        | .012       | .077        | .401    | .6908   |
| Log Desat <90%   | -.276       | .166       | -.320       | -1.665  | .1039   |

Thus, the relationship between the magnitude of the hypoxic insult, the magnitude of NREM sleep apnoea and the decline in working memory should be considered non-significant when the additional insult of sleep fragmentation is taken into account. This suggests that not all components of hypothesis pathway 2 are independent of the other variables of sleep disordered breathing, namely the input of pathway 1 (sleep fragmentation and cognitive impairment).

### 3.9.4 Steer Clear versus the log of the desat% < 90.

In order to further understand this intriguing and novel finding and having determined that AI confounded the relationship between the log desat%<90 and Digitspan reverse, the same statistical principles were applied to the relationship between Steer Clear (SC) and this measure of hypoxia, given the correlation by simple regression. Having entered the normed scores for Steer Clear as the dependent variable, log desat%<90 was entered independently. Vt was forced into the equation to control for general intellectual ability. The total arousal index was then separately entered. The regression analyses demonstrated that, in fact, the relationship was strengthened when Vt was entered to control for general intellect ( $p = 0.014$ ). Furthermore, when AI was forced into the matrix, the statistical significance became clearer (see below).

**Regression Coefficients**  
**Z scores for S.C. vs. 3 Independents**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 26.488      | 11.766     | 26.488      | 2.251   | .0301   |
| Shipley Vt score | -.627       | .194       | -.436       | -3.241  | .0024   |
| Arousal Index    | .385        | .156       | .427        | 2.471   | .0179   |
| Log Desat <90%   | -8.014      | 2.180      | -.636       | -3.677  | .0007   |

Thus, the relationship between vigilance and the magnitude of the hypoxic insult, unlike that of working memory, remains significant. Indeed, contrary to the finding of a diminished correlation, the magnitude of sleep fragmentation appears to augment the existing relationship between vigilance decrement and magnitude of the hypoxic insult. Again, this in part supports hypothesis pathway 2, and suggests that some performance decrements within the test battery are significantly related to separate components of sleep disordered breathing.

### **3.10 Secondary analysis of outcomes and the derivation of odds ratios.**

The major findings of the study and those deemed to be of most clinical significance were the relationship between REM RDI and speed of information processing and that of sleep fragmentation and short term memory impairment. Given that adequate numbers of subjects had been studied and the correlations were sufficiently significant, secondary analysis of these two outcomes was undertaken. Each neuropsychological test was normed and then divided into quartiles of performance. The intersection of the specificity and sensitivity curves was determined by inspection against the respiratory parameter of interest ( i.e. REM RDI for Digit Symbol and arousal index for LM1 and LM2). The odds ratio at each quartile of cognitive performance versus the level of sleep disturbance was then calculated using the standard formula and are presented in the tables below.

#### **RDI REM versus the performance of Symbol Digit**

| <b>Performance<br/>Percentile</b> | <b>REM<br/>RDI</b> | <b>odds<br/>ratio</b> | <b>C.I.</b> |
|-----------------------------------|--------------------|-----------------------|-------------|
| 25th %tile                        | 37                 | 2.7                   | 0.7 - 10.38 |
| 50th %tile                        | 14                 | 3.2                   | 1.04 - 9.65 |
| 75th %tile                        | 5                  | 3.6                   | 0.96 - 13.8 |

#### **AI versus the performance of Logical memory passages I**

| <b>Performance<br/>Percentile</b> | <b>Arousal<br/>Index</b> | <b>odds<br/>ratio</b> | <b>C.I.</b> |
|-----------------------------------|--------------------------|-----------------------|-------------|
| 25th %tile                        | 37                       | 2.35                  | 0.57 - 3.67 |
| 50th %tile                        | 26                       | 1.94                  | 0.66 - 5.67 |
| 75th %tile                        | 19                       | 2.3                   | 0.60 - 8.74 |

#### **AI versus the performance of Logical memory passages II**

| <b>Performance<br/>Percentile</b> | <b>Arousal<br/>Index</b> | <b>odds<br/>ratio</b> | <b>C.I.</b>  |
|-----------------------------------|--------------------------|-----------------------|--------------|
| 25th %tile                        | 34                       | 5                     | 1.3 - 18.84  |
| 50th %tile                        | 26                       | 4.1                   | 1.12 - 15.25 |
| 75th %tile                        | 19                       | 2.6                   | 0.69 - 10.54 |

Thus, a predicted level of cognitive decrement (and the odds ratio) were able to be calculated for a given level of sleep fragmentation and REM related sleep apnoea. The clinical importance of these findings is discussed in the following Chapter 4.



- 4.3 The effects of sleep fragmentation, as defined by modified criteria, on outcomes of cognitive function testing. p. 191**
- 4.3.1 The effect of brief (type I) and intermediate duration (type II) arousals on immediate and delayed short term memory.**
- 4.3.2 Effects of shifts in sleep stage (type III) and arousals to wakefulness (type IV) on working memory.**
- 4.3.3 Implications for sleep disordered breathing.**
- 4.3.4 Limitations of the modified arousal scoring procedure.**
- 4.4 Final summary of the experimental data. p. 195**

## **DISCUSSION CHAPTER**

### **4.1 The role of melatonin in the genesis of daytime sleepiness.**

#### **4.1.1 Outcome of the Study to examine total melatonin production.**

The results of the experiment performed did not demonstrate any significant correlation between the production of melatonin (as measured by urinary metabolite) and any variable of sleep disordered breathing. Despite the hypothesis reasonably suggesting a possible physiological link, none was determined. In an effort to discriminate between normal subjects ie those with a total RDI < 5, and moderate OSA subjects (RDI > 20) unpaired t-testing on both daytime and nighttime samples failed to demonstrate any statistically significant difference. Inspection of the data spread and examination of the p and r values of the analyses would suggest that the absence of a positive finding was not related to insufficient numbers and that increasing sample size would be unlikely to alter the outcome.

In summary, there is no evidence from the data presented, to support the hypotheses that there is excess production of melatonin secondary to sleep disordered breathing. It is therefore unlikely that melatonin production as measured in this manner, contributes to daytime sleepiness in OSA.

The findings of this study are in keeping with those of Entzian et al<sup>135</sup> who similarly failed to demonstrate abnormal melatonin profiles in OSA patients versus normals.

#### 4.1.2

#### Limitations of the study.

Although all steps to exclude confounding variables (age, alcohol consumption, medications and other serious medical conditions) were taken, formal drug screening and blood alcohol levels were not performed, and may have been useful in excluding some subjects.

The question of whether the overnight profile of melatonin secretion in OSA is abnormal was not examined. However, the previous data of Entzian et al would not support this hypothesis, at least not in the small numbers which were studied.

Although all steps to calculate urinary volumes by indirect methods were taken, it is possible that either the indirect measurements or the actual volumes were inaccurate which may have confounded the data. In fact simple linear regression between measured volumes and indirect calculated volumes demonstrate r-values  $> 0.85$  for both diurnal and nocturnal measures suggesting reasonable patient compliance and making the possibility of error in total excretion seem unlikely.

Finally, the selection of patients from a group presenting to a Sleep Disorders Unit may suggest an element of selection bias. This may confound the data if indeed all subjects were being studied on the basis of excessive sleepiness. However, many of the subjects had little in the way of sleepiness but were being studied primarily for investigation of snoring and/or witnessed apnoeic events.

The alternate protocol of using matched normals was considered, but the limitations of the laboratory made this difficult and would have substantially extended the study time. While it is reasonable to accept that an alternate outcome may have been determined, the investigators were primarily interested in the patient group presenting to a Sleep Unit and in that setting the negative finding remains valid.

### **4.1.3 Further investigations.**

It is evident from the previous chapter that several alternate studies could be undertaken to further explore the primary hypothesis. It would be ideal to measure either continuous or hourly serum levels of melatonin over the course of the night to demonstrate whether there is measurable phase shift. Additionally, the use of normal controls matched for age, sex and health status should be considered. It is likely that moderate numbers would be required and access to accurate serum assay techniques would be essential.

## **4.2 The relationship between variables of sleep disordered breathing and cognitive function.**

### **4.2.1 The effects of sleep fragmentation on immediate and delayed short term memory.**

The outcome of this study clearly demonstrates a relationship between sleep fragmentation, as measured by the standard arousal criteria, and decrements in both immediate and delayed short term memory. The relationship, by multiple regression, has been demonstrated to be independent of the total RDI and the NREM RDI when general intellectual ability is entered as a controlled variable. This finding is supported by the work of Telakivi<sup>77</sup> who confirmed that sleep fragmentation with mild hypoxia and daytime somnolence were the main causes of memory dysfunction. Unfortunately, while the group had been adjusted for age and obesity to exclude confounders, there is no evidence that they had been controlled for levels of education.

Other confirmatory evidence can be found in the previous work of Bedard et al<sup>85</sup>. In a small study of only 20 patients, they demonstrated progressive deficits in

immediate and delayed recall in moderate to severe OSA patients. Unfortunately, no quantification of sleep fragmentation was reported and no data to define the magnitude of the insult required for a given deficit was demonstrated.

The relationship between sleep fragmentation and memory dysfunction is significant. The large sample size, the construct of using normal data and controlling for intellectual ability have allowed useful analysis with respect to clinical outcomes to be determined (see Chapter 4.2.4). The regression analyses which confirm this finding to be independent of other sleep disordered variables, in particular the total RDI is one of major clinical importance. For the group of patients with repetitive arousals in whom there is insufficient desaturation or apnoeas of less than 10 seconds, it demonstrates that they may well have cognitive dysfunction without sleep apnoea as defined by standard criteria.

#### **4.2.2           The effect of REM related OSA on information processing speed.**

The findings of a discrete relationship between sleep apnoea in REM and a decline in information processing speed is both novel and clinically pertinent.

To date there have been no reports to confirm this relationship, although most studies have not separated NREM and REM respiratory events for separate analysis. The relationship is independent of the arousal index, the amount of apnoea in NREM sleep and the total RDI.

It appears that disruption of REM sleep by repetitive apnoea gives rise to a unique decrement in information processing speed. The clinical importance of this finding is most obvious for the common group of OSA patients with predominantly REM OSA in whom the total RDI and the arousal indices may be only mildly elevated. The question of whether this patient group require treatment has until now been very

unclear. The findings reported in this study would suggest that these subjects are at risk of cognitive decline and this may colour clinical decision making.

#### **4.2.3 The relationship between sleep hypoxaemia and vigilance.**

This study has demonstrated a relationship between vigilance (as measured by Steer Clear) and the magnitude of the hypoxic injury as measured by the log of the time with a saturation < 90%. Previous work by Flemons et al<sup>99</sup> using the same simulator found no relationship between SC hits and the severity of desaturation as measured by the lowest recorded saturation. Indeed, this study also failed to demonstrate a correlation with this parameter in either REM or NREM sleep. This suggests it is not the minimum level which is critical in determining vigilance decrement, but the total time of the hypoxic insult.

Of note is the augmentation of the relationship when Vt (measure of general intellectual ability) is entered into the regression analysis. This supports the argument to control for this variable in studies which relate to cognitive outcomes and suggests that general intellectual ability may play a part in diminishing the effect of hypoxia on vigilance. This may help to explain the inability of previous data to demonstrate similar relationships.

The addition of the arousal index to the multiple regression equation further increases the statistical significance of the relationship. This augmentation would support the hypothesis that while hypoxia directly contributes to vigilance decrement, the addition of sleep fragmentation to hypoxia magnifies the impact of this insult on the ability of the individual to maintain vigilance.

#### **4.2.3.1**

#### **Implications for driving.**

The work of Flemons et al<sup>99</sup> and the previous studies by Findley et al<sup>97, 98</sup> have attempted to demonstrate a relationship between motor vehicle accidents (MVA) and OSA. However, none of the studies were able to demonstrate any single respiratory variable as being primarily related to accident rates. The more recent work by George et al<sup>100, 101</sup> demonstrated more tracking errors in OSA patients versus normals. This error in tracking is only weakly associated with sleepiness as measured by MSLT and overall the AHI and the MSLT explain less than 25% of the variance. The findings of the previous Chapter 4.2.3, would appear to be unique in identifying a strong correlation between a single sleep variable and the number of collisions on Steer Clear. Furthermore, the addition of sleep fragmentation to the model increases the strength of the relationship. This study has not attempted to define thresholds for hypoxia or arousal which may delimit the risk for a given number of S. C. collision errors as this may not accurately reflect true driving risk. There is no data which directly correlates Steer Clear errors to the expectant risk of an MVA and as such it may not be the ideal tool for defining MVA risk in OSA. The findings do however suggest that specific variables of sleep disordered breathing may be able to be individually identified which in turn may be used to define the risk. This work, for the first time identifies one possible factor, although the suggestion from the work of Flemons & George is that it is likely to be multifactorial.

#### **4.2.3.2**

#### **Further investigations.**

Given the findings outlined above, it would be useful to develop a tool which incorporates both the reaction time component of Steer Clear with the tracking error function of the Divided Attention Driving Test. The need for large numbers of matched normals and the imperative for controlling for general intellectual ability are evident. The relationship between errors of judgement, reaction time and parameters

of sleep disordered breathing are likely to be important in defining driving risks but will need to be measured in parallel with actual on road accidents to be meaningful.

#### **4.2.4 Implications for intention to treat. Interpretation of secondary analysis.**

The most pertinent clinical findings of the study were determined to be the relationship between the arousal index and short term memory and REM sleep apnoea and information processing. This does not diminish the value of the other findings such as the relationship between Type III & IV arousals and working memory (see Chapter 4.3.2) or that of hypoxia and vigilance. However, since both the AI and the REM RDI are data derived by most clinical sleep laboratories, it was felt that they may have the most immediate value in the clinical setting.

Following the methods of analysis described in Chapter 2.6.3, and given the strength of correlation between AI and Logical Memory 1 & 2, the data was re-analysed to derive the relative risk of performing at or below a given quartile for a given degree of sleep disordered breathing. Thus it can be said that at an arousal index of 37 per hour there is a 2.35 chance of an individual performing a test of immediate short term memory in the lowest quartile. At an arousal index of 34 per hour, they are 5 times more likely to perform a test of delayed short term memory in the lowest quartile. It is important to recognise that all data was normed according to age and level of education prior to analysis which would exclude the confounding variable of skewed distribution. Indeed, by dividing the values for each test into quartiles, all values are re-distributed in a Gaussian fashion further diminishing the effect of skewed performance as a confounder. Of note, the mean arousal index for the group is 29/hour suggesting that a moderate proportion of all patients attending a sleep clinic are likely to demonstrate a modicum of short term memory decrement. In as much as the 55 subjects were all randomly selected, it is likely that they are representative of the group as a whole.

At a REM RDI of 37 per hour a subject is 2.7 times more likely to perform a test of information processing speed in the lowest quartile. Furthermore, at a REM RDI of 14/hour, they are 3.2 times more likely to perform at or below the 50% percentile. To ensure that this outcome was not a product of the quantity of REM sleep present, further analyses were performed which demonstrated that the relationship between the total number of respiratory events in REM and information processing speed remains significant and independent of the time spent in REM sleep and the other variables of sleep disordered breathing (AI, total RDI, and the log of the desat < 90%).

Thus while a REM RDI of 15 per hour, with a normal total RDI would be considered by many to be trivial OSA, this data demonstrates this may not be so. In fact, it may indicate a new threshold for considering therapy particularly if the subject is symptomatic.

#### **4.2.5 Study Limitations.**

A summary of the major studies to-date demonstrates several flaws in design. Clearly the timing of the test battery is important both to ensure blinding by the administrators but also to ensure that direct correlations to the degree of sleep disturbance can be made. Difficulties in matching OSA patients for level of education as well as age, sex and pre-morbid cognitive function need to be considered. Sufficient numbers are required if a clinically pertinent finding is to be extrapolated to the OSA population as a whole, to define an 'intention to treat' decrement in cognitive function. Furthermore, given the diversity of tests used in the various batteries described above, there would not appear to be any single tool which could be universally applied to assess cognitive abnormality in OSA.

Given the limitations of previous studies in the area, this study has been developed in an effort to more rigorously blind the test administrators. The tests were chosen and administered in such a manner as to accomplish the greatest yield in a relatively short administration time to avoid deteriorating function due to fatigue. Furthermore, all tests were delivered immediately following PSG to ensure that the results were able to be directly linked to the magnitude of sleep disturbance on the prior night. All cognitive variables were normed against published values for each test and the effect of general intellect was controlled for in the analysis to ensure all subjects could be considered on par.

Despite these efforts, several possible limitations within the study are evident. Given the night-to-night variability of OSA<sup>169</sup>, one cannot be certain that all subjects were studied on a night which was representative of the usual magnitude of their sleep apnoea. Confounders such as increased alcohol at home cannot be accounted for in this analysis. The study may well have been further strengthened by confirmatory domiciliary PSG on one or possibly more nights. This facility however, is resource intensive and complex. While it may have provided additional information it is unlikely that it would diminish the findings as presented.

The concomitant issues of microvascular disease or alcohol related brain damage cannot be entirely dismissed. Although every effort was made to screen patients for confounding intercurrent illnesses, blood alcohol screening and CT scans of the brain were not performed primarily for reasons of time and cost.

The single most important criticism of this work lies in both the number and low  $r$ -squared values for the correlations. There is no doubt that 17 correlations out of 147 possible analyses is small indeed. One would have imagined that potentially more positive findings may have surfaced given the previous literature suggesting relationships between OSA and cognitive dysfunction. However, it was hoped that the use of stepwise regression to ascertain by filtering which of the relationships was

most significant, would diminish the impact of a Type I error. There are several possible explanations for both the poor number of positive outcomes and the low variance derived for each correlation.

1. The fashion in which sleep studies are scored remains arbitrary. As yet there is no universally accepted rule for defining respiratory events and little understanding regarding the inter-relationship between arousals and upper airway events. Indeed, even the degree of desaturation required for a respiratory event remains non-standard. Therefore, the sensitivity of the polysomnograph remains ill-defined as a tool for determining the total insult of OSA in this setting. Perhaps alternate methods of scoring events, both respiratory and cortical are needed to improve the correlation between OSA and cognitive decrement.

2. The tools used for this experiment have been largely developed for use in disease states outside of OSA, including stroke and closed head injury. They have relatively large standard errors about the mean, and do not necessarily define the exact derivation of the normal group which may be critical in appraising the sensitivity of these tools. At best there is a poor correlation between OSA and cognitive decrement, as determined by the r-squared values in this work, suggesting that a direct cause and effect relationship between OSA and cognitive dysfunction is ill-defined. There are likely to be several co-factors including motivation, general well being and sleepiness which are at best poorly measured both here and in general.

3. Several of the tests used the experimental paradigm clearly overlap in terms of the outcome being measured. Indeed, simple inattention to the test instructions can impair the performance of the task assigned. While this work has sought to define the most important measurement parameter, it is fair to say that this is arbitrary and perhaps a little unrealistic. However, there are no current validated tools which can simply measure a single cognitive function in isolation.

Development of such tools may improve the ability to detect decrement in OSA patients.

4. The selection of tests was determined in consultation with a clinical neuropsychologist and based upon a review of all of the previous literature available in the area. The majority of the tests were developed in Europe or America as were the derived normative tables. It is an accepted criticism that Australian populations may differ in performance accounting for some of the lack of positive correlations found in this experiment. This unfortunately is a weakness which could not be overcome.

It is possible that further enrollment may have established other relationships beyond those demonstrated. However, since interim analysis demonstrated adequate power, the study was terminated. Analysis of the non-significant results demonstrates very low  $r$ -values and suggests that larger numbers would be very unlikely to have defined further relevant relationships. Having achieved a pre-determined power of  $\geq 90\%$  at 55 subjects, Type II error is deemed unlikely to have confounded the study outcomes.

In summary, the possibility of deriving further relationships based upon test selection is an issue for consideration. A substantial range of tests have been used in this and previous studies looking for ways to define the cognitive insult in OSA. The tests used in this battery were selected for simplicity and brevity. It is possible that more sensitive and sophisticated tools may have demonstrated greater outcomes although the tools used for this work are the standard instruments of clinical neuropsychology. It is hoped that these somewhat blunt instruments, having demonstrated the abnormalities described, will be used to develop better tools for assessing cognitive dysfunction in OSA, which is a predictably more subtle disease than dementia or closed head injury.

### **4.3 The effects of sleep fragmentation, as defined by modified criteria, on outcomes of cognitive function.**

#### **4.3.1 The effects of brief (Type I) and intermediate (Type II) duration arousals on immediate and delayed short term memory (STM).**

Despite the evidence of a strong correlation between the AI scored by standard criteria (AI-S) and outcomes of immediate and delayed STM, the division of arousals into brief and intermediate failed to demonstrate such a relationship. Indeed, the Type I arousals did not correlate with any outcomes of short term memory, although a relationship to subjective sleepiness (ESS) was demonstrated. This outcome was also seen in the simple linear regression of ESS against AI-S. The r-value of 0.27 would imply that brief arousals make at least a minor contribution to the genesis of daytime somnolence. This finding is supported by the work of Martin et al<sup>21</sup> who demonstrated a similar increase in somnolence on MSLT in an experimental sleep fragmentation model. Indeed, the arousals in Martin's study were at least three seconds in duration and would suitably mimic the Type I and/or Type II arousals of this study.

The lack of any definable relationship between Type I arousals and outcomes of short term memory suggests that it is not necessarily the brief arousals of sleep which determine the short term memory decrement which has been described. Furthermore, while Type II arousals do correlate with a decline in immediate short term memory, there is a non-significant relationship with delayed short term memory.

Simple linear regression of the AI-S versus Type I and Type II arousals demonstrate very significant correlations (Type I  $p < 0.0001$ ,  $r^2 = 0.68$ , Type II  $p < 0.0001$ ,  $r^2 = 0.30$ ). Despite this, as separate entities neither arousal sub-type is able to generate the same degree of significance when correlated with either immediate or delayed

short term memory. The implications of these findings are that there is likely to be some other component of sleep fragmentation, when measured by arousals scored by standard R & K criteria, which determines the short term decrement previously demonstrated in this work. At this point, there is no obvious evidence within the data analysis to suggest a likely contributor.

#### 4.3.2

#### Effects of shifts in sleep stage (Type III) and arousals to wakefulness (Type IV) on working memory.

The findings of a very significant relationship between these two arousal sub-types and decrements in working memory is both novel and potentially clinically relevant.

The data supports the hypothesis that repetitive shifts to a lesser stage of sleep and repetitive wakefulness correlates with a decline in working memory and that this is independent of all major variables of sleep disordered breathing (AI-S, log desat < 90%, Total RDI). Of note, unlike the Type I and II arousals, these arousals demonstrate a much lesser internal correlation with the AI-S (Type III  $p = 0.89$ , Type IV  $p < 0.05$ ,  $r^2 = 0.17$ ).

This new data may have implications for clinical entities other than OSA, particularly insomnia and in the elderly whose usual sleep is characterised by poor efficiency, inability to sustain deep sleep and repetitive awakenings. This data may also suggest plausible reasons for poor performance amongst shift workers and on-call medical staff who demonstrate similar sleep fragmentation and cognitive decline<sup>58, 170</sup>.

The original paper by Stepanski et al<sup>38</sup> did not, unfortunately, incorporate cognitive outcomes although it did confirm that arousals to wakefulness did not correlate with daytime sleepiness, a finding in keeping with this data.

The only corroborative data which supports the finding of this study is the earlier work of Cheshire et al<sup>80</sup>. They demonstrated a similar relationship between the mean shifts in sleep stage/hour and a decrement in PASAT performance. Unfortunately the study used a subset of more moderate OSA patients (AHI > 15/hour plus symptoms) in whom there are fewer sleep stage shifts and wakeful

periods as demonstrated by the work of Stepanski. It therefore supports the proposed hypothesis but may have underestimated the true strength of the relationship due to smaller numbers and selection bias.

#### **4.3.3 Implications for sleep disordered breathing.**

The data presented in this work with respect to arousal subscore may have limited application for sleep disordered breathing. The magnitude of the relationship between standard arousal scoring and cognitive decrement is clearly of greater importance than the results of this sub-classification. As Stepanski<sup>38</sup> demonstrated, sleep apnoeic patients demonstrated fewer Type III and IV arousals although both this study and that of Cheshire et al confirms their relevance to working memory decrement. The findings of this analysis may, however, have a bearing on cognitive performance within other sub-groups of sleep disorders. Patients with insomnia, in whom there is an absence of demonstrable sleep disordered breathing, have been shown to perform less well than normals<sup>78, 171, 172</sup>. It is conceivable that cognitive decrement is a function of poor sleep efficiency and repetitive wakefulness in this group, a hypothesis which deserves further investigation.

#### **4.3.4 Limitations of the modified arousal scoring procedure.**

Although the criteria for the modified arousal scoring were based on the previous published works of Stepanski and Cheshire, substantial corroborative evidence is missing. The work presented here demonstrates similar but not identical findings to the two previous studies. The variations in outcomes probably reflects the differing sample sizes and patient selection between this and the previous work.

The lack of correlation between the lesser indices of arousal and short term memory decrement or indeed Type III or IV arousals and this outcome may be seen as

inconsistent with the work of Martin et al<sup>21, 173</sup>. However, the tests of memory decrement (logical memory I and II) were not utilised by these authors and the arousals of these previous studies were experimentally induced to mimick OSA sleep fragmentation rather than being related to possible upper airway events. Thus a true comparative analysis of this work and the previous data is not possible.

Finally, the data have not been subjected to subclassification between NREM and REM sleep as have much of the other analyses in this work. At this point it remains a plan for further investigation and ongoing research.

#### **4.4 Final summary of the experimental data.**

It has been a long and often arduous journey to have arrived at the completion of this study.

Although many of the outcomes were predicted on the basis of previous work, many appear to be both new and deserving of further investigation.

It is the belief of this author that much about the genesis of cognitive dysfunction in sleep disordered breathing can be explained by the analyses performed on this data set. The enrollment of adequate numbers and a study construct which allowed the development of new treatment thresholds may have much worth for all the workers in this area. Unexpected findings such as that between major arousals and working memory as well as that between vigilance and the total hypoxic insult will hopefully raise new questions regarding functional daytime impairment and sleep disturbance. This author hopes to continue to seek answers to these questions and hopefully develop more sensitive tools and techniques for characterising the numerous cognitive decrements which have their genesis in sleep.

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## **PUBLICATIONS**

### **Abstracts:**

1. Circadian Rhythm In Obstructive Sleep Apnoea: Are There Other Causes For Daytime Somnolence. Joffe, D. Kennaway, D. Robinson, B. Berend, N. (Abstract publication) March 1995 *Proceedings of Australasian Thoracic Society Annual Scientific Meeting* Hobart.
2. Circadian Rhythm In Obstructive Sleep Apnoea. Joffe, D. Kennaway, D. Robinson, B. Berend, N. (Abstract) *Journal of Respiratory and Critical Care Medicine* 1996. April. Vol. 153(4) pA351.
3. The role of hypoxia and arousal in the genesis of daytime somnolence and cognitive impairment. Joffe, D. Marshall, G. Herkes, G. Berend, N. (Abstract) 148 March 1997 *Proceedings of Australasian Thoracic Society Annual Scientific Meeting*. P 214.
4. Effect of hypoxia on cognitive function in obstructive sleep apnoea (OSA). Joffe, D. Marshall, G. Herkes, G. Berend, N. (Abstract). *Journal of Respiratory and Critical Care Medicine* 1997 April. Vol. 155(4) pA848.

## **APPENDIX 1**

### **Simple linear correlations**

The following appendix includes all linear regression analyses performed between each cognitive test outcome and all variables of sleep disordered breathing. The clinically important outcomes are discussed in detail within the body of the thesis. See Chapter 3.4.

#### **1. NREM RDI versus cognitive test battery**

##### **Regression Coefficients**

###### **RDI NREM vs. Digitspan forward**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 12.235      | 2.725      | 12.235      | 4.490   | <.0001  |
| Digitspan forward | .996        | 2.887      | .047        | .345    | .7316   |

##### **Regression Coefficients**

###### **RDI NREM vs. Trails A**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 11.583      | 2.687      | 11.583      | 4.311   | <.0001  |
| Trails A  | 1.712       | 2.596      | .091        | .659    | .5125   |

##### **Regression Coefficients**

###### **RDI NREM vs. Trails B**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 12.305      | 2.775      | 12.305      | 4.434   | <.0001  |
| Trails B  | 1.078       | 3.677      | .041        | .293    | .7706   |

##### **Regression Coefficients**

###### **RDI NREM vs. Symbol digit**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 11.769      | 2.562      | 11.769      | 4.594   | <.0001  |
| Symbol digit | -4.989      | 2.721      | -.244       | -1.833  | .0724   |

**Regression Coefficients****RDI NREM vs. COWA**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 13.030      | 2.740      | 13.030      | 4.756   | <.0001  |
| COWA      | 1.328       | 2.203      | .083        | .603    | .5492   |

**Regression Coefficients****RDI NREM vs. Rey complex**

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 12.521      | 2.638      | 12.521      | 4.746   | <.0001  |
| Rey complex | -.060       | 2.035      | -.004       | -.030   | .9765   |

**Regression Coefficients****RDI NREM vs. Serial digit percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 22.803      | 7.508      | 22.803      | 3.037   | .0037   |
| Serial digit percentiles | -.142       | .098       | -.196       | -1.458  | .1506   |

**Regression Coefficients****RDI NREM vs. Block design percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 22.644      | 9.616      | 22.644      | 2.355   | .0224   |
| Block design percentiles | -.139       | .125       | -.154       | -1.113  | .2707   |

**Regression Coefficients****RDI NREM vs. BVR (correct)**

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 31.057      | 12.352     | 31.057      | 2.514   | .0151   |
| BVR (correct) | -2.606      | 1.719      | -.208       | -1.516  | .1357   |

**Regression Coefficients****RDI NREM vs. Shipley Vt score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 14.700      | 18.389     | 14.700      | .799    | .4277   |
| Shipley Vt score | -.037       | .310       | -.017       | -.120   | .9047   |

### Regression Coefficients

#### RDI NREM vs. Shipley At score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 24.694      | 18.690     | 24.694      | 1.321   | .1921   |
| Shipley At score | -.203       | .308       | -.090       | -.658   | .5132   |

### Regression Coefficients

#### RDI NREM vs. Shipley IQ

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 35.213      | 24.729     | 35.213      | 1.424   | .1603   |
| Shipley IQ | -.199       | .216       | -.126       | -.923   | .3601   |

### Regression Coefficients

#### RDI NREM vs. Beck Depression

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 11.078      | 4.250      | 11.078      | 2.606   | .0119   |
| Beck Depression | .207        | .486       | .058        | .426    | .6717   |

### Regression Coefficients

#### RDI NREM vs. Epworth SS

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 4.991       | 6.038      | 4.991       | .827    | .4122   |
| Epworth SS | .814        | .592       | .186        | 1.375   | .1748   |

### Regression Coefficients

#### RDI NREM vs. Digitspan reverse

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 12.865      | 2.630      | 12.865      | 4.892   | <.0001  |
| Digitspan reverse | -2.121      | 2.621      | -.110       | -.809   | .4222   |

### Regression Coefficients

#### RDI NREM vs. Perdue Dom (Norm)

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 11.880      | 3.064      | 11.880      | 3.877   | .0003   |
| Perdue Dom (Norm) | .934        | 2.396      | .053        | .390    | .6983   |

**Regression Coefficients****RDI NREM vs. Perdue Non-Dom (norm)**

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 12.584      | 2.968      | 12.584      | 4.240   | <.0001  |
| Perdue Non-Dom (norm) | -.128       | 2.428      | -.007       | -.053   | .9582   |

**Regression Coefficients****RDI NREM vs. Z scores for S.C.**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 14.541      | 3.244      | 14.541      | 4.483   | <.0001  |
| Z scores for S.C. | -.209       | .202       | -.141       | -1.036  | .3051   |

**2. REM RDI versus cognitive test battery****Regression Coefficients****RDI REM vs. Digitspan forward**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 21.997      | 3.386      | 21.997      | 6.496   | <.0001  |
| Digitspan forward | 3.097       | 3.588      | .118        | .863    | .3919   |

**Regression Coefficients****RDI REM vs. Trails A**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 21.951      | 3.403      | 21.951      | 6.450   | <.0001  |
| Trails A  | 3.015       | 3.288      | .126        | .917    | .3635   |

**Regression Coefficients****RDI REM vs. Trails B**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 23.742      | 3.508      | 23.742      | 6.769   | <.0001  |
| Trails B  | 3.917       | 4.648      | .116        | .843    | .4032   |

**Regression Coefficients**  
**RDI REM vs. Serial digit percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 30.057      | 9.513      | 30.057      | 3.160   | .0026   |
| Serial digit percentiles | -.100       | .124       | -.110       | -.806   | .4240   |

**Regression Coefficients**  
**RDI REM vs. Block design percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 38.593      | 11.791     | 38.593      | 3.273   | .0019   |
| Block design percentiles | -.219       | .153       | -.197       | -1.432  | .1582   |

**Regression Coefficients**  
**RDI REM vs. Logical MP 1**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 28.621      | 10.111     | 28.621      | 2.831   | .0065   |
| Logical MP 1 | -.080       | .133       | -.083       | -.603   | .5493   |

**Regression Coefficients**  
**RDI REM vs. Logical MP 2**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 25.082      | 9.713      | 25.082      | 2.582   | .0126   |
| Logical MP 2 | -.031       | .128       | -.033       | -.244   | .8083   |

**Regression Coefficients**  
**RDI REM vs. BVR (correct)**

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 41.392      | 15.517     | 41.392      | 2.667   | .0102   |
| BVR (correct) | -2.563      | 2.160      | -.164       | -1.187  | .2409   |

**Regression Coefficients**  
**RDI REM vs. Shipley Vt score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 36.602      | 22.910     | 36.602      | 1.598   | .1161   |
| Shipley Vt score | -.234       | .386       | -.083       | -.606   | .5469   |

**Regression Coefficients****RDI REM vs. Shipley At score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 31.829      | 23.425     | 31.829      | 1.359   | .1800   |
| Shipley At score | -.150       | .387       | -.053       | -.387   | .7003   |

**Regression Coefficients****RDI REM vs. Shipley IQ**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 70.877      | 30.445     | 70.877      | 2.328   | .0238   |
| Shipley IQ | -.421       | .265       | -.213       | -1.586  | .1186   |

**Regression Coefficients****RDI REM vs. Beck Depression**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 21.602      | 5.317      | 21.602      | 4.063   | .0002   |
| Beck Depression | .181        | .608       | .041        | .297    | .7675   |

**Regression Coefficients****RDI REM vs. Epworth SS**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 13.619      | 7.552      | 13.619      | 1.803   | .0770   |
| Epworth SS | 1.000       | .740       | .182        | 1.350   | .1827   |

**Regression Coefficients****RDI REM vs. PASAT**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 22.428      | 3.384      | 22.428      | 6.627   | <.0001  |
| PASAT     | -5.213      | 3.257      | -.221       | -1.601  | .1157   |

**Regression Coefficients****RDI REM vs. Digitspan reverse**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 22.931      | 3.307      | 22.931      | 6.934   | <.0001  |
| Digitspan reverse | -.476       | 3.296      | -.020       | -.144   | .8857   |

# Regression Coefficients

## RDI REM vs. Perdue Dom (Norm)

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 24.596      | 3.809      | 24.596      | 6.457   | <.0001  |
| Perdue Dom (Norm) | -2.591      | 2.978      | -.119       | -.870   | .3883   |

# Regression Coefficients

## RDI REM vs. Perdue Non-Dom (norm)

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 21.491      | 3.689      | 21.491      | 5.826   | <.0001  |
| Perdue Non-Dom (norm) | 2.333       | 3.018      | .106        | .773    | .4429   |

# Regression Coefficients

## RDI REM vs. Z scores for S.C.

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 25.811      | 4.040      | 25.811      | 6.389   | <.0001  |
| Z scores for S.C. | -.304       | .251       | -.164       | -1.211  | .2312   |

# Regression Coefficients

## RDI REM vs. COWA

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 23.520      | 3.424      | 23.520      | 6.870   | <.0001  |
| COWA      | 1.707       | 2.753      | .085        | .620    | .5379   |

# Regression Coefficients

## RDI REM vs. Reye complex

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 23.371      | 3.262      | 23.371      | 7.164   | <.0001  |
| Rye complex | -2.707      | 2.517      | -.146       | -1.076  | .2870   |

### 3. Log desat% < 90 versus cognitive test battery

#### Regression Coefficients

##### Log Desat <90% vs. Digitspan forward

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | -.966       | .172       | -.966       | -5.627  | <.0001  |
| Digitspan forward | .001        | .179       | .001        | .004    | .9968   |

#### Regression Coefficients

##### Log Desat <90% vs. Trails A

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | -.996       | .168       | -.996       | -5.929  | <.0001  |
| Trails A  | .055        | .205       | .042        | .269    | .7894   |

#### Regression Coefficients

##### Log Desat <90% vs. Trails B

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | -1.033      | .173       | -1.033      | -5.973  | <.0001  |
| Trails B  | -.178       | .217       | -.128       | -.817   | .4187   |

#### Regression Coefficients

##### Log Desat <90% vs. Symbol digit

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | -1.001      | .162       | -1.001      | -6.196  | <.0001  |
| Symbol digit | -.212       | .163       | -.199       | -1.301  | .2006   |

#### Regression Coefficients

##### Log Desat <90% vs. COWA

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | -.925       | .169       | -.925       | -5.477  | <.0001  |
| COWA      | .107        | .134       | .124        | .800    | .4282   |

#### Regression Coefficients

##### Log Desat <90% vs. Rey complex

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | -.963       | .163       | -.963       | -5.890  | <.0001  |
| Reye complex | -.017       | .113       | -.023       | -.149   | .8819   |

# Regression Coefficients

## Log Desat <90% vs. Serial digit percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | -.182       | .445       | -.182       | -.408   | .6851   |
| Serial digit percentiles | -.011       | .006       | -.281       | -1.877  | .0676   |

# Regression Coefficients

## Log Desat <90% vs. Block design percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | -.094       | .572       | -.094       | -.164   | .8702   |
| Block design percentiles | -.012       | .007       | -.244       | -1.574  | .1237   |

# Regression Coefficients

## Log Desat <90% vs. BVR (correct)

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | .256        | .780       | .256        | .329    | .7443   |
| BVR (correct) | -.169       | .109       | -.242       | -1.555  | .1281   |

# Regression Coefficients

## Log Desat <90% vs. Shipley Vt score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | -.232       | 1.051      | -.232       | -.221   | .8260   |
| Shipley Vt score | -.013       | .018       | -.110       | -.706   | .4843   |

# Regression Coefficients

## Log Desat <90% vs. Shipley At score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | .248        | 1.107      | .248        | .224    | .8241   |
| Shipley At score | -.020       | .018       | -.170       | -1.108  | .2744   |

# Regression Coefficients

## Log Desat <90% vs. Shipley IQ

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 1.446       | 1.407      | 1.446       | 1.028   | .3102   |
| Shipley IQ | -.021       | .012       | -.260       | -1.724  | .0922   |

# **Regression Coefficients**

## **Log Desat <90% vs. Beck Depression**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | -1.114      | .266       | -1.114      | -4.187  | .0001   |
| Beck Depression | .026        | .037       | .109        | .703    | .4859   |

# **Regression Coefficients**

## **Log Desat <90% vs. Epworth SS**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | -1.215      | .406       | -1.215      | -2.992  | .0047   |
| Epworth SS | .027        | .040       | .104        | .670    | .5065   |

# **Regression Coefficients**

## **Log Desat <90% vs. PASAT**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | -1.000      | .173       | -1.000      | -5.775  | <.0001  |
| PASAT     | -.194       | .163       | -.190       | -1.190  | .2414   |

# **Regression Coefficients**

## **Log Desat <90% vs. Perdue Dom (Norm)**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | -1.015      | .190       | -1.015      | -5.348  | <.0001  |
| Perdue Dom (Norm) | .091        | .181       | .078        | .503    | .6174   |

# **Regression Coefficients**

## **Log Desat <90% vs. Perdue Non-Dom (norm)**

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | -1.023      | .183       | -1.023      | -5.596  | <.0001  |
| Perdue Non-Dom (norm) | .113        | .168       | .104        | .671    | .5058   |

#### 4. Total RDI versus cognitive test battery

##### Regression Coefficients

##### RDI total vs. Digitspan forward

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 13.711      | 2.716      | 13.711      | 5.048   | <.0001  |
| Digitspan forward | 1.234       | 2.878      | .059        | .429    | .6697   |

##### Regression Coefficients

##### RDI total vs. Trails A

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 13.218      | 2.697      | 13.218      | 4.900   | <.0001  |
| Trails A  | 1.741       | 2.606      | .092        | .668    | .5071   |

##### Regression Coefficients

##### RDI total vs. Trails B

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 14.134      | 2.782      | 14.134      | 5.080   | <.0001  |
| Trails B  | 1.806       | 3.687      | .068        | .490    | .6263   |

##### Regression Coefficients

##### RDI total vs. COWA

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 14.581      | 2.732      | 14.581      | 5.337   | <.0001  |
| COWA      | 1.352       | 2.197      | .084        | .615    | .5410   |

##### Regression Coefficients

##### RDI total vs. Rey complex

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 14.184      | 2.628      | 14.184      | 5.397   | <.0001  |
| Rey complex | -.691       | 2.028      | -.047       | -.341   | .7346   |

##### Regression Coefficients

##### RDI total vs. Serial digit percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 24.366      | 7.486      | 24.366      | 3.255   | .0020   |
| Serial digit percentiles | -.143       | .097       | -.197       | -1.466  | .1486   |

**Regression Coefficients**  
RDI total vs. Block design percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 25.873      | 9.561      | 25.873      | 2.706   | .0092   |
| Block design percentiles | -.161       | .124       | -.179       | -1.300  | .1993   |

**Regression Coefficients**  
RDI total vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 28.486      | 7.819      | 28.486      | 3.643   | .0006   |
| Logical MP 1 | -.201       | .103       | -.259       | -1.950  | .0565   |

**Regression Coefficients**  
RDI total vs. Logical MP 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 28.638      | 7.456      | 28.638      | 3.841   | .0003   |
| Logical MP 2 | -.204       | .098       | -.274       | -2.077  | .0427   |

**Regression Coefficients**  
RDI total vs. BVR (correct)

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 33.012      | 12.300     | 33.012      | 2.684   | .0098   |
| BVR (correct) | -2.658      | 1.712      | -.212       | -1.553  | .1266   |

**Regression Coefficients**  
RDI total vs. Shipley Vt score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 19.684      | 18.326     | 19.684      | 1.074   | .2876   |
| Shipley Vt score | -.096       | .309       | -.043       | -.311   | .7574   |

**Regression Coefficients**  
RDI total vs. Shipley At score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 25.357      | 18.650     | 25.357      | 1.360   | .1797   |
| Shipley At score | -.188       | .308       | -.084       | -.612   | .5430   |

**Regression Coefficients**  
RDI total vs. Shipley IQ

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 41.495      | 24.570     | 41.495      | 1.689   | .0971   |
| Shipley IQ | -.241       | .214       | -.152       | -1.123  | .2664   |

**Regression Coefficients**  
RDI total vs. Beck Depression

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 12.689      | 4.239      | 12.689      | 2.993   | .0042   |
| Beck Depression | .197        | .485       | .056        | .407    | .6860   |

**Regression Coefficients**  
RDI total vs. Epworth SS

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 6.456       | 6.019      | 6.456       | 1.073   | .2883   |
| Epworth SS | .822        | .590       | .188        | 1.394   | .1692   |

**Regression Coefficients**  
RDI total vs. Digitspan reverse

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 14.387      | 2.625      | 14.387      | 5.482   | <.0001  |
| Digitspan reverse | -2.003      | 2.616      | -.105       | -.766   | .4473   |

**Regression Coefficients**  
RDI total vs. Perdue Dom (Norm)

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 13.799      | 3.060      | 13.799      | 4.509   | <.0001  |
| Perdue Dom (Norm) | .375        | 2.392      | .022        | .157    | .8761   |

**Regression Coefficients**  
RDI total vs. Perdue Non-Dom (norm)

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 13.765      | 2.959      | 13.765      | 4.652   | <.0001  |
| Perdue Non-Dom (norm) | .491        | 2.420      | .028        | .203    | .8401   |

**Regression Coefficients****RDI total vs. Z scores for S.C.**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 16.268      | 3.228      | 16.268      | 5.039   | <.0001  |
| Z scores for S.C. | -.228       | .201       | -.154       | -1.135  | .2614   |

**5. Arousal index versus cognitive test battery****Regression Coefficients****Arousal Index vs. Digitspan forward**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 29.287      | 2.067      | 29.287      | 14.169  | <.0001  |
| Digitspan forward | .121        | 2.190      | .008        | .055    | .9563   |

**Regression Coefficients****Arousal Index vs. Trails A**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 28.925      | 2.017      | 28.925      | 14.340  | <.0001  |
| Trails A  | -.325       | 1.949      | -.023       | -.167   | .8681   |

**Regression Coefficients****Arousal Index vs. Trails B**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 28.918      | 2.077      | 28.918      | 13.924  | <.0001  |
| Trails B  | .301        | 2.752      | .015        | .110    | .9132   |

**Regression Coefficients****Arousal Index vs. Symbol digit**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 29.101      | 1.993      | 29.101      | 14.603  | <.0001  |
| Symbol digit | -1.476      | 2.117      | -.095       | -.697   | .4886   |

**Regression Coefficients**  
**Arousal Index vs. COWA**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 30.689      | 1.996      | 30.689      | 15.377  | <.0001  |
| COWA      | 3.493       | 1.605      | .286        | 2.176   | .0340   |

**Regression Coefficients**  
**Arousal Index vs. Reye complex**

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 29.144      | 1.992      | 29.144      | 14.628  | <.0001  |
| Rye complex | .915        | 1.537      | .081        | .595    | .5544   |

**Regression Coefficients**  
**Arousal Index vs. Serial digit percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 38.408      | 5.648      | 38.408      | 6.800   | <.0001  |
| Serial digit percentiles | -.126       | .073       | -.229       | -1.711  | .0928   |

**Regression Coefficients**  
**Arousal Index vs. Block design percentiles**

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 32.325      | 7.248      | 32.325      | 4.460   | <.0001  |
| Block design percentiles | -.048       | .094       | -.071       | -.510   | .6121   |

**Regression Coefficients**  
**Arousal Index vs. BVR (correct)**

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 37.978      | 9.431      | 37.978      | 4.027   | .0002   |
| BVR (correct) | -1.180      | 1.313      | -.125       | -.899   | .3729   |

**Regression Coefficients**  
**Arousal Index vs. Shipley Vt score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 19.147      | 13.865     | 19.147      | 1.381   | .1731   |
| Shipley Vt score | .173        | .234       | .101        | .741    | .4618   |

**Regression Coefficients****Arousal Index vs. Shipley At score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 35.159      | 14.197     | 35.159      | 2.476   | .0165   |
| Shipley At score | -.097       | .234       | -.057       | -.415   | .6796   |

**Regression Coefficients****Arousal Index vs. Shipley IQ**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 28.373      | 18.888     | 28.373      | 1.502   | .1390   |
| Shipley IQ | .008        | .165       | .007        | .050    | .9600   |

**Regression Coefficients****Arousal Index vs. Beck Depression**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 31.675      | 3.200      | 31.675      | 9.898   | <.0001  |
| Beck Depression | -.341       | .366       | -.127       | -.931   | .3559   |

**Regression Coefficients****Arousal Index vs. PASAT**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 28.551      | 1.985      | 28.551      | 14.385  | <.0001  |
| PASAT     | -2.994      | 1.910      | -.216       | -1.568  | .1233   |

**Regression Coefficients****Arousal Index vs. Digitspan reverse**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 29.680      | 1.983      | 29.680      | 14.966  | <.0001  |
| Digitspan reverse | -2.147      | 1.977      | -.148       | -1.086  | .2824   |

**Regression Coefficients****Arousal Index vs. Perdue Dom (Norm)**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 29.114      | 2.325      | 29.114      | 12.523  | <.0001  |
| Perdue Dom (Norm) | .306        | 1.818      | .023        | .169    | .8668   |

**Regression Coefficients****Arousal Index vs. Perdue Non-Dom (norm)**

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 28.875      | 2.245      | 28.875      | 12.861  | <.0001  |
| Perdue Non-Dom (norm) | .764        | 1.837      | .057        | .416    | .6791   |

**Regression Coefficients****Arousal Index vs. Z scores for S.C.**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 29.042      | 2.482      | 29.042      | 11.702  | <.0001  |
| Z scores for S.C. | .029        | .154       | .025        | .185    | .8539   |

**6. Minimum saturation in NREM versus cognitive test battery****Regression Coefficients****Min desat% NREM vs. Digitspan forward**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 86.352      | .757       | 86.352      | 114.098 | <.0001  |
| Digitspan forward | -.616       | .802       | -.105       | -.769   | .4455   |

**Regression Coefficients****Min desat% NREM vs. Trails A**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 86.449      | .727       | 86.449      | 118.857 | <.0001  |
| Trails A  | -.158       | .703       | -.031       | -.225   | .8225   |

**Regression Coefficients****Min desat% NREM vs. Trails B**

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 86.440      | .749       | 86.440      | 115.407 | <.0001  |
| Trails B  | .127        | .992       | .018        | .128    | .8990   |

#### Regression Coefficients

Min desat% NREM vs. Symbol digit

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 86.332      | .725       | 86.332      | 119.034 | <.0001  |
| Symbol digit | 1.014       | .770       | .178        | 1.317   | .1936   |

#### Regression Coefficients

Min desat% NREM vs. COWA

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 86.097      | .766       | 86.097      | 112.394 | <.0001  |
| COWA      | -.216       | .616       | -.048       | -.350   | .7278   |

#### Regression Coefficients

Min desat% NREM vs. Rey complex

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 86.100      | .732       | 86.100      | 117.613 | <.0001  |
| Rey complex | .426        | .565       | .103        | .754    | .4543   |

#### Regression Coefficients

Min desat% NREM vs. Serial digit percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 83.825      | 2.108      | 83.825      | 39.762  | <.0001  |
| Serial digit percentiles | .033        | .027       | .161        | 1.189   | .2398   |

#### Regression Coefficients

Min desat% NREM vs. Block design percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 83.012      | 2.707      | 83.012      | 30.660  | <.0001  |
| Block design percentiles | .043        | .035       | .170        | 1.235   | .2226   |

#### Regression Coefficients

Min desat% NREM vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 82.784      | 2.210      | 82.784      | 37.459  | <.0001  |
| Logical MP 1 | .047        | .029       | .218        | 1.624   | .1103   |

**Regression Coefficients****Min desat% NREM vs. Logical MP 2**

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 83.067      | 2.121      | 83.067      | 39.167  | <.0001  |
| Logical MP 2 | .044        | .028       | .209        | 1.559   | .1249   |

**Regression Coefficients****Min desat% NREM vs. BVR (correct)**

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 80.949      | 3.432      | 80.949      | 23.584  | <.0001  |
| BVR (correct) | .728        | .478       | .209        | 1.523   | .1339   |

**Regression Coefficients****Min desat% NREM vs. Shipley Vt score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 83.705      | 5.120      | 83.705      | 16.350  | <.0001  |
| Shipley Vt score | .042        | .086       | .067        | .489    | .6271   |

**Regression Coefficients****Min desat% NREM vs. Shipley At score**

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 81.969      | 5.203      | 81.969      | 15.755  | <.0001  |
| Shipley At score | .070        | .086       | .112        | .818    | .4172   |

**Regression Coefficients****Min desat% NREM vs. Shipley IQ**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 75.618      | 6.800      | 75.618      | 11.121  | <.0001  |
| Shipley IQ | .093        | .059       | .210        | 1.562   | .1242   |

**Regression Coefficients****Min desat% NREM vs. Beck Depression**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 86.038      | 1.188      | 86.038      | 72.452  | <.0001  |
| Beck Depression | .021        | .136       | .021        | .153    | .8786   |

**Regression Coefficients****Min desat% NREM vs. Digitspan reverse**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 85.970      | .717       | 85.970      | 119.836 | <.0001  |
| Digitspan reverse | 1.263       | .715       | .236        | 1.767   | .0830   |

**Regression Coefficients****Min desat% NREM vs. Perdue Dom (Norm)**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 86.128      | .856       | 86.128      | 100.610 | <.0001  |
| Perdue Dom (Norm) | .080        | .669       | .017        | .120    | .9048   |

**Regression Coefficients****Min desat% NREM vs. Perdue Non-Dom (norm)**

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 85.995      | .826       | 85.995      | 104.082 | <.0001  |
| Perdue Non-Dom (norm) | .321        | .676       | .065        | .475    | .6367   |

**Regression Coefficients****Min desat% NREM vs. Z scores for S.C.**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 85.526      | .902       | 85.526      | 94.837  | <.0001  |
| Z scores for S.C. | .067        | .056       | .163        | 1.202   | .2349   |

## 6. Minimum saturation in REM versus cognitive test battery

### Regression Coefficients

#### Min desat% REM vs. Digitspan forward

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 84.505      | .973       | 84.505      | 86.888  | <.0001  |
| Digitspan forward | -.434       | 1.027      | -.059       | -.423   | .6740   |

### Regression Coefficients

#### Min desat% REM vs. Trails A

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 84.523      | .983       | 84.523      | 85.957  | <.0001  |
| Trails A  | -.186       | .944       | -.028       | -.197   | .8448   |

### Regression Coefficients

#### Min desat% REM vs. Trails B

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 84.351      | 1.006      | 84.351      | 83.878  | <.0001  |
| Trails B  | -.476       | 1.323      | -.050       | -.359   | .7207   |

### Regression Coefficients

#### Min desat% REM vs. COWA

|           | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------|-------------|------------|-------------|---------|---------|
| Intercept | 84.143      | .981       | 84.143      | 85.784  | <.0001  |
| COWA      | -.612       | .782       | -.108       | -.783   | .4372   |

### Regression Coefficients

#### Min desat% REM vs. Rey complex

|             | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------|-------------|------------|-------------|---------|---------|
| Intercept   | 84.327      | .942       | 84.327      | 89.474  | <.0001  |
| Rey complex | .331        | .721       | .063        | .459    | .6484   |

### Regression Coefficients

#### Min desat% REM vs. Serial digit percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 81.689      | 2.693      | 81.689      | 30.337  | <.0001  |
| Serial digit percentiles | .038        | .035       | .146        | 1.068   | .2906   |

#### Regression Coefficients

##### Min desat% REM vs. Block design percentiles

|                          | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------------------|-------------|------------|-------------|---------|---------|
| Intercept                | 78.767      | 3.404      | 78.767      | 23.139  | <.0001  |
| Block design percentiles | .076        | .044       | .237        | 1.723   | .0910   |

#### Regression Coefficients

##### Min desat% REM vs. Logical MP 1

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 81.880      | 2.868      | 81.880      | 28.549  | <.0001  |
| Logical MP 1 | .035        | .038       | .127        | .924    | .3596   |

#### Regression Coefficients

##### Min desat% REM vs. Logical MP 2

|              | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|--------------|-------------|------------|-------------|---------|---------|
| Intercept    | 82.471      | 2.757      | 82.471      | 29.908  | <.0001  |
| Logical MP 2 | .027        | .036       | .102        | .739    | .4635   |

#### Regression Coefficients

##### Min desat% REM vs. BVR (correct)

|               | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|---------------|-------------|------------|-------------|---------|---------|
| Intercept     | 77.233      | 4.378      | 77.233      | 17.643  | <.0001  |
| BVR (correct) | 1.013       | .609       | .229        | 1.664   | .1023   |

#### Regression Coefficients

##### Min desat% REM vs. Shipley Vt score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 77.608      | 6.463      | 77.608      | 12.009  | <.0001  |
| Shipley Vt score | .116        | .109       | .145        | 1.060   | .2940   |

#### Regression Coefficients

##### Min desat% REM vs. Shipley At score

|                  | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------------|-------------|------------|-------------|---------|---------|
| Intercept        | 81.522      | 6.672      | 81.522      | 12.218  | <.0001  |
| Shipley At score | .048        | .110       | .060        | .434    | .6661   |

**Regression Coefficients****Min desat% REM vs. Shipley IQ**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 74.393      | 8.740      | 74.393      | 8.512   | <.0001  |
| Shipley IQ | .088        | .076       | .158        | 1.150   | .2553   |

**Regression Coefficients****Min desat% REM vs. Beck Depression**

|                 | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------|-------------|------------|-------------|---------|---------|
| Intercept       | 83.897      | 1.509      | 83.897      | 55.604  | <.0001  |
| Beck Depression | .072        | .174       | .057        | .415    | .6797   |

**Regression Coefficients****Min desat% REM vs. Epworth SS**

|            | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|------------|-------------|------------|-------------|---------|---------|
| Intercept  | 85.825      | 2.232      | 85.825      | 38.448  | <.0001  |
| Epworth SS | -.154       | .217       | -.098       | -.708   | .4823   |

**Regression Coefficients****Min desat% REM vs. Digitspan reverse**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 84.203      | .935       | 84.203      | 90.026  | <.0001  |
| Digitspan reverse | 1.098       | .924       | .163        | 1.188   | .2402   |

**Regression Coefficients****Min desat% REM vs. Perdue Dom (Norm)**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 83.992      | 1.093      | 83.992      | 76.826  | <.0001  |
| Perdue Dom (Norm) | .585        | .848       | .095        | .690    | .4930   |

**Regression Coefficients****Min desat% REM vs. Perdue Non-Dom (norm)**

|                       | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-----------------------|-------------|------------|-------------|---------|---------|
| Intercept             | 84.715      | 1.056      | 84.715      | 80.240  | <.0001  |
| Perdue Non-Dom (norm) | -.562       | .858       | -.090       | -.654   | .5158   |

**Regression Coefficients****Min desat% REM vs. Z scores for S.C.**

|                   | Coefficient | Std. Error | Std. Coeff. | t-Value | P-Value |
|-------------------|-------------|------------|-------------|---------|---------|
| Intercept         | 83.250      | 1.146      | 83.250      | 72.663  | <.0001  |
| Z scores for S.C. | .116        | .071       | .222        | 1.640   | .1070   |

## **APPENDIX 2**

### **Stepwise regression analyses**

The following appendix includes all stepwise regression analyses performed between cognitive test outcomes and all variables of sleep disordered breathing. The clinically important outcomes are discussed in detail within the body of the thesis. See Chapter 3.8.

#### **1. Digitspan forward versus variables of sleep disordered breathing.**

##### **Stepwise Regression Summary Digitspan forward vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

##### **Variables In Model Digitspan forward vs. 7 Independents Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .309        | .140       | .309        | 4.852       |

##### **Variables Not In Model Digitspan forward vs. 7 Independents Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .026         | .028       |
| RDI REM         | .109         | .489       |
| Arousal Index   | -.002        | 9.673E-5   |
| Min desat% NREM | -.097        | .393       |
| Min desat% REM  | -.025        | .026       |
| RDI total       | .037         | .055       |
| Log Desat <90%  | .001         | 1.678E-5   |

## 2. Trails A versus variables of sleep disordered breathing.

### Stepwise Regression Summary

#### Trails A vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

### Variables In Model

#### Trails A vs. 7 Independents

##### Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .160        | .125       | .160        | 1.622       |

### Variables Not In Model

#### Trails A vs. 7 Independents

##### Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .233         | 2.289      |
| RDI REM         | .324         | 4.706      |
| Arousal Index   | .183         | 1.378      |
| Min desat% NREM | -.248        | 2.614      |
| Min desat% REM  | -.282        | 3.465      |
| RDI total       | .246         | 2.584      |
| Log Desat <90%  | .042         | .072       |

**Variables In Model**  
**Trails A vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.144       | .185       | -.144       | .611        |
| RDI REM   | .011        | .005       | .324        | 4.706       |

**Variables Not In Model**  
**Trails A vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.024        | .023       |
| Arousal Index   | -.009        | .003       |
| Min desat% NREM | -.071        | .196       |
| Min desat% REM  | -.087        | .299       |
| RDI total       | -.052        | .105       |
| Log Desat <90%  | -.235        | 2.278      |

### 3. Trails B versus variables of sleep disordered breathing.

#### Stepwise Regression Summary

Trails B vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

#### Variables In Model

Trails B vs. 7 Independents

Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.260       | .117       | -.260       | 4.886       |

#### Variables Not In Model

Trails B vs. 7 Independents

Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .050         | .102       |
| RDI REM         | .146         | .870       |
| Arousal Index   | .064         | .164       |
| Min desat% NREM | .016         | .011       |
| Min desat% REM  | -.080        | .259       |
| RDI total       | .083         | .279       |
| Log Desat <90%  | -.128        | .668       |

#### 4. Symbol digit versus variables of sleep disordered breathing.

##### Stepwise Regression Summary Symbol digit vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

##### Variables In Model Symbol digit vs. 7 Independents Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.170       | .151       | -.170       | 1.270       |

##### Variables Not In Model Symbol digit vs. 7 Independents Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.262        | 3.015      |
| RDI REM         | -.436        | 9.636      |
| Arousal Index   | -.139        | .813       |
| Min desat% NREM | .184         | 1.436      |
| Min desat% REM  | .348         | 5.648      |
| RDI total       | -.316        | 4.563      |
| Log Desat <90%  | -.199        | 1.692      |

##### Variables In Model Symbol digit vs. 7 Independents Step: 1

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .334        | .213       | .334        | 2.463       |
| RDI REM   | -.018       | .006       | -.436       | 9.636       |

##### Variables Not In Model Symbol digit vs. 7 Independents Step: 1

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .112         | .511       |
| Arousal Index   | .144         | .848       |
| Min desat% NREM | -.085        | .290       |
| Min desat% REM  | .076         | .229       |
| RDI total       | .096         | .372       |
| Log Desat <90%  | .120         | .585       |

## 5. COWA versus variables of sleep disordered breathing.

### Stepwise Regression Summary

#### COWA vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

### Variables In Model

#### COWA vs. 7 Independents

##### Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.376       | .186       | -.376       | 4.097       |

### Variables Not In Model

#### COWA vs. 7 Independents

##### Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .075         | .235       |
| RDI REM         | .085         | .300       |
| Arousal Index   | .251         | 2.755      |
| Min desat% NREM | -.002        | 2.334E-4   |
| Min desat% REM  | -.099        | .403       |
| RDI total       | .076         | .241       |
| Log Desat <90%  | .124         | .640       |

## 6. RCFT versus variables of sleep disordered breathing.

### Stepwise Regression Summary Reye complex vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

### Variables In Model Reye complex vs. 7 Independents Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .160        | .221       | .160        | .520        |

### Variables Not In Model Reye complex vs. 7 Independents Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .011         | .005       |
| RDI REM         | -.135        | .758       |
| Arousal Index   | .109         | .495       |
| Min desat% NREM | .074         | .226       |
| Min desat% REM  | .036         | .053       |
| RDI total       | -.031        | .041       |
| Log Desat <90%  | -.023        | .022       |

## 7. Serial digit percentile versus variables of sleep disordered breathing.

### Stepwise Regression Summary

#### Serial digit percentiles vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

### Variables In Model

#### Serial digit percentiles vs. 7 Independents

##### Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 70.372      | 4.057      | 70.372      | 300.912     |

### Variables Not In Model

#### Serial digit percentiles vs. 7 Independents

##### Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.175        | 1.294      |
| RDI REM         | -.072        | .213       |
| Arousal Index   | -.240        | 2.495      |
| Min desat% NREM | .086         | .303       |
| Min desat% REM  | .097         | .387       |
| RDI total       | -.174        | 1.285      |
| Log Desat <90%  | -.281        | 3.524      |

8. Block design versus variables of sleep disordered breathing.

Stepwise Regression Summary

Block design percentiles vs. 7 Independents

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

Variables In Model

Block design percentiles vs. 7 Independents

Step: 0

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 73.707      | 3.513      | 73.707      | 440.281     |

Variables Not In Model

Block design percentiles vs. 7 Independents

Step: 0

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.155        | .958       |
| RDI REM         | -.221        | 1.999      |
| Arousal Index   | -.162        | 1.054      |
| Min desat% NREM | .191         | 1.473      |
| Min desat% REM  | .324         | 4.583      |
| RDI total       | -.188        | 1.434      |
| Log Desat <90%  | -.244        | 2.476      |

**Variables In Model****Block design percentiles vs. 7 Independents****Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | -18.825     | 43.352     | -18.825     | .189        |
| Min desat% REM | 1.122       | .524       | .324        | 4.583       |

**Variables Not In Model****Block design percentiles vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .075         | .217       |
| RDI REM         | .013         | .006       |
| Arousal Index   | -.022        | .019       |
| Min desat% NREM | .010         | .004       |
| RDI total       | .050         | .096       |
| Log Desat <90%  | .005         | .001       |

9. LM1 versus variables of sleep disordered breathing.

**Stepwise Regression Summary**  
**Logical MP 1 vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 73.558      | 3.646      | 73.558      | 406.983     |

**Variables Not In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.383        | 7.063      |
| RDI REM         | -.179        | 1.359      |
| Arousal Index   | -.373        | 6.626      |
| Min desat% NREM | .318         | 4.628      |
| Min desat% REM  | .227         | 2.221      |
| RDI total       | -.365        | 6.310      |
| Log Desat <90%  | -.307        | 4.261      |

**Variables In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 80.458      | 4.285      | 80.458      | 352.619     |
| RDI NREM  | -.443       | .167       | -.383       | 7.063       |

**Variables Not In Model**  
**Logical MP 1 vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .180         | 1.336      |
| Arousal Index   | -.110        | .488       |
| Min desat% NREM | .038         | .059       |
| Min desat% REM  | -.023        | .022       |
| RDI total       | .099         | .396       |
| Log Desat <90%  | -.027        | .030       |

**10. LMII versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**  
**Logical MP 2 vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 2       |
| Variables Entered  | 2       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 74.047      | 3.750      | 74.047      | 389.878     |

**Variables Not In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.457        | 10.816     |
| RDI REM         | -.141        | .831       |
| Arousal Index   | -.439        | 9.772      |
| Min desat% NREM | .380         | 6.914      |
| Min desat% REM  | .245         | 2.624      |
| RDI total       | -.417        | 8.625      |
| Log Desat <90%  | -.375        | 6.693      |

**Variables In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 82.504      | 4.244      | 82.504      | 377.908     |
| RDI NREM  | -.543       | .165       | -.457       | 10.816      |

**Variables Not In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .346         | 5.452      |
| Arousal Index   | -.124        | .627       |
| Min desat% NREM | .048         | .093       |
| Min desat% REM  | -.065        | .171       |
| RDI total       | .260         | 2.895      |
| Log Desat <90%  | -.049        | .096       |

**Variables In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 2**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 75.595      | 5.000      | 75.595      | 228.553     |
| RDI NREM  | -.962       | .238       | -.809       | 16.302      |
| RDI REM   | .473        | .203       | .468        | 5.452       |

**Variables Not In Model**  
**Logical MP 2 vs. 7 Independents**  
**Step: 2**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| Arousal Index   | -.080        | .251       |
| Min desat% NREM | .038         | .058       |
| Min desat% REM  | .088         | .301       |
| RDI total       | -.148        | .869       |
| Log Desat <90%  | -.119        | .559       |

**11. BVRT versus variables of sleep disordered breathing.**

**Stepwise Regression Summary  
BVR (correct) vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model  
BVR (correct) vs. 7 Independents  
Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 7.000       | .237       | 7.000       | 873.478     |

**Variables Not In Model  
BVR (correct) vs. 7 Independents  
Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.225        | 2.086      |
| RDI REM         | -.206        | 1.726      |
| Arousal Index   | -.151        | .914       |
| Min desat% NREM | .238         | 2.348      |
| Min desat% REM  | .309         | 4.103      |
| RDI total       | -.238        | 2.339      |
| Log Desat <90%  | -.242        | 2.418      |

**Variables In Model**  
**BVR (correct) vs. 7 Independents**  
**Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | 1.037       | 2.953      | 1.037       | .123        |
| Min desat% REM | .072        | .036       | .309        | 4.103       |

**Variables Not In Model**  
**BVR (correct) vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.042        | .067       |
| RDI REM         | .006         | .002       |
| Arousal Index   | -.030        | .034       |
| Min desat% NREM | .083         | .265       |
| RDI total       | -.043        | .071       |
| Log Desat <90%  | -.012        | .006       |

**12. Shipley IQ versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**Shipley IQ vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables in Model**

**Shipley IQ vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 114.395     | 1.981      | 114.395     | 3336.098    |

**Variables Not in Model**

**Shipley IQ vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.154        | .997       |
| RDI REM         | -.271        | 3.244      |
| Arousal Index   | -.084        | .294       |
| Min desat% NREM | .291         | 3.804      |
| Min desat% REM  | .233         | 2.357      |
| RDI total       | -.188        | 1.505      |
| Log Desat <90%  | -.260        | 2.974      |

**13. BDI versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**Beck Depression vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables in Model**

**Beck Depression vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 5.791       | .682       | 5.791       | 71.999      |

**Variables Not in Model**

**Beck Depression vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .242         | 2.548      |
| RDI REM         | .304         | 4.163      |
| Arousal Index   | .087         | .311       |
| Min desat% NREM | -.294        | 3.871      |
| Min desat% REM  | -.251        | 2.767      |
| RDI total       | .264         | 3.064      |
| Log Desat <90%  | .109         | .495       |

**Variables In Model****Beck Depression vs. 7 Independents****Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 4.205       | 1.018      | 4.205       | 17.050      |
| RDI REM   | .056        | .027       | .304        | 4.163       |

**Variables Not In Model****Beck Depression vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .021         | .018       |
| Arousal Index   | -.108        | .471       |
| Min desat% NREM | -.155        | .986       |
| Min desat% REM  | -.063        | .159       |
| RDI total       | .020         | .016       |
| Log Desat <90%  | -.119        | .577       |

**14. ESS versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**  
**Epworth SS vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**  
**Epworth SS vs. 7 Independents**  
**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 9.279       | .621       | 9.279       | 223.209     |

**Variables Not In Model**  
**Epworth SS vs. 7 Independents**  
**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .225         | 2.192      |
| RDI REM         | .237         | 2.439      |
| Arousal Index   | .264         | 3.078      |
| Min desat% NREM | -.010        | .004       |
| Min desat% REM  | -.133        | .737       |
| RDI total       | .228         | 2.240      |
| Log Desat <90%  | .104         | .449       |

**15. PASAT versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**PASAT vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**

**PASAT vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | -.268       | .165       | -.268       | 2.643       |

**Variables Not In Model**

**PASAT vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.346        | 5.154      |
| RDI REM         | -.201        | 1.601      |
| Arousal Index   | -.244        | 2.415      |
| Min desat% NREM | .333         | 4.749      |
| Min desat% REM  | .311         | 4.069      |
| RDI total       | -.330        | 4.632      |
| Log Desat <90%  | -.190        | 1.416      |

**Variables In Model**  
**PASAT vs. 7 Independents**  
**Step: 1**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .002        | .197       | .002        | 1.116E-4    |
| RDI NREM  | -.017       | .008       | -.346       | 5.154       |

**Variables Not In Model**  
**PASAT vs. 7 Independents**  
**Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI REM         | .100         | .376       |
| Arousal Index   | .075         | .207       |
| Min desat% NREM | .110         | .456       |
| Min desat% REM  | .128         | .612       |
| RDI total       | .090         | .301       |
| Log Desat <90%  | .111         | .459       |

**16. Digitspan reverse versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**Digitspan reverse vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 2       |
| Variables Entered  | 2       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**

**Digitspan reverse vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .097        | .138       | .097        | .488        |

**Variables Not In Model**

**Digitspan reverse vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.087        | .310       |
| RDI REM         | .068         | .189       |
| Arousal Index   | -.099        | .407       |
| Min desat% NREM | .208         | 1.854      |
| Min desat% REM  | .108         | .482       |
| RDI total       | -.074        | .227       |
| Log Desat <90%  | -.302        | 4.115      |

**Variables In Model****Digitspan reverse vs. 7 Independents****Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | -.155       | .182       | -.155       | .721        |
| Log Desat <90% | -.260       | .128       | -.302       | 4.115       |

**Variables Not In Model****Digitspan reverse vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .228         | 2.203      |
| RDI REM         | .361         | 5.989      |
| Arousal Index   | .125         | .634       |
| Min desat% NREM | -.023        | .021       |
| Min desat% REM  | -.198        | 1.634      |
| RDI total       | .267         | 3.068      |

**Variables In Model****Digitspan reverse vs. 7 Independents****Step: 2**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | -.874       | .341       | -.874       | 6.586       |
| RDI REM        | .017        | .007       | .450        | 5.989       |
| Log Desat <90% | -.511       | .159       | -.593       | 10.372      |

**Variables Not In Model****Digitspan reverse vs. 7 Independents****Step: 2**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .048         | .089       |
| Arousal Index   | .033         | .043       |
| Min desat% NREM | .044         | .075       |
| Min desat% REM  | -.067        | .178       |
| RDI total       | .025         | .025       |

17. Pegboard (non-dom) versus variables of sleep disordered breathing.

**Stepwise Regression Summary**

**Perdue Non-Dom (norm) vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**

**Perdue Non-Dom (norm) vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .507        | .148       | .507        | 11.714      |

**Variables Not In Model**

**Perdue Non-Dom (norm) vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .031         | .038       |
| RDI REM         | .256         | 2.881      |
| Arousal Index   | .097         | .390       |
| Min desat% NREM | .045         | .082       |
| Min desat% REM  | -.259        | 2.955      |
| RDI total       | .092         | .347       |
| Log Desat <90%  | .104         | .451       |

**18. Pegboard (dom) versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**Perdue Dom (Norm) vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 0       |
| Variables Entered  | 0       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables in Model**

**Perdue Dom (Norm) vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | .546        | .138       | .546        | 15.682      |

**Variables Not in Model**

**Perdue Dom (Norm) vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .166         | 1.164      |
| RDI REM         | -.006        | .001       |
| Arousal Index   | .156         | 1.022      |
| Min desat% NREM | -.104        | .451       |
| Min desat% REM  | -.084        | .293       |
| RDI total       | .140         | .816       |
| Log Desat <90%  | .078         | .253       |

**19. Z-scores for Steer Clear versus variables of sleep disordered breathing.**

**Stepwise Regression Summary**

**Z scores for S.C. vs. 7 Independents**

|                    |         |
|--------------------|---------|
| F-to-Enter         | 4.000   |
| F-to-Remove        | 3.996   |
| Number of Steps    | 1       |
| Variables Entered  | 1       |
| Variables Forced   | 0       |
| Stepwise Procedure | Forward |

**Variables In Model**

**Z scores for S.C. vs. 7 Independents**

**Step: 0**

|           | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|-----------|-------------|------------|-------------|-------------|
| Intercept | 9.507       | 2.023      | 9.507       | 22.087      |

**Variables Not In Model**

**Z scores for S.C. vs. 7 Independents**

**Step: 0**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | -.145        | .879       |
| RDI REM         | -.179        | 1.354      |
| Arousal Index   | -.018        | .013       |
| Min desat% NREM | .227         | 2.229      |
| Min desat% REM  | .277         | 3.405      |
| RDI total       | -.162        | 1.108      |
| Log Desat <90%  | -.318        | 4.603      |

**Variables In Model****Z scores for S.C. vs. 7 Independents****Step: 1**

|                | Coefficient | Std. Error | Std. Coeff. | F-to-Remove |
|----------------|-------------|------------|-------------|-------------|
| Intercept      | 5.642       | 2.649      | 5.642       | 4.538       |
| Log Desat <90% | -4.004      | 1.866      | -.318       | 4.603       |

**Variables Not In Model****Z scores for S.C. vs. 7 Independents****Step: 1**

|                 | Partial Cor. | F-to-Enter |
|-----------------|--------------|------------|
| RDI NREM        | .155         | .982       |
| RDI REM         | .036         | .053       |
| Arousal Index   | .250         | 2.663      |
| Min desat% NREM | -.011        | .005       |
| Min desat% REM  | .057         | .129       |
| RDI total       | .141         | .816       |