THE EFFECTS OF SLEEP RESTRICTION AND ALCOHOL ON SIMULATED DRIVING AND CORTICAL FUNCTION IN OBSTRUCTIVE SLEEP APNOEA

by

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ABSTRACT

Obstructive sleep apnoea (OSA) is a common sleep disorder associated with neurobehavioural daytime abnormalities including poor driving simulator performance and an increased risk of motor-vehicle accidents. Treating OSA with continuous positive airway pressure (CPAP) significantly improves many of the daytime consequences of OSA. Until recently it was believed that CPAP treatment can completely resolve excessive daytime sleepiness and neurobehavioural abnormalities associated with OSA. However, recent evidence suggests that compared to results in well-matched healthy subjects, levels of daytime vigilance and cortical activation and some domains of cognitive function in OSA patients may not return to normal, even after effective OSA treatment with good treatment compliance.

Sleep restriction and low-dose alcohol consumption are common "life style" factors that have a negative impact on the central nervous system and driving performance in healthy subjects. However, their impact on driving simulator performance and cortical information processing in patients with OSA has not been examined.

The hypotheses tested in the work presented in this thesis were that:

a) Sleep restriction and alcohol have a greater deleterious effect on driving simulator performance and cortical information processing in untreated OSA patients than in healthy subjects.

b) Treatment of severe OSA with CPAP improves, but does not normalise driving simulator performance and cortical information processing.

Consequently, the broad aims were:

a) To compare the effects of sleep restriction and alcohol on driving simulator performance and auditory cortical event-related potentials in OSA patients and healthy age and gender-matched controls.

b) To compare driving simulator performance and auditory cortical event-related potentials in severe OSA patients before and after 3-months of CPAP therapy and to compare these results with those of healthy, untreated subjects also studied 3-months apart.

Study 1 (CHAPTER 2) compared performance during a 90-minute simulated drive in 38 patients with OSA and 20 healthy age and gender-matched control subjects under 3 conditions studied in random order: 1) normal sleep, 2) sleep restriction (4 hours in bed on the night prior to study) and 3) low-dose alcohol (blood alcohol concentration 0.05 g/dL). Compared to control subjects, OSA patients exhibited a higher crash rate, increased overall steering deviation and more steering deterioration with time-on-task. Following sleep restriction and alcohol there was a ~40% greater increase in steering deviation in OSA patients than in control subjects. Crashes were more likely to occur in patients with OSA compared with control subjects. OSA patients were more likely to crash under sleep restriction and alcohol conditions compared to the normal sleep condition. Simulator crashes were associated with behavioural and physiological evidence of increased sleepiness. The results of this study showed that compared with healthy subjects, OSA patients have worse driving simulator performance and are more vulnerable to the effects of prior alcohol and sleep restriction on various driving performance parameters. To the extent that these simulator findings may be indicative of real on-road driving

performance, it may be advisable for untreated OSA patients to avoid sleep restriction and even legal doses of alcohol prior to extended driving.

Study 2 (CHAPTER 3) assessed the effectiveness of ~3 months CPAP treatment in improving driving simulator performance. Eleven severe OSA patients and nine age- and gender-matched controls were studied on two occasions 3 months apart using the same protocol as in Study 1. In the intervening period OSA patients were treated with CPAP during which they showed a high level of compliance with therapy (mean ± SD, 6.0 ± 1.4 hours/night). At baseline, OSA patients demonstrated worse driving simulator performance compared to controls under all conditions, and showed greater steering decrements following sleep restriction and alcohol than control subjects. After CPAP treatment, OSA patients showed significant improvements in steering deviation under all conditions, but steering deviation did not reach the level of control subjects and crash frequency remained significantly elevated. Braking reaction time was not significantly different between groups, conditions, or treatments and there were no significant interaction effects. Taken together, these findings suggest that CPAP treatment is only partially effective in improving driving performance during simulated long and monotonous driving. To the extent that driving simulator findings may be indicative of real on-road driving performance it may be appropriate to advise patients, even after apparent optimal CPAP treatment, to be cautious when undertaking long distance driving, as they could remain at higher than normal accident risk.

Given the behavioural finding of residual driving simulator impairment in CPAP-treated, severe OSA patients in studies 1 and 2, the final study (CHAPTER 4)

explored whether cortical information processing during a simple attention task demonstrated similar treatment resistant abnormalities. The effects of CPAP treatment on cortical information processing in OSA patients were examined by comparing early and late components of auditory target (odd-ball) event-related potential responses in 9 patients with severe OSA and 9 healthy age- and gender-matched controls. The results showed that compared to controls, early and late auditory event related potentials were abnormal in severe OSA patients at baseline. Specifically, N2 and P3 peaks were smaller and delayed in latency, and P2 amplitude was larger. At follow-up, P3 latency was the only measure to show improvement following CPAP treatment, but remained prolonged in patients compared to control subjects despite high CPAP treatment compliance in OSA patients (mean ± SD, 6.0 ± 1.6 hours/night). None of the abnormalities in earlier components (N2 and P2) observed at baseline changed in CPAP-treated OSA patients.

In summary, driving simulator performance is impaired in patients with OSA compared to healthy controls, and patients demonstrate a greater susceptibility to the detrimental effects of sleep restriction and alcohol. Driving simulator performance is only partially improved in CPAP-treated OSA patients. Thus, it may be prudent to advise patients with OSA to be cautious and avoid sleep loss or alcohol prior to long distance driving, even when optimally treated. Residual abnormalities were also evident in auditory cortical evoked responses in optimally treated OSA patients, suggesting the possibility of a permanent reduction in information processing capacity. The mechanisms underlying the observed vulnerability to additional stressors (sleep loss and alcohol) and the residual driving

performance and electrophysiological abnormalities observed in CPAP-treated patients warrants further investigation. In addition, examining how these driving simulator and electrophysiological findings relate to on-road motor vehicle accident risk in patients with OSA is another important question worthy of further investigation.

PUBLICATIONS

The following are publications that have arisen from work conducted towards this thesis:

Journal articles:

Vakulin A, Baulk SD, Catcheside PG, Antic NA, van den Heuvel CJ, Dorrian J & McEvoy RD. Effects of Alcohol and Sleep Restriction on Simulated Driving Performance in Untreated Patients with Obstructive Sleep Apnea and Health. Annals of Internal Medicine 2009; **151**:447-455.

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Book Chapters:

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Published abstracts:

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Vakulin, A, Baulk, S.D, Catcheside, P. G, Antic, N, van den Heuvel, C, Banks, S & McEvoy. R.D. The Effects of Sleep Restriction and Alcohol on Cognitive Function and P300 in Obstructive Sleep Apnoea Patients Before and After CPAP Treatment. *Sleep and Biological Rhythms* 2010; **8**(Suppl s1): OP04.

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Baulk, S.D, **Vakulin, A**, Catcheside, P.G, Dorrian, J, Antic, N, van den Heuvel, C.J & McEvoy, R.D. Are OSA Patients Vulnerable to Sleep Restriction? Effects on Sleepiness and Perception During Simulated Driving. *(Proceedings of the 10th International Sleep and Breathing Meeting 2007)*

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DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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GLOSSARY OF ABBREVIATIONS

AERP(s)   Auditory event related potential(s)

AHI   Apnoea hypopnoea index

BAC   Blood alcohol concentration

BMI   Body mass index

COPD   Chronic obstructive pulmonary disease

CPAP   Continuous positive airway pressure

EDS   Excessive day-time sleepiness

EEG   Electroencephalogram

ERP(s)   Event related potential(s)

ESS   Epworth sleepiness scale

FA   Fractional anisotropy

fMRI   Functional magnetic resonance imaging

GABA   γ-Aminobutyric acid

IH   Intermittent hypoxia

MRI   Magnetic resonance imaging

MSLT   Multiple sleep latency test

MVA(s)   Motor vehicle accident(s)

MWT   Maintenance of wakefulness test

NMDA   N-methyl D-aspartate

NREM   Non-rapid eye movement

N1 & N2   First and second negative peak of the ERP respectively

OSA   Obstructive sleep apnoea

P2 & P3   First and second positive peak of the ERP respectively

PFC	Pre-frontal cortex
PVT	Psychomotor vigilance test
REM	Rapid eye movement

CHAPTER 1.   GENERAL INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder affecting up to 10 % of the middle-aged population (1-4). This number is likely rising due to strong links between OSA, ageing (5-7) and obesity (8, 9), all of which are increasing globally (2, 10). The symptoms of OSA include snoring, repetitive hypopnoea (reduced airflow) and/or complete collapse (apnoea) of the pharyngeal upper airway (UA) during sleep. These nocturnal respiratory disturbances are typically associated with marked oxygen desaturation (hypoxaemia), carbon dioxide retention (hypercapnia) and brief arousals from sleep leading to sleep fragmentation. Although arousals help rapidly restore upper airway patency, compensate ventilation and stabilise blood gases, arousal related ventilatory "overshoot" and consequent reduced breathing and upper airway muscle activity may help promote continuing cyclical airway obstruction. Both sleep fragmentation (11, 12) and hypoxia (13-21) resulting from these cyclic respiratory events have been linked to excessive daytime sleepiness (EDS), impairments in neurocognitive function (11-13, 22-33), poor driving performance (34-37), heightened motor vehicle accident (MVA) risk (35, 37-40) and increased all cause and cardiovascular mortality (41-43). Continuous positive airway pressure (CPAP) is the treatment of choice for OSA. Despite many benefits of treatment, compliance with therapy is often poor (44-46) and the degree of treatment benefit on daytime function is unclear as some recent evidence suggests the presence of residual sleepiness and neurocognitive dysfunction in CPAP-treated OSA patients (47-54).

The first part of this Chapter briefly describes the epidemiology, pathogenesis and treatment of OSA and discusses in detail the literature on neurobehavioural daytime consequences of OSA including driving impairments and associated MVA risk.

Alcohol and sleep loss are two "lifestyle factors" or central nervous system "stressors" that are commonly experienced in modern society (55-59). These factors cause many negative neurobehavioural consequences (60-62) independently and in combination and have been found experimentally to interact, possibly by acting upon common neuronal circuitry (63-67). The cognitive functions affected by alcohol and sleep loss, particularly frontal lobe controlled executive attention functions (such as sustained attention/vigilance, divided attention visual spatial coordination, response inhibition and simple reaction) (68-71) are essential to and are collectively utilised by the brain to maintain safe driving. To date a large body of evidence has demonstrated that alcohol and more recently sleep restriction have serious consequences for driving performance (55, 72-79) and increase the risk of sleepiness and alcohol related traffic and occupational accidents (80-94). Thus, the second part of this introduction summarises the evidence regarding the independent and interactive effects of alcohol and sleep restriction on brain neurochemistry, neurobehavioural function, driving performance and MVA risk. In addition, potential mechanisms of cognitive impairment in OSA are discussed. Finally, the central importance of the neural control of attention and vigilance in all cognitive performance is discussed focusing on the apparent rise in attention failures (i.e. lapses, microsleeps) as the most likely primary mechanism underlying

performance impairments caused by central nervous system stressors such as sleep loss, alcohol and OSA (alone or in combination).

Although the effects of sleep loss, alcohol and their interactions have been extensively investigated in healthy subjects, the impact of these common central nervous system stressors on long monotonous driving performance in individuals suffering from OSA has not been investigated. Years of prior sleep disturbance and sleep-related hypoxia may potentially render OSA patients more vulnerable to the adverse effects of sleep loss and alcohol. There is also uncertainty about how well CPAP treatment normalises driving simulator performance and cortical information processing in patients with severe OSA and it is unknown to what extent treatment affects the vulnerability to stressors such as sleep loss and alcohol. These clinical and basic research questions form the basis of the experimental work presented in this thesis.

1.1 Epidemiology, pathogenesis and consequences of obstructive sleep apnoea (OSA)

1.1.1 Prevalence of OSA

Based on large epidemiological studies from the US (4, 95), Australia (1), China (96, 97), Korea (98) and India (99), the community prevalence of OSA is approximately 5-10% in the middle aged population. When considering the presence of accompanying daytime sleepiness, OSA prevalence is approximately 3-7% in adult men and 2-5% in adult women (2). It appears that health care

services are unable to cope with the burden of disease as up to 80% of patients with OSA in the community remain undiagnosed (3, 7, 100). Obesity is one of the strongest risk factors for OSA (101, 102). Using polysomnographic data from 602 employed adults between the ages of 30-60 years, Young et al. (4) demonstrated an odds ratio of 4.2 for having an apnoea hypopnoea index (AHI) greater than 5 events per hour for a 1-standard deviation increase in body mass index (BMI). Given that between 1999 and 2004 the prevalence of obesity (BMI > 30 kg/m^2) particularly in males rose from 27.5 to ~32% in the US (101) with similar trends in Europe (102), it is likely that the prevalence of OSA in other Western countries is also rising. Of concern is that surveys have found a higher prevalence of OSA (ranging from 18 to 26%) in commercial (35, 103), taxi (104) and railway drivers (105).

1.1.2   Risk factors for OSA

The major risks factors for OSA are male gender, older age and obesity (2, 6-10, 106, 107). The physiological mechanisms contributing to UA instability and increased collapsibility are incompletely understood, but appear to be multiple and vary between affected individuals. The factors that have been linked to UA collapse during sleep in OSA include an anatomically narrower pharyngeal airway, reduced neuromuscular compensation in UA dilator muscles, heightened arousal responses and reduced lung volume secondary to obesity. More recently several genetic markers have been associated with OSA (2, 10, 106, 107).

In addition to the physiological and anatomical factors, sedating substances such as alcohol ingested prior to bedtime have been shown to worsen OSA (108-112). In an early study by Scrima et al. (110) consumption of alcohol (0.08 g/dL) just prior to bedtime in OSA patients resulted in a significant increase in the number and frequency of hypoxic events (oxygen desaturation to at least 92%) and a shortened sleep latency. Most severe hypoxic events occurred within 80-160 minutes from sleep onset. Similar results have been reported subsequently by other investigators (109, 111). A study of 1,465 Japanese truck drivers aged 20-69 years showed that compared to non-drinkers, drivers who consumed 0.5-1.0 and 1.0 or more grams/kg per day of alcohol had odds ratios for having sleep disordered breathing (measured by 3% oxygen desaturation index) of 1.5 and 3.4 respectively (108). More than 50% (803 out of 1,465) of these professional drivers drank alcohol. Surprisingly, the association between alcohol and OSA appeared stronger in drivers with BMI < 23.4 kg/m^2 compared with heavier drivers (BMI ≥ 23.4 kg/m^2).

1.2   Daytime consequences of OSA

OSA is associated with EDS, deficits in neurocognitive function (11-13, 22-33, 113) and driving performance (34-37), heightened MVA risk (35, 37-40) and increased all-cause and cardiovascular mortality (41, 43, 114, 115). The following section summarises the literature on the daytime consequences of OSA with a particular emphasis on OSA effects related to driving performance and MVA risk.

1.2.1 Excessive daytime sleepiness associated with OSA

The main complaint and clinical symptom of OSA is EDS, which refers to an increased propensity for sleep or increased sleep "pressure" experienced at inappropriate times (e.g. during daytime activities). EDS is associated with negative health outcomes and quality of life (116-120). It can also develop as part of the pathology of other sleep disorders such as insomnia and circadian abnormalities (1, 3, 10, 121-124). In healthy individuals, EDS often occurs as a result of acute or chronic sleep restriction (see section 1.3.1) which in modern society can stem from occupational, social and family factors (56-60).

Current clinical tests to assess daytime sleepiness include the Epworth Sleepiness Scale (ESS) questionnaire (125), which asks subjects to subjectively rate their level of sleepiness in eight common situations. Objective measures of sleepiness include the multiple sleep latency test (MSLT) which measures the average time to fall asleep during 4 to 5 daytime nap opportunities (126, 127) and the maintenance of wakefulness test (MWT) which measures how well subjects can maintain wakefulness when placed in a soporific environment (126).

In OSA patients, EDS is believed to be the result of sleep fragmentation and/or hypoxia brought about by cyclic obstructive respiratory events and frequent arousals. The mechanisms and relative contributions of sleep fragmentation and hypoxia to EDS and daytime function in OSA remain a matter of debate (see section 1.4.1). Nonetheless, EDS makes it difficult for OSA patients to maintain

vigilance and attention, especially in monotonous situations conducive to sleepiness such as long distance driving.

1.2.2 Neurocognitive deficits associated with OSA

It is generally accepted that OSA is associated with deficits in neurocognitive daytime functions (22, 23, 27). The various cognitive domains that have been examined in OSA include general intelligence (18, 23, 128), verbal abilities (23, 113), visual perception/processing (23, 129), short term verbal and visual memory (23, 130, 131), long term verbal and visual memory (23, 27, 130), executive functioning (13, 22, 23, 27, 128, 130-132), motor functioning (23, 129, 133) and vigilance/attention (18, 23, 134, 135). Electrophysiological studies support the neurobehavioural literature and demonstrate abnormalities in cortical activation in OSA patients (51, 54, 136-142).

1.2.2.1 Behavioural evidence

Executive function, although defined differently by various investigators, is the ability to develop and maintain a flexible, organised and future-oriented approach to problem situations and includes at least six components (22). These components are behavioural inhibition; set-shifting; sustained attention/vigilance (argued to be a separate cognitive domain by some investigators); working memory; analysis/synthesis and contextual memory. In this section the cognitive domains of attention, vigilance and concentration are categorised under the executive function classification.

In the mid 1980s, investigators observed deficits in OSA patients in tests that measure attention, concentration, complex problem-solving and short-term recall of verbal and spatial information (143). Bedard et al. (18) demonstrated that OSA patients were impaired in tasks that measure focal attention/concentration, attention shifting capacity, vigilance and general intelligence when compared to healthy matched controls, with patients with more severe OSA showing the greatest impairment. Naegale et al. (27) found that OSA patients had impaired short-term memory and impaired verbal and visual learning abilities. In contrast to the findings of Bedard et al., these authors found that attention shifting capacity via assessment of resistance to interfering stimuli (Stroop Test) was significantly impaired in OSA patients of all OSA severities. A large community based study of 841 employed men and women aged 30-60 enrolled in the Wisconsin Sleep Cohort Study concluded that impairments in fine visual-spatial coordination, sustained attention and concentration were significantly associated with sleep disordered breathing in this population (130). No evidence of memory deficits were found, which is in contrast to previous studies (18, 20, 27, 143).

It is evident that findings of studies on neurocognitive function in OSA vary widely with often conflicting results. This is likely due to the different cognitive domains targeted for assessment, cognitive tasks used, differences in selection criteria for patient and control populations and small sample sizes. Several reviews (22, 132) and a meta-analysis (23) have attempted to better quantify, categorise and summarise the cognitive deficits associated with OSA. In a review by Engelman et al. (132) the authors summarised the effect size of cognitive impairment associated with OSA. Broadly, cognitive deficits worsened with increasing OSA severity. The

greatest impairment was evident in attention/vigilance and executive function scores, moderate impairments were evident in memory related functions and negligible effects were observed in intellectual abilities. In 2003, Beebe et al. (23) conducted a comprehensive meta-analysis of 25 studies of neuropsychological function in OSA. Cognitive test results were compared to healthy case-control data or normative population data for each cognitive domain examined. In agreement with Engleman et al. (132) the main findings were that general intelligence and verbal abilities were unaffected in OSA patients, but attention/vigilance, executive function and fine motor coordination were significantly impaired, while inconsistent results were reported for visual/motor skills and memory (23).

The finding that vigilance, attention and executive function were consistently impaired in OSA patients across behavioural studies is important, as it is these cognitive domains that underpin safety critical tasks such as driving.

1.2.2.2 Electrophysiological evidence: Event related potentials

In addition to psychological tasks used to assess cognitive function, cortical electrophysiological responses to various stimuli can be evaluated from the average electroencephalographic (EEG) response to repeated presentations of a specific stimulus. These EEG responses are most commonly elicited by auditory stimuli in an odd-ball paradigm (e.g. 80% standard and 20% target stimuli) and are termed event related potentials (ERPs) (144, 145). ERPs are believed to represent an objective marker of cortical information processing (144-147), sensitive to the

state of arousal, attention and vigilance (148, 149). ERPs have proven to be useful as a clinical assay when assessing cognitive deficits in many neurological conditions (144, 150, 151), and as a result of experimental interventions such as sleep deprivation (152, 153). The EEG waveforms of ERPs are measured in terms of their peak latency (time from stimulus onset) and amplitude (the height of the peak compared to pre-stimulus baseline and/or other peaks). Components of ERP waveforms are designated (negative, N) or (positive, P) according to the wave polarity and the time from stimulus onset to peak amplitude. ERP components elicited by target stimuli during an odd-ball paradigm include N1, P2, N2 and P3 (Figure 1.1). The N1 component is thought to index the initial automatic stimulus detection mechanisms that depend on an individual's cortical state (arousal, circadian, homeostatic, drugs and alcohol) (154, 155). P2 is poorly understood, but growing evidence suggests that in contrast to the automatic N1, the P2 represents the beginning of a central process responsible for stimulus classification/identification and inhibition processes (154, 156, 157), with some authors (156, 158) suggesting that P2 is a prerequisite step before the P3 can be elicited. In addition, P2 amplitude has been found to be sensitive to age, sleep onset and sleep deprivation (152, 156). The N2 component is elicited by active target detection processes related to stimulus discrimination (recognising the target as being different to non-target) (159). The P3 is the most commonly investigated waveform and is thought to provide an index of the perception of the magnitude and quality of a stimulus, and the speed and efficiency of information processing in response to the stimulus (144, 145).

Figure 1.1 Grand average auditory target event related potential (ERP)
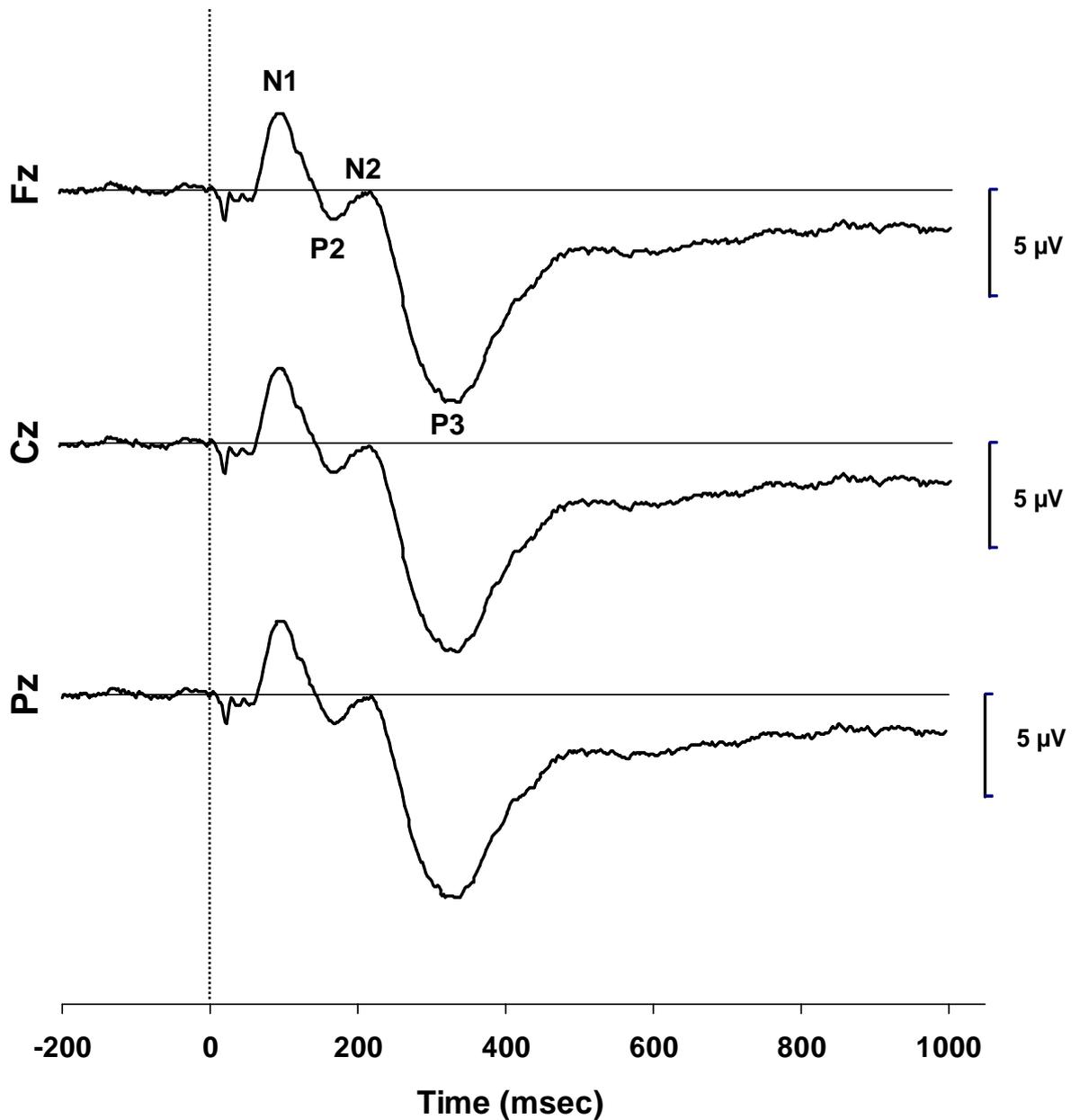
Grand average auditory target event related potentials recorded from the mid-line electrode sites in 19 healthy subjects demonstrating the negative and positive deflections, N1, P2, N2 and P3. Time zero indicates auditory stimulus onset.

Although each ERP component is thought to represent a distinct stage of information processing (157, 160), evidence suggests that ERP components are part of a complex chain of interdependent cortical information processing events. Consequently, a better understanding of the underlying neural mechanisms of neurocognition may require ERP waveforms to be considered as whole rather than as independent components (157). The P3 has been the most studied in untreated OSA patients (51, 54, 136-142), with the majority of studies indicating delayed P3 latency in OSA patients compared to controls (51, 54, 138, 161), although reduced P3 amplitudes have also been reported (136, 137). These results suggest that in OSA patients there is general slowing of information processing and this may underlie cognitive behavioural deficits associated with OSA. Despite numerous studies examining the P3 in OSA patients, earlier ERP components preceding the P3 have been rarely investigated. The few studies that have studied these components in untreated OSA patients have reported abnormalities in P2 and N2 (136, 137, 139, 141).

These electrophysiological observations suggest that OSA is associated with overall slowing of early automatic and higher order information processing, which may be related to the behavioural performance impairments observed in these patients. Therefore, ERPs appear to provide a sensitive and potentially useful tool for assessing neurocognitive deficits in OSA.

1.2.3 The association of OSA with increased motor vehicle accident risk and poor driving simulator performance

In recent years, landmark population studies have found a strong relationship between OSA and MVAs with a 2-7 fold increased risk of accidents, particularly amongst patients with moderate to severe OSA (35, 37-40, 162-165). Laboratory studies have found that patients with OSA have significantly impaired driving simulator performance, including greater steering deviation, increased crash frequency and more attention lapses (34, 36, 166-169) when compared to healthy drivers, supporting the findings of clinical observation studies. In 2004 the estimated indirect MVA cost per annum associated with OSA was approximately US $538 million (170).

Studies first linked OSA to a higher MVA risk almost two decades ago (162, 164, 169). In 1988 Findley et al. (162) compared accident rates in a relatively small sample of 29 OSA patients and 35 controls and found that OSA patients had a 7-fold greater MVA rate and that OSA patients were approximately 5 times more likely to have had multiple crashes compared to controls. In the late 1990s Young et al. (40) demonstrated in a large sample of 913 employed adults, that having an AHI of >15 events/hour was associated with an elevated risk of having had multiple MVAs in the previous 5 years (odds ratio 7.3). Another study (39), that accounted for multiple confounders such as alcohol consumption, visual-refraction disorders, BMI, years of driving, age, history with respect to traffic accidents, use of medications causing drowsiness, and sleep schedule also reported that an AHI >10 events/hour was associated with significantly increased MVA risk (odds ratio 6.3).

The early reports of higher MVA risk in OSA patients (162, 163) prompted investigators to begin objectively assessing driving impairments in these patients. In 1989 Findley and colleagues (169) were one of the first groups to report abnormalities in driving simulator performance in OSA patients compared to controls. In another early study, George et al. (34) used a 20 minute divided attention driving task prior to each daytime nap of the MSLT to compare driving performance in OSA patients and age/sex matched healthy controls. The authors found that all driving measures were significantly impaired in OSA patients, with tracking error (steering deviation) being the most affected parameter. Using a different 30 minute steering simulator, Juniper et al. (36) also demonstrated that OSA patients had significant increases in steering deviation, reaction time and off-road (crash) incidents compared to healthy controls matched for age, sex and driving experience. In addition to driving performance decrements, another study (166) found that during an hour long driving simulation, OSA patients experienced a greater duration and frequency of EEG attention lapses (>3 seconds alpha or theta EEG activity) compared to healthy controls, and this measure of sleepiness was correlated with steering deviation and crash frequency. The authors also observed that steering deviation, crashes and attention lapses increased over time with increasing impairments up to 50 minutes into the drive. This latter finding raises the possibility that shorter divided attention tasks used in other studies (34, 36) may be relatively insensitive for detecting driving impairments in OSA patients.

The observation that driving performance continued to deteriorate during an hour long driving simulator task (166) is important, particularly with respect to longer country driving during which MVAs, although not as frequent as in metropolitan

areas, are likely to be more severe due to higher speeds. In addition, commercial vehicle operators such as truck drivers, of whom almost 16% have been found to have OSA (35), work for long periods under monotonous conditions; a scenario highly conducive to sleep related attention lapses that may lead to severe MVAs.

1.2.4 Cardiovascular disease, stroke and mortality associated with OSA

In addition to the daytime consequences, strong links have been established between OSA and hypertension, cardiac disease, stroke and all-cause mortality (41, 43, 171-174). In a study of 41 adults with drug-resistant hypertension, the prevalence of OSA defined as AHI ≥10 events/hour was 83% (171). Peker et al. (172) studied 182 middle-aged men with and without OSA who were free of cardiovascular disease, pulmonary disease, diabetes mellitus, psychiatric disorder, alcohol dependency and malignancy at baseline. The authors followed these patients for 7 years and found that 36.7% of men with OSA had incident cardiovascular disease compared to 6.6% of men without OSA. Only OSA and age were significant predictors of cardiovascular disease after adjusting for BMI, systolic blood pressure and diastolic blood pressure. Another large population study (173) reported that subjects with an AHI ≥20 events/hour had an increased likelihood of having a stroke (odds ratio 4.3). Marshall et al. (43) demonstrated that among 380 participants, moderate to severe OSA was an independent risk factor for all-cause mortality (fully adjusted hazard ratio [HR] 6.2), while mild OSA was not. Another two studies have also reported an association between OSA and increased mortality (41, 42).

1.2.5   Treatment of OSA

1.2.5.1   Behavioural treatment options

A number of conservative "lifestyle" treatment options are available for patients with OSA. Weight loss has been shown to reduce AHI and improve symptoms particularly amongst patients with mild OSA (175-178). The limitation of weight reduction as a treatment for OSA is that losing weight is challenging for many patients. Few achieve sufficient weight loss to significantly improve their OSA and an even smaller number of patients are able maintain weight loss long term (177). Other behavioural treatment options include smoking cessation, reduced alcohol consumption (particularly before bedtime) and wearing devices to avoid supine sleep, as all of these factors have been associated with worsening OSA and OSA-related symptoms (108, 110, 177, 179, 180). Again, however, these behavioural treatment options are more suited to mild OSA patients and are often used in conjunction with clinical treatments such as mandibular advancement splints, UA surgery and continuous positive airway pressure (CPAP).

1.2.5.2   Other treatment options

Altering the size and/or anatomy of the UA can be achieved by treatments such as a mandibular advancement splint and UA surgery (181, 182). Mandibular advancement splint treatment works by advancing the mandible and tongue thereby increasing pharyngeal size. It has been shown, particularly in milder OSA,

to be effective in reducing AHI, improving sleep and reducing nocturnal blood pressure (181, 183, 184). UA surgery is a treatment option sometimes prescribed for OSA, however the treatment benefit varies widely and, overall, significant benefits have not been consistently demonstrated (182). Mandibular advancement splint and UA surgery are most frequently prescribed to patients with mild to moderate OSA and who are intolerant to CPAP treatment, the more commonly used and gold standard treatment for OSA (177).

CPAP has been the predominant form of treatment for OSA for the last three decades since first described by Sullivan et al. in 1981 (185). By applying air pressure through a mask secured over the patient's mouth and/or nose, CPAP creates a pneumatic splint that stabilises the UA and reduces hypoxia and sleep fragmentation associated with repetitive obstructive events (186). Despite the ability of CPAP treatment to almost completely abolish UA obstruction, stabilise blood gases, reduce sleep fragmentation and improve EDS (49, 187), as many as 46-83% of patients fail to adhere to treatment over the long term (46). A number of side-effects limit adherence to CPAP therapy. These include mask problems (skin irritation/allergies, claustrophobia, mask leak), pressure related problems (headaches, sinusitis, rhinitis) and equipment related issues (noise, smell) (186). In addition, a perceived lack of treatment benefit or dislike of the treatment can lead to poor CPAP adherence (188). Some of the factors that influence whether or not a patient accepts CPAP treatment over the long term have been evaluated in large clinical trials. These studies have concluded that adherence is related to pre-treatment OSA severity (i.e. higher AHI results in better long term adherence) (186, 188-190), mask interface type and effective humidification (nasal masks and

humidification lead to better adherence) (191), while CPAP pressure levels do not appear to influence adherence levels (192, 193). However, a growing body of recent evidence has highlighted that in addition to the biophysical factors contributing to CPAP adherence, psychosocial attitudes and patient's health beliefs may play a more important role in determining adherence (194-196). For example Sayer et al. (194) reported differences between OSA patients who adhere to CPAP and those who do not, including perception of risk associated with OSA, symptom recognition, outcome expectations, treatment goals and perceived treatment facilitators and barriers.

1.2.6 Effects of CPAP treatment on daytime sleepiness, cognitive function, driving performance and MVA risk

An important clinical question is how effective is CPAP therapy in improving and/or normalising daytime sleepiness, cognitive function, driving performance and reducing MVA risk associated with OSA. A number of studies designed to address this question have demonstrated that CPAP treatment is effective in significantly reducing daytime sleepiness (48, 49, 186, 197-200), improving driving simulator performance (199, 201-204) and decreasing MVA risk (205-210). However, there remains uncertainty whether CPAP improves performance impairments to the level of healthy subjects. Several studies have shown improvements in driving performance (199, 202-204) and reductions in MVA risk post-CPAP (205-207, 209, 210), but many of these studies did not include an appropriate comparator control group (199, 203, 206, 207, 209). In addition, some recent studies suggest that when compared to controls, only partial improvements in neurocognitive

performance (47, 50, 54, 211), cortical evoked responses (51, 54) and daytime sleepiness (52, 53) are observed, even when patients are well treated with an average of 6 or more hours of CPAP use per night (53). These observations raise the possibility that there may be irreversible central nervous system damage by the time that patients present for treatment, perhaps as a result of many years of unrecognised repetitive hypoxia and sleep fragmentation.

1.2.6.1 CPAP and excessive daytime sleepiness (EDS)

Excessive daytime sleepiness, as measured by the ESS, has been shown to improve more with CPAP than a placebo treatment (187, 192, 198, 212). Engelman and colleagues (198) found that compared to an oral placebo, four weeks of CPAP treatment (~3 hours per night) decreased the ESS score from 12 (out of a maximum score of 24) to 6 in 23 patients with moderate OSA (mean AHI 43 ± 37 events/hr). Another study (192) found that the change in the median ESS score was greater in OSA patients following therapeutic CPAP (4 weeks, 5.4 hours per night) than that with sub-therapeutic CPAP (15.5 to 7.0 versus 15.0 to 13.0 respectively). In a meta analysis, Marshall et al. (213) demonstrated that major therapeutic benefit from CPAP is more difficult to show in OSA of mild severity, with only small changes in sleepiness that are likely of negligible clinical significance.

When EDS is objectively measured using the MWT, therapeutic CPAP results in greater improvements in EDS than sham CPAP (192, 199). CPAP has also been shown to be superior to a placebo pill in improving objective daytime sleepiness in patients with moderate-severe OSA (45, 198). However, this was not the case for

patients with mild OSA, where similar improvements in objective sleepiness were observed (183, 214, 215).

1.2.6.2 Evidence for residual sleepiness following CPAP

Although the benefit of CPAP in mild OSA may be small, it is clear that in patients with moderate-severe OSA, CPAP is associated with significant improvements in objective daytime sleepiness. However, when comparing sleepiness scores of treated OSA patients with those of healthy non-apnoeic subjects, some evidence supports that daytime sleepiness in OSA patients does not "normalise" to the level of controls (47, 52, 216). Bedard et al. (47) showed that 6 months of CPAP treatment improved daytime sleepiness in OSA patients, but patients remained sleepier compared to healthy controls. Sforza and Krieger (216) made a similar observation after a much longer CPAP treatment period (mean 554 days) and using a modified MWT protocol that simulated real-life sedentary conditions (six 30 min sessions without instruction to try to sleep or stay awake). During this protocol, fifty eight OSA patients (mean apnoea index of 71 apneas per hour) used the device about 5 hours/night and showed an increase in sleep latency from 16.6 minutes at baseline to 20.2 minutes at follow-up. However, this was still shorter than the 26.9 minute sleep latency in a healthy control group (216).

Recently Weaver and coworkers (53) evaluated how different levels of CPAP use over a three month period impacted on both subjective and objective daytime sleepiness. These authors found that ~40% of OSA patients (mean AHI ~64 events per hour) who had abnormal ESS scores (≥10) prior to CPAP treatment, remained

abnormal after 3 months of using the device between 4-6 hours/night. Even in patients who complied remarkably well with treatment (mean CPAP use of 8 hours/night), 20% remained subjectively sleepy post-treatment. In the same study (53), when daytime sleepiness was assessed objectively by MSLT, only ~35% of patients who used CPAP on average 5.1 hours/night obtained normal scores (sleep latency >7.5 minutes) post-treatment.

Potential explanations for residual daytime sleepiness in CPAP treated patients include; an inadequate treatment period, other factors that may influence sleepiness (i.e. alcohol intake, medications, co-morbidities and obesity) and possible irreversible OSA effects on the wake-sleep promoting regions of the brain. The presence of residual daytime sleepiness may be an important component of persistent cognitive deficits observed in treated OSA patients, and may have profound implications for performance during long vigilance demanding tasks such as country driving.

1.2.6.3 CPAP and neurocognitive function

In addition to EDS, OSA is associated with significant deficits in neurocognitive function (22, 23, 27). The effectiveness of CPAP treatment in improving cognitive function in OSA has been extensively investigated (47-51, 54, 131, 133, 198, 200, 211, 214, 215, 217-220). Many of these studies were randomised controlled trials that evaluated the effects of therapeutic CPAP versus sub-therapeutic sham CPAP (200, 211, 217, 219), oral placebo (tablet) (49, 198, 214, 215, 220), or conservative treatment (48, 133, 221).

Improvements in cognitive function after OSA treatment have not been consistently demonstrated. For example, Bardwell et al. (217) failed to show any significant cognitive improvement with either therapeutic CPAP or sham CPAP in 21 of 22 cognitive tasks assessed, although the authors acknowledged that a 1 week treatment period may not have been adequate to achieve significant cognitive improvements. Another study (200) in 46 severe OSA patients (mean AHI approximately 65 events/hour) showed neuropsychological improvements with therapeutic CPAP treatment (mean treatment duration 15-20 days, mean usage approximately 5.5 hours/night). However, this was also the case in the sham CPAP arm (0-1 cmH$_2$O), and no significant differences between therapeutic and sham CPAP treatments were found. Trials using oral placebo have reported similar but less consistent findings. In an early study by Engleman et al. (49), 4 weeks of therapeutic CPAP was found to be superior to placebo in improving cognitive function on tests of divided attention/vigilance, working memory, visual processing speed and reaction time in patients with a median AHI of 28 (range 7-129) events/hour. However, a more recent cross-over trial in 23 moderate-severe OSA patients (mean AHI 43 events/hour) by the same group (198), using similar tasks, failed to demonstrate cognitive performance improvements after 4 weeks of CPAP or placebo. Barnes et al. (214) also found no treatment benefits on neurocognitive function following 8 weeks of CPAP or oral placebo, although only patients with mild OSA were studied. Thus, while there appears to be some agreement that patients with more severe OSA may experience greater cognitive improvements with CPAP compared to patients with milder OSA (49, 220, 221), there are some conflicting data. These studies highlight the importance of a placebo control when

evaluating treatment effectiveness, and suggest cognitive improvement in severe OSA following treatment. However, these studies do not allow for the comparison of cognitive impairment and any improvements with treatment between OSA patients and healthy subjects.

1.2.6.4 Evidence for residual cognitive and cortical function abnormalities following CPAP treatment

None of the placebo controlled trials to date have included a healthy matched comparator group to assess if cognitive functions "normalise" following treatment. Only a few studies (47, 50, 51, 54, 222) have compared cognitive function and cortical activation in OSA patients before and after CPAP treatment to that of a healthy control population. These studies suggest variable degrees of improvement, but generally only a partial and small reversal of function towards normal compared to healthy controls. Ferini-Strambi et al. (50) evaluated cognitive function in 23 severe OSA patients before and after 15 and 40 days of CPAP treatment and compared the results to age and education matched healthy controls. Visual-spatial learning and motor performance improved and even "normalised" to control levels following 15 days, without further improvements after 40 days of CPAP treatment (mean use 5.2 hours/night). In contrast, performance deficits in the cognitive domains of executive function and constructional ability did not improve after 15 or 40 days of treatment. Also, Kotterba et al. (54) showed that while OSA patients treated with CPAP for 6 months (mean use of 5.4 hours/night) had significant improvements in cognitive tests of alertness and divided and sustained attention, test scores in treated OSA patients remained significantly

impaired compared to healthy subjects. Of note in all of these studies is that healthy control subjects were evaluated once, while OSA patients had repeat testing following treatment, and in general showed only small improvements. Cognitive tests are often associated with learning effects, and thus it is possible that small improvements in OSA patients reflect repeat testing and learning rather than CPAP therapy effects *per se*. Consequently, repeat testing in control groups is needed to eliminate this possible important confounder.

In addition to cognitive tests, several studies have evaluated cortical activation and information processing using ERPs elicited using an odd-ball stimulus paradigm (51, 54, 136-138). Kotterba et al. (54) focused on the P3 component, believed to reflect higher order cognitive information processing, and found that the peak latency of this ERP waveform was significantly prolonged in OSA patients compared to controls, with no improvement following CPAP treatment. Other studies have also demonstrated CPAP treatment resistant P3 abnormalities in OSA patients (51, 136-138). Only two early studies (136, 137) have evaluated the effects of CPAP on early ERP components in addition to the P3. These studies found persistent abnormalities in P2 and N2 in CPAP treated OSA patients compared to controls. This suggests that cortical information processing deficits effect not only higher order P3 associated mechanisms but also earlier stimulus identification/classification processes. Similar to the neurobehavioural literature, there are several possible confounders that may have influenced the results of previous ERP studies. For example, ERP studies have generally assessed control groups only once, or relied on historical control data (51, 54, 137). In three studies (51, 54, 136), it was unclear if the time of ERP recording was matched between

patients and controls, and in another if the controls were age-matched (137). More carefully controlled investigations of CPAP effects on ERP responses in OSA patients versus appropriate controls are warranted given strong evidence that ERPs are importantly influenced by many exogenous and endogenous factors such as age, circadian factors, fatigue, food/drink intake and prior sleep (144, 145).

1.2.6.5 Do persistent neurobehavioural deficits in treated OSA patients imply residual driving impairment?

Evidence that neurocognitive abnormalities associated with OSA persist despite adequate CPAP treatment may have serious implications for tasks such as driving. Driving a vehicle involves many of the cognitive parameters found to be impaired in OSA patients including attention, vigilance, visual-spatial coordination, reaction and motor-coordination. Cognitive tests are limited, however, in their ability to replicate many cognitive domains simultaneously engaged while driving in environments such as busy metropolitan areas, and are even less able to replicate the vigilance demands of monotonous long distance driving. Driving simulator performance measures have been shown to correlate with on-road driving performance (223-226) and allow for examination of driving performance as well treatment effectiveness in a safe and controlled environment.

1.2.6.6   Effects of CPAP on driving simulator performance and MVA risk

A number of investigators have assessed the effectiveness of CPAP treatment on driving simulator performance (199, 201-204) and MVA risk (205-210) in OSA patients. Hack et al. (199) evaluated simulated steering performance in 59 patients with OSA before and after 1 month of therapeutic (mean use of 5.6 hours/night) or sub-therapeutic (mean use of 5.0 hours/night) CPAP treatment. Compared to sub-therapeutic CPAP, therapeutic treatment significantly improved steering deviation, deterioration in steering over time and reaction times to target stimuli. Orth et al. (203) evaluated the effects of short term (2 days) and longer term (42 days) CPAP treatment on driving simulator performance and cognitive function relevant to driving in severe OSA patients. The authors demonstrated that following both short and long term treatment there were significant improvements in subjective daytime sleepiness, crash frequency, concentration faults, alertness and divided attention. Interestingly, however, vigilance (responding to a rare target during a 10 minute task) did not improve with either short or long term treatment. Turkington et al. (204) did not formally evaluate vigilance, but similar to Orth et al. (203) found significant performance improvements during a 20 minute divided attention driving simulator task, including tracking error (steering deviation), reaction times and off-road crash events after less than one week of using CPAP for 4.9 hours/night.

Most previous driving simulator studies assessing the effectiveness of CPAP treatment during relatively short (20-30 minutes) divided attention tasks (199, 202, 204) did not include a healthy control comparator group. Thus, they did not assess

whether or not CPAP "normalises" driving simulator performance in treated OSA patients. Only one earlier study by George et al. (201) included a healthy age- and gender-matched control group and demonstrated that, in OSA patients, driving simulator performance during a 20 minute divided attention driving simulator task improved significantly following OSA treatment, with tracking errors (steering deviation) reaching normal control levels post-treatment. However, short divided attention tasks are likely more relevant to busy metropolitan driving environments than the attention and vigilance demands of long monotonous driving situations in which the risk for sleepiness related attention failures and MVAs is greater. Risser et al. (166) demonstrated that driving simulator performance deteriorates after 30 minutes during an hour long drive. They found that steering deviation was the most sensitive measure of performance deterioration and was related to attention lapses which increased in frequency during the long monotonous driving task. Similarly, a more recent study using a 70 minute driving simulation task found that steering deviation continued to deteriorate throughout the drive (79). The question of whether or not driving performance during a long monotonous driving situation "normalises" in CPAP treated patients compared to controls has, until now, not been investigated.

In addition to laboratory driving simulator studies, the effects of CPAP treatment on MVA risk has been assessed by several epidemiological studies (205-210). Cassel et al. (206) showed that accident rates in 59 patients with moderate to severe OSA (AHI 38.9 ± 3.4 events/hour) who used CPAP for 1 year (mean use 6.1 hours/night) reduced significantly from 0.8 to 0.15 accidents per 100,000 km. When considering accidents that were identified as sleep related due to fatigue and inability to

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maintain a sufficient level of concentration, CPAP also reduced these types of accidents from 0.6 to 0.06 per 100,000 km. Another larger study (209) of 547 severe OSA patients (AHI 59.8 ± 25.8 events/hour) also observed a significant reduction in MVAs following 3, 6 and 12 months of CPAP treatment (mean use 5.6 hours/night). However, unlike the study of Cassel et al. (206), information regarding driving exposure before and after treatment was not collected, thus the reduction in accidents may have been due to patients curtailing their driving rather than CPAP treatment *per se.* The effect of a longer 2 year CPAP treatment period has been evaluated in one study of 45 severe OSA patients (210). Decreased daytime sleepiness and a reduced number of patients experiencing accidents (13 before to 0 after treatment) and near miss accidents (32 to 4) were reported. Although all but one patient used CPAP for the 2 year treatment period, such that patient compliance was reported as 97.8% (44 out of 45), the average nightly CPAP use and driving exposure (kilometres driven) before and after treatment were not reported.

There are some common limitations and potential confounders in epidemiological accident studies. One is that the majority of studies have relied on self-report questionnaires to collect information regarding accidents. Self-report is subject to recall bias and can therefore under- or over-estimate true accident rates. This has been demonstrated by Findley et al. (207) when evaluating accident rates in 50 moderate to severe OSA patients before and after 2 years of CPAP. Actual accident rates in this study were obtained from the Department of Motor Vehicles of the State of Colorado, which recorded any accident costing over $500 or resulting in personal injury for which the driver was convicted (207). Patient questionnaires

to assess driving exposure and accidents 2 years before and after diagnosis were also administered. OSA patients reported only one third of accidents that they were recorded to have been involved in, indicating that self-reported accident rates are highly unreliable. Under-reporting of accidents in patients diagnosed with and treated for OSA could be further confounded following diagnosis and treatment due to newly acquired knowledge that OSA is associated with increased accident risk and the expectation of improved driving following treatment. A second limitation of epidemiological studies, in common with driving simulator studies, is that most investigations have failed to include a healthy matched comparator group (206, 209, 210), or have used unmatched and inappropriate controls (207). This represents a significant limitation when trying to evaluate if CPAP reduces the accident rate of treated OSA patients to the level of a healthy population. Only two studies (205, 208) have included a matched control group and these reached different conclusions. George et al. (208) compared accident rates from a traffic record database in 210 severe OSA patients and 210 age, sex and licence type matched control subjects for the periods 3 years before and 3 years after CPAP treatment (mean use 5.9 ± 0.6 hours/night). This study showed that OSA patients had more MVAs/year/driver compared to controls, and that following CPAP treatment the number of MVAs/year/driver fell to the level of the control group. Barbe et al. (205) examined accident rates in 80 severe OSA patients and 80 age and sex matched healthy controls 2 years before and after CPAP treatment. In contrast to the results of George et al. these investigators found that accident rates decreased equally in control subjects and CPAP-treated patients (mean use 5.9 ± 0.3 hours/night) during the 2-year follow-up period. Strengths of this study included that patient and control groups were followed prospectively, information regarding

potential confounders such as caffeine, medication and alcohol use were also collected, and CPAP use was monitored objectively. When the authors controlled for BMI, alcohol intake and ESS (something not possible in the study by George et al.), the MVA rate was found to have reduced by approximately one half in both patients and controls. The authors concluded that although CPAP treatment was associated with a significant reduction in MVA rate, this could not be directly attributed to CPAP treatment *per se* since other factors such as changes in driving habits and behaviours due the patients' participation in a trial investigating accident risk may have also contributed.

In summary, OSA is a common sleep disorder associated with significant abnormalities in daytime functioning including poor driving performance and elevated MVA risk. CPAP treatment is the gold standard therapy for OSA with marked improvements expected in sleep quality, daytime function and quality of life. However, when compared to healthy non-apnoeic populations, residual abnormalities in daytime sleepiness, cognitive function and driving simulator performance may be evident in OSA patients following short and long term treatment. It remains unclear if MVA rates reduce to control levels in treated OSA patients, as existing evidence is conflicting. Further investigation is required.

Excessive daytime sleepiness and daytime abnormalities which characterise OSA are in some ways similar to the states produced in healthy subjects by common "lifestyle" factors such as sleep loss and alcohol. The impact of these central nervous system stressors have been extensively studied in healthy individuals, however their effects on people who are pathologically sleepy such as patients with

OSA are not clear. The following sections highlight the current state of knowledge and theories regarding the effects of sleep restriction, alcohol and their interaction on neurobehavioural function and driving performance in healthy subjects, with a particular focus on how these factors impact on vigilance and attention.

1.3 The effects of sleep restriction and alcohol on neurobehavioural performance, driving ability and motor vehicle accident risk

An inadequate amount or quality of sleep (chronically or acutely) and sedating substances such as alcohol can result in EDS and deficits in neurocognitive function, poor driving performance and higher MVA risk in healthy individuals. The effects of these central nervous system stressors have been shown to interact, possibly through common or additive brain circuitry effects. Neurobehavioural daytime abnormalities resulting from sleep loss and alcohol are not dissimilar to daytime deficits observed in OSA patients. As with OSA, deficits in vigilance and attention leading to behavioural attention lapses (microsleeps), an important contributor to the occurrence and risk of MVAs, are likely outcomes of sleep loss and alcohol.

1.3.1 Sleep deprivation and neurobehavioural performance

Sleep is essential for survival, and getting sufficient sleep is important for maintaining human well-being, health and safety. In the modern 24-hour society sleep restriction is a common phenomenon due to social and family commitments and demanding work schedules (55-59). Chronic sleep deprivation is prevalent in

modern society (56, 57, 60, 227) with often serious health, economic and safety consequences (58, 59, 81, 116, 119). Evidence suggests that sleep debt amongst male private and professional drivers correlates with accidents, and professional drivers appear to show greater sleep debt and more MVAs compared to private drivers (228). The human sleep wake cycle is under the control of circadian and homeostatic factors, and sleep pressure (the need for sleep) varies according to the time of day and the duration of prior wakefulness (229). Independent of the amount of prior sleep, there are two distinct peaks of heightened sleepiness, reduced performance and increased accident risk in the 24-hour day, with one in the early morning (1:00-6:00 am) and the other in the mid-afternoon (2:00-6:00 pm) (82-84, 230, 231). There are large between-individual differences in the susceptibility to sleep deprivation effects, although within-subject responses are highly consistent and appear to be trait-like (232-236).

Numerous laboratory investigations have demonstrated that both acute and chronic sleep deprivation negatively impact brain function and neurobehavioural performance, including vigilance/attention, working memory, long term memory, visual-motor performance, decision making, verbal function, and response inhibition (60, 70, 237, 238). The most important cognitive domains for everyday monotonous tasks such as long distance driving are vigilance and attention. These are grossly impaired due to an increase in attention lapses following sleep loss (68, 70, 71, 239-241).

1.3.1.1 Chronic partial sleep restriction

Laboratory studies have revealed cumulative effects of chronic partial sleep restriction (which is the more commonly occurring type of sleep loss) (60, 238, 242-244). In the early 1980s, Carskadon and Dement (242) evaluated changes in daytime sleepiness over a 12 day protocol during which healthy subjects slept for 10 hours for the first three nights, followed by 7 nights of sleep restricted to 5 hours and two final nights of recovery. Using two subjective sleepiness scales (Stanford sleepiness scale and an analog sleepiness rating scale) and the objective MSLT the authors demonstrated that subjective sleepiness increased after 1 to 2 days of sleep restriction reaching a plateau after day 4, while objective sleep latency decreased significantly after the second day and progressively worsened until the 7th day. Following one night of recovery sleep all measures returned to baseline levels. Dinges et al. (243) extended this work using a similar protocol but, in addition to sleepiness, measured mood, performance (including the psychomotor vigilance test, PVT), memory and responses to a serial addition test. Performance on these tests declined throughout the sleep restriction protocol, with worst performance observed during the first two and last two days, and requiring two full recovery days to return to baseline levels.

More recently, two landmark studies have used more refined chronic sleep restriction protocols to evaluate dose-response effects of different levels of sleep ranging from 0 to 10 hours, on various subjective and objective measures of sleepiness and performance (238, 244). These studies provide further support for the notion that sleep is a basic "need", with accumulated reduced sleep resulting in

cumulative deterioration in neurobehavioural function. For example, Belenky and colleagues (244) kept 66 truck drivers in the laboratory under controlled experimental conditions for 14 days. Participants were randomly allocated to seven nights of 3, 5, 7, or 9 hours in bed. Subjects in the 3 and 5 hour sleep conditions showed a progressive decline in PVT reaction speeds and increasing lapses (reaction times >500 msec), while those in the 7 hour condition declined only in reaction speed. The 9 hour condition resulted in no deficits throughout the 7 day protocol. Another study randomised healthy young subjects into 4, 6 or 8 hours in bed for 14 consecutive nights and found that PVT and working memory performance declined cumulatively in the 4 and 6 hour conditions but not in the 8 hour condition (238). This study also included a 3 day total sleep deprivation condition thus allowing comparisons of neurobehavioural deficits with partial sleep restriction to total sleep deprivation. This revealed that both the 4 and 6 hour partial sleep restriction conditions produced behavioural alertness deficits comparable to 1, 2 and even 3 days of total sleep loss (238). What is clear from these studies is that performance and alertness decline cumulatively when nocturnal sleep is consecutively reduced below 7 hours (244), or when wakefulness is extended beyond 15.8 hours (238). It has been proposed that declining neurobehavioural performance resulting from consecutive nights of sleep loss is governed by an intrinsic neurobiological modulator (244). Some evidence suggests that the cumulative nature of neurobehavioural decline may involve the extra-cellular build-up of the neuromodulator adenosine, a by-product of metabolism, in the basal forebrain (245-248).

1.3.1.2   Acute sleep deprivation evokes a compensatory cortical response

Studies of the effects of total sleep deprivation, ranging from 24-88 hours, on brain function and neurobehavioural performance have provided invaluable insights into the workings of the human brain and its susceptibility to sleep loss (61, 62, 233, 237, 249-253).

In studies focusing solely on cognitive performance, acute sleep deprivation for one night is generally found to have a negative effect on working memory (254, 255), attention and vigilance components of cognition (256-258), while minimal impairments are observed in reading, writing, arithmetic, and general intellectual functions (237). Some studies have collected functional brain imaging and/or EEG data during task performance, thus providing the opportunity to correlate cognitive performance with regional brain function. Functional magnetic resonance imaging (fMRI) techniques have been used extensively to measure cortical function during neurobehavioural task performance in healthy subjects following normal sleep and various levels of total sleep deprivation (68, 251, 254, 256, 259-264). From a series of experiments by Drummond et al. (256, 259-264) and others (258, 265), it appears that the brain adapts to the stress of total sleep deprivation by altering, modulating and recruiting additional brain regions (compensatory recruitment), apparently in an attempt to compensate for the stress of sleep loss and maintain performance (259, 260). Evidence suggests that these cortical responses are not uniform for all cognitive domains but depend on the type and difficulty of the task (261). Briefly, in healthy subjects, it appears that performance on memory and

verbal learning tasks following total sleep deprivation evokes a greater cortical activation response than in a non sleep deprived state. Furthermore, the degree of increased activation correlates with the level of impairment and may be sufficient to achieve intact performance, suggesting that increased activation is protective against uncompensated neurocognitive deficits (259, 260). Similarly, intellectual functioning during a logical reasoning task was found to be unaffected by 35 hours of total sleep deprivation, with a progressive linear increase in cortical activation with increasing task difficulty (261). A verbal learning task evoked an increase in cortical activation following 36 hours of sleep loss, however, this only occurred with a difficult task, with no effect of sleep loss on cortical activation observed with an easy task (263). During an arithmetic task of serial subtraction, a decrease in cortical activation was noted following one night of sleep loss and was associated with decreased performance (256). Performance during a divided attention task combining both components of verbal learning and arithmetic proficiency was mildly impaired following sleep loss and was associated with increased activation in brain regions thought to be responsible for maintaining attention (262). Divided attention between tasks makes individual tasks more difficult but less monotonous. Consequently, recruitment of additional attentional resources in divided attention tasks may evoke a more effective compensatory response leading to better performance than more monotonous individual tasks, perhaps explaining relatively small impairments under conditions of divided attention. Attention and response inhibition during a go no-go task was significantly impaired following 48 hours of sleep loss with significantly more false positive responses and errors of omission (missing 'go' targets) observed (264). However, no imaging data were collected

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during the go no-go task, such that compensatory brain activity responses could not be evaluated.

In addition to brain imaging, cortical ERPs have been utilised to evaluate general cognitive information processing in healthy subjects exposed to sleep deprivation (152, 153, 266-268). From these investigations it is evident that later ERP components (reflecting the efficiency of cognitive processing) are impaired during task performance, with a reduction in P3 amplitude and increased latency. Although these studies provide further evidence for a general affect of sleep loss on brain function, with an overall slowing of cortical information processing, unlike imaging studies, ERPs are unable to provide more specific information regarding activation in particular brain regions that may govern specific cognitive domains.

Brain imaging and ERP experiments highlight the dynamic and plastic nature of the brain and its ability to adapt to stresses such as sleep deprivation. It is clear, however, that only a certain amount of stress can be compensated, and sleep pressure as a result of sleep loss eventually saturates the brain's ability to maintain cognitive performance without deficit. Therefore, in individuals exhibiting excessive sleepiness, such as in patients with OSA, maintaining cognitive performance may be compromised due to more limited compensatory "reserve". Consequently, it is possible that OSA patients are more vulnerable to deficits from any additional stress (such as further sleep loss), as a lower cortical "threshold" may result in greater performance impairment compared to healthy individuals for any given level of additional stress.

1.3.1.3 The importance of task duration

Cognitive tasks assessing vigilance and attention are consistently found to be impaired by sleep loss (60, 237). Continuous maintenance of vigilance and attention are crucial to maintain performance over long time periods in real life, and may be safety critical in tasks such as long distance driving. Thus, time on task is an important consideration when evaluating an individual's ability to maintain vigilance. In an early experiment, Glenville et al. (269) demonstrated that short duration (10 minute) reaction time tests were significantly but only mildly affected by one night of sleep loss, while a one hour long Wilkinson vigilance task appeared to show greater performance decrements. Sagaspe et al. (270) found that a short (2 minute) response inhibition task (assessing working memory and requiring subjects to ignore non-relevant information) was unaffected by 36 hours of wakefulness, whereas a 10 minute reaction time test (attention/vigilance) showed deterioration in reaction speeds after the first 2 minutes. PVT used in chronic and acute sleep deprivation experiments is the most common and sensitive test used to assess vigilance and attention. The PVT test lasts 10 minutes and allows the assessment of reaction speed and attention lapses (reaction time > 500 msec) (271, 272). Behavioural lapses in attention likely reflect predominantly microsleeps, and typically range from 0.5 seconds to 10 seconds but can include complete fall-asleep episodes (60). Chronic sleep restriction studies demonstrate cumulative deterioration in PVT lapses and reaction speed. However, when the effects after the first night of a chronic sleep loss protocol were compared to baseline, Belenky et al. (244) found that a single night of 5 hours sleep did not result in significantly more lapses or slower responses. Increased lapses and slower responses were

only observed after 6 and 3 days of consecutive sleep loss, respectively. Even sleep restriction to 3 hours in bed did not cause significant PVT impairment until at least the second day of sleep restriction. However, in a study using the PVT for 30 minutes instead of 10 minutes, significant increases in lapses and reduced response speed were found after sleep was reduced to 5 hours for a single night (273). Therefore, while a 10 minute PVT appears to be sensitive to chronic and acute total sleep loss, longer tests appear to be needed to detect impairments after more moderate sleep restriction (e.g. a single night of sleep restricted to 4-6 hours). Previous studies examining the effects of sleep restriction on driving simulator performance have often used very modest levels of sleep restriction (1 night of 3-5 hours of sleep) yet have still shown significant driving impairments (55, 78, 79, 274-280). Consequently, driving simulator performance measures appear to be particularly sensitive to sleep restriction effects. Driving simulator studies are also more relevant to real word task performance (i.e. driving) as they engage cognitive domains most pertinent to real on-road driving, and task duration has more ecologically meaningful implications.

1.3.1.4   Individual variability in performance and susceptibility to sleep loss

A common observation arising from sleep deprivation studies is that there are remarkable individual differences in susceptibility to deficits following sleep loss, both in terms of daytime sleepiness and performance (232-234, 236). Although cognitive performance may be similar in well rested subjects, sleep loss increases variability in cognitive performance within-subjects, thereby exposing cognitive

performance differences between subjects who are either vulnerable or resistant to sleep loss (232-234, 236). In addition, inter-individual differences following sleep loss appear to be dependent on the type of task (232). Van Dongen et al. (236) found that although neurobehavioural performance varied substantially between sleep deprived individuals (wakefulness sustained for 36 hours) performance scores were highly stable within subjects and were not related to prior sleep opportunity (a week of 6 hours sleep/night or 12 hours sleep/night). This strongly suggests that individual differences in vulnerability to the effect of sleep loss are systemic and trait-like. The neural basis for this variation in vulnerability is not well understood and is attracting considerable research attention. Some evidence suggests that individuals who are more or less vulnerable or resistant to sleep loss can be identified by the pattern of their brain activation during task performance. For example, Chuah et al. (234) demonstrated that compared to subjects with poor performance after 24 hour sleep loss, individuals who maintained better performance on a go no-go inhibition/attention task showed lower phasic cortical activation under rested conditions and displayed greater cortical activation following sleep deprivation. In a more recent investigation, military cadets performed a simple visual-motor task following 24 hour sleep deprivation and were separated based on their performance into two groups, one vulnerable and the other resistant to sleep loss effects (235). Fractional anisotropy (FA - a measure of the number of fibres, myelination and compactness of white matter tracts) was calculated from diffusion tensor magnetic resonance imaging scans before and after sleep loss. This revealed that individuals susceptible to sleep loss had lower FA measures in multiple white matter regions, while those resistant to sleep loss had higher FA

values. This suggests that increased neural connectivity and white matter organisation may be a key moderator of cognitive deficits following sleep loss.

1.3.2 The effects of alcohol on neurocognitive function and its interaction with sleepiness

Alcohol is a socially accepted and commonly consumed substance with both sedating and alerting properties depending on alcohol dose and the time elapsed after consumption (66, 94, 281-284). It is widely accepted that alcohol results in significant dose-dependent cognitive impairments, poor driving performance and increased MVA risk (55, 74, 83, 86-94, 274, 275, 285-288). Similar to the effects of sleep loss, impairments in driving performance due to alcohol are likely to be related, at least in part, to decreased attention and vigilance (289-296). Furthermore, recent evidence suggests that alcohol interacts with sleepiness to produce greater decrements in performance, for example when alcohol is given to subjects when they are sleep deprived or performing during circadian nadirs in alertness (280, 287, 297-301). These data are concerning from a community safety perspective given that the consumption of alcohol occurs predominantly at night when homeostatic and circadian sleep pressures are increased. Consistent with these concerns are data showing the incidence of fatal and non-fatal alcohol-related MVAs is highest in the early morning when sleep pressure is also at its highest (83, 84, 302).

1.3.2.1   Alcohol and neurocognitive function

The effects of alcohol may vary according to whether the concentration of alcohol in the blood is rising or falling. Schweiser et al. (283, 303, 304) consistently observed that acute low dose alcohol resulted in slower performance speed during the rising blood alcohol concentration (BAC) curve, but not during the fall in BAC (acute tolerance). Errors in performance (mistakes, lapses, inappropriate responses etc), however, were impaired regardless of whether BAC was rising or falling (304). The implications of these findings for driving, for example, might be that planning and prompt execution of a particular skill (e.g. braking, steering and direction change in response to a sudden obstacle) returns to normal during the descending BAC curve, but that the performance of the task remains impaired (e.g. braking too hard/soft, over steering/under steering in response to the stimulus). Generally, alcohol has been shown to cause an overall slowing of cortical information processing resulting in impaired working memory, visual-motor functions, coordination, and importantly impaired sustained/divided attention and vigilance (76, 283, 285, 289, 292, 293, 295, 296, 303-309). For example, Gengo et al. (285) found in 20 healthy young men that alcohol at four different BAC levels (0-placebo, 0.07, 0.1 and 0.14 g/dL) showed a negative dose-dependent effect on cognitive tasks of working memory and divided attention (digit symbol substitution task), and simulated driving reaction and choice reaction test performance, which were all assessed 1, 2, 3.5 and 4.5 hours post alcohol ingestion. In contrast to other studies (283, 303, 304), the authors did not observe acute tolerance effects with alcohol, since impairments were equivalent for the same BACs during both the rising and falling phases of the BAC curve, and the greatest impairments were observed at

peak BACs (285). The threshold BAC for detecting significant performance impairment compared to placebo was 0.06 g/dL for the working memory task, whereas driving and choice reaction time impairments were observed at BACs as low as 0.04 g/dL. In addition to performance, the authors found that subjective feelings of intoxication did not match performance impairments during the fall in BAC, an affect that has been observed by others (78, 310) and one that may partly explain why individuals inappropriately choose to drive while still intoxicated and likely impaired.

Functional MRI studies following alcohol show abnormalities in brain function according to the task performed (311, 312). Van horn et al. (312) found that alcohol suppressed blood oxygen level activity in the cerebellum and fronto-parietal cortical networks during a goal directed visual-motor task. In another study, episodic memory (long term memory) for object and face pairs was found to be impaired with alcohol, and this impairment was associated with decreased bilateral prefrontal cortical activation (311). Some investigators have measured brain function via fMRI while subjects performed a driving simulation task (313-316), providing valuable insights into the neural correlates of this complex human behaviour. For example alcohol has been found to impair frontal-basal-temporal brain circuitry governing driving related performance, such as planning and control of goal directed function, visual-motor coordination, error monitoring and memory in a dose-dependant manner (315). In contrast, another recent study (309) found that although driving performance declined following alcohol, no significant brain activity changes were observed. Further systematic imaging studies are needed to properly elucidate the neural correlates of behavioural impairments induced by acute alcohol ingestion.

Similar to the effects of prior sleep deprivation, alcohol, even at low and legal doses, can impair an individual's ability to maintain vigilance and attention, particularly during long monotonous tasks. The effects of low dose alcohol on vigilance and attention have been extensively studied (289-296, 317) and shown to cause deterioration in vigilance with increasing dose and task duration. In an early study, Erwin et al. (289) tested vigilance during a 30 minute stimulus-response task in 15 young subjects following four doses of alcohol (BACs: 0.0-placebo 0.05, 0.08 and 0.12 g/dL) and observed a dose and time dependent decline in correct stimulus detection and prolonged response times compared with placebo. In addition, the authors found that the frequency of prolonged eye closures (indicating drowsiness) increased with alcohol and were associated with around 26% of all response misses. A number of studies have found that alcohol slowed psychomotor reaction times to auditory and visual stimuli, with faster deterioration (prolongation) in reaction throughout the task compared to no alcohol conditions (290-292). An interesting observation in these experiments was that throughout the 30 minute vigilance task, alcohol caused a progressive increase in the frequency of very slow reaction times (behavioural lapses) referred to by the authors as "blockings" (290-292) which appear to parallel the effects on vigilance observed following sleep loss (68, 70, 71, 239-241). Another investigation (296) tested 12 subjects on a short 5-10 minute vigilance task at different BACs ranging from 0.0-0.1 g/dL and similarly found that alcohol impaired overall performance in a dose-dependent manner with increasing BAC associated with greater deterioration in performance over time. The authors suggested that alcohol has an overall deleterious effect on central processing capacity, which progressively diminishes throughout the task. These

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observations have implications for real-life continuous task performance (such as driving) and may help to explain why some accidents occur in situations where the demand for continuous attention and vigilance is high.

Another relevant observation in an early uncontrolled study (318) was that for a given alcohol dose, performance impairment differed according to the time of day. Other investigators have also found that the effect of alcohol varied with circadian changes in alertness (293), suggesting the existence of an interactive effect of alcohol and sleepiness on brain function.

1.3.2.2 The interactive effects of alcohol and prior sleep opportunity on objective levels of sleepiness and cognitive performance

1.3.2.2.1 The interactive effects of alcohol and sleep restriction

Almost 30 years ago, investigators observed that the combination of sleep loss and alcohol resulted in greater decrements in cognitive performance than occurred with either factor alone (319). Another early investigation by Zwyghuizen-Doorenbos et al. (299) provided more compelling evidence for an interactive effect of sleep restriction and alcohol. These investigators measured the effect of alcohol on sleepiness using the MSLT in thirty healthy men who received either 0.04, 0.06, or 0.08% alcohol following one normal night sleep (8 hours in bed), following one night of reduced sleep (5 hours in bed) and after four consecutive nights of reduced sleep (5 hours per night in bed). On day one (normal sleep), sleep latency was

shortest for the highest BAC of 0.08%, longest for lowest BAC of 0.04% and intermediate for BAC of 0.06%. Following sleep restriction, a BAC of 0.04% resulted in similar sleep latencies on day five as were observed with a BAC of 0.06% on day two, and were similar to BAC 0.08% on day one (normal sleep) (299). That is, following sleep restriction, particularly cumulative sleep restriction, small amounts of alcohol caused levels of sedation that were equivalent to those observed with higher alcohol doses following normal sleep.

1.3.2.2.2   The interactive effects of alcohol and sleep extension

In a follow-up experiment by the same group, Roehrs et al. (298) assessed the effect of alcohol on sleepiness and performance during a divided attention task under conditions of reduced sleepiness achieved by extending sleep time. Healthy young men had a time in bed opportunity of 8 hours on the first night and 10 hours for the 7 following nights with 0.06% alcohol or placebo administered between 0900-0930 hours. MSLT was performed at 1000, 1200, 1400 and 1600 hours, and divided attention measured at 1100 hours on days 1 and 8. Following 8 hours of sleep, alcohol reduced sleep latencies and impaired performance. After 7 days of sleep extension the effect of alcohol was attenuated, with sleep latencies and divided attention performance comparable to the 8 hour sleep-placebo condition (298). Thus, in contrast to sleep restriction where the sedating effect of alcohol was increased, sleep extension for one week appeared to attenuate alcohol's sedating effects.

1.3.2.2.3   The interactive effects of alcohol and inter-individual differences in
basal levels of sleepiness

Separate from any effects of experimental or environmental sleep restriction or extension, healthy individuals naturally vary with respect to their basal levels of sleepiness under normal sleep conditions (300). It is possible that the effects of alcohol may therefore also differ between subjects depending on intrinsic levels of sleepiness. This question was addressed by Zwyghuizen-Doorenbos et al. (300) who compared the effects of alcohol on sleepiness and performance during a divided attention task in groups of naturally sleepy (sleep latency ≤6 min) versus alert (sleep latency ≥16 min) subjects, using the same protocol as in their previous study (298). Either alcohol (to achieve a BAC of 0.075%) or a placebo drink was consumed between 0900 and 0930. Alert subjects, although affected by alcohol, had longer sleep latencies and better performance following alcohol compared to sleepy subjects after placebo.

1.3.2.3   Residual effects of alcohol

In several experiments described above (298-300), the authors noted that soon after alcohol was administered between 0900-0930 BACs peaked, then gradually declined during the remainder of the day. Despite at or near zero BAC levels during the last MSLT test at 1600 hours, both objective sleepiness and performance on the divided attention task remained significantly impaired compared to placebo. This residual effect of alcohol was also observed in the mid-1980s by Yesavage et al. (320) while investigating the hangover effects of alcohol in aircraft pilots. These

authors found that some simulated flying performance parameters remained impaired 14 hours after alcohol ingestion to achieve a peak BAC of 0.1%. A more recent driving simulator study (287) demonstrated that when alcohol was consumed 90 minutes prior to starting the test, driving performance was still impaired in comparison to a no prior alcohol condition, despite the BAC having returned to almost zero levels.

Taken together, these early experiments provide important insights into how increased baseline levels of sleepiness may exaggerate the sedating and performance-inhibiting effects of alcohol. The results show, amongst other things, that alcohol consumed at times of the day when sleepiness levels are naturally higher (i.e. early morning and mid-afternoon) has a much greater negative impact on sustained vigilance and attention (both critically important for driving), than at other times of the day. Similarly, sleep deprived subjects display greater vulnerability to performance deficits following alcohol compared with well rested subjects. The implication of these observations to safety during driving and the risk of MVAs are significant, given that alcohol is often consumed by already sleepy individuals. In addition, these observations may have important implications for individuals, such as those with OSA, who experience pathological sleepiness due to a sleep disorder, and suggest that such patients could be more impaired by alcohol than healthy individuals.

1.3.3 The impact of alcohol and sleepiness on motor vehicle accidents and driving simulator performance

1.3.3.1 Alcohol, sleepiness and MVAs

The results of epidemiological studies, supported by driving simulator experiments, have unequivocally established a causal link between alcohol consumption and MVAs (302). In the year 2000, alcohol was associated with approximately 17,000 fatal crashes and 258,000 MVA related injuries in the US alone, with an estimated cost of $51 billion (94). Some important driving performance measures are impaired at blood alcohol concentration (BAC) levels as low as 0.02% (321). Based on driver fatalities in single vehicle crashes it is estimated that for each 0.02% increase in BAC, the risk of fatal crashes doubles for all age groups and both sexes (92). When BAC reaches between 0.05% and 0.09% the relative risk of a crash is nine times higher than at a BAC of 0.00% and this risk is higher in males compared to females (92). Crash risk increases exponentially to between 300-600 times with even higher BAC >0.15% (92).

Although alcohol consumption patterns differ between countries, generally alcohol is mostly consumed during the evening and early morning hours (322). Given what is known about the interaction between sleepiness and alcohol it is not surprising that most alcohol-related MVAs occur in the early morning between 2400 and 0600 hours (322). The incidence of alcohol related MVAs is further increased during the weekend nights (i.e. Friday and Saturday nights) (322) when more alcohol is typically consumed (323). Reynaud et al. (323) determined that alcohol was involved in around 10% of all types of MVAs and 32% of fatal MVAs, with the latter

varying depending on the time of day/week and type of accident, reaching 71% in single vehicle accidents (loss of control) occurring at night on the weekend. The mid afternoon is another period of naturally increased sleepiness (229) and alcohol has been shown to have a greater detrimental effect on driving performance and vigilance when consumed in the afternoon (during circadian nadirs in alertness) compared to early evening (74-76).

While more difficult to measure, there is now very strong epidemiological and experimental evidence that excessive sleepiness is also a leading cause of MVAs (83, 85, 119, 230, 231, 324-328). The prevalence of sleepiness-related MVAs is reported in various countries to range from 1% to 30% (83, 85, 119, 230, 231, 324-328), with annual cost estimates varying between $1.75-56 billion (118, 329). Low-dose alcohol consumption and increased sleepiness due to moderate sleep restriction or sleep disorders such as OSA are remarkably common in Western societies (1, 3, 40, 56, 57, 60, 227, 330-332) and may often co-occur in the same individual.

Circadian and sleep homeostatic influences combine to produce two distinct periods of heightened sleepiness in the 24-hour day: the early morning (0100-0600 hours) when sleep propensity is greatest and the mid-afternoon (1400-1800 hours) (229). During these times there are peaks in the frequency of sleepiness-related MVAs and driving performance is most affected by sleepiness (82-85). As a way of highlighting the potential risks of excessive sleepiness for driving, a number of investigators have compared effects of sleep deprivation versus acute alcohol ingestion on vigilance, sleep latency, divided attention and driving simulator

performance in the same individuals (91, 275, 333-335). An early landmark study in this area demonstrated that sleepiness caused by 17 and 24 hours of prior wakefulness produced impairments in psychomotor performance (hand-eye coordination) that were equivalent to those observed following BAC of 0.05% and 0.1% respectively (333).

The relative proportion of MVAs attributed to sleepiness differs widely between studies and countries, but this may be due more to different interpretations and definitions of sleepiness and differences in accident reporting than real differences in the prevalence of sleepiness-related accidents (85). It is generally agreed that sleepiness can be attributed as the primary cause of a MVA if it involves a single vehicle running off the road in good weather, with no evidence of mechanical failure, alcohol, speeding or avoidance manoeuvres (231). However, unlike alcohol-related MVAs, the true prevalence of sleepiness-related MVAs is very difficult to ascertain because it is impossible at present to reliably quantify sleepiness or sleep history at the roadside, and because there is no agreement about the level of sleep deprivation or duration of wakefulness at which accident risk becomes significant (85).

1.3.3.2   Alcohol, sleepiness and driving simulator performance

Driving simulators provide an important and relatively new opportunity for investigating the effects alcohol, sleepiness and their interactions, providing the means to evaluate the behavioural correlates of these "life style" factors that lead to

real MVAs. Various experimental manipulations and combinations of alcohol and sleep restriction can be studied in a controlled and safe environment. Driving simulators test many of the key neurocognitive functions required for driving (e.g. vigilance, divided attention, concentration) and measure some of the relevant motor skills and reactions (e.g. steering deviation, speed control and braking reaction time) (336). A major question, however, is to what extent the findings from driving simulator studies can be used to infer likely on-road driving performance and safety. Several studies which have compared simulated driving to on-road driving (337-340) conclude that although simulated driving tends to overestimate the on-road performance decrements caused by various interventions, they nevertheless remain useful tools for assessing important aspects of driving and do correlate with on-road performance.

Driving simulator performance (in the absence of any interventions) has been shown to vary according to the time of day, with greatest performance decrements observed in the early morning and the mid-afternoon, in keeping with the known higher sleepiness-related MVA rates at these times (82-84). Prior acute sleep restriction has been shown to negatively impact driving simulator performance throughout the day, also with greater performance decrements in the early morning and mid-afternoon compared to normal sleep conditions (73, 82). Further data suggest that alcohol's sedating and performance impairing effects also vary across the 24-hour period with the same alcohol dose resulting in worse driving simulator performance during the mid-afternoon (Figure 1.2A) and early morning (Figure 1.2B) compared to the evening (2000-2200 hours) (74-77).

Figure 1.2 Time of day influence on the deleterious effect of sleepiness, alcohol and their combination

A

B

NOTE:
This figure is included on page 53
of the print copy of the thesis held in
the University of Adelaide Library.
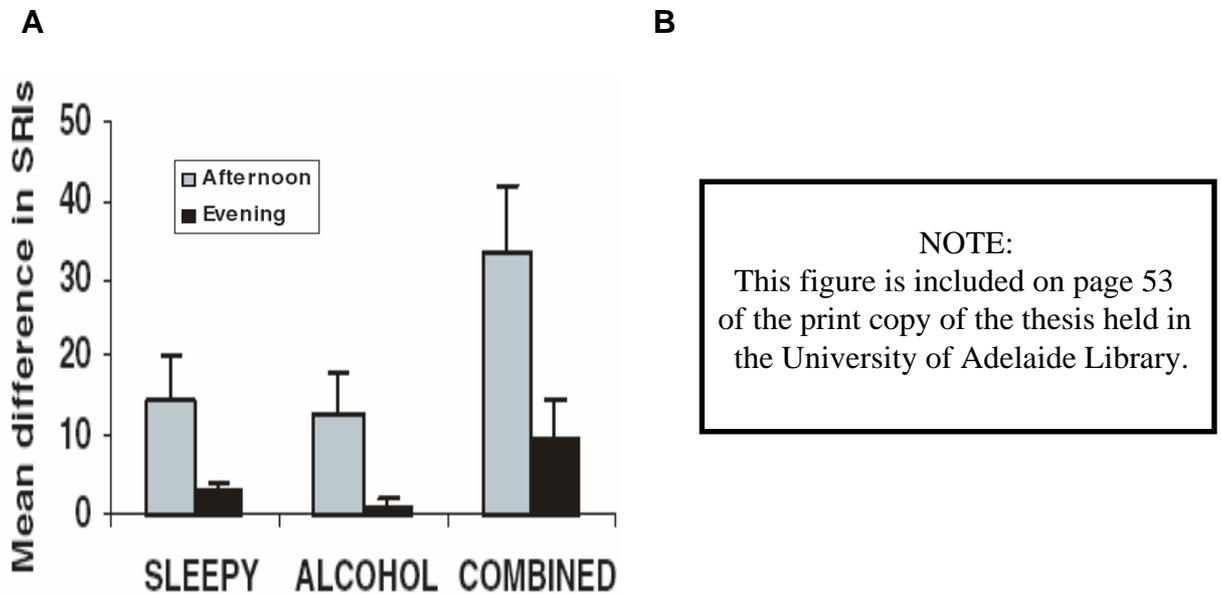
(A) Reproduced with permission from Reproduced with permission of John Wiley & Sons Ltd from Barrett et al, Human Psychopharmacol Clin Exp 2005; 20:287-290 (74). Changes from respective baseline condition for sleep related incidents (SRIs), for an evening study compared with a previous study of an afternoon drive under identical protocols. Mean and SEM SRIs are shown for each of the three treatment conditions. Both time of day and treatment condition effects were statistically significant. (B) *Reproduced with permission from Howard et al. 2007 (77).* Mean and SEM of variation in lane position at BAC of 0.0 and 0.03% in a non-sleep deprived state (2200 hours) and following extended wakefulness (0100 hours).

The combination of prior sleep deprivation and alcohol has been shown repeatedly to have at least an additive effect on driving simulator performance, with greater performance decrements compared to sleepiness or alcohol alone (Fig 1.2A and Fig 1.2B) (55, 77-79). Horne and colleagues (78) found that in healthy young men, driving performance and objective EEG sleepiness during a 2-hour mid-afternoon driving simulator test were significantly impaired following sleep restriction and following alcohol, but that impairments were greater when sleep restriction and alcohol were combined (Figure 1.3). Banks et al. (55) and Vakulin et al. (79) also demonstrated that relatively small doses of alcohol exaggerated the effects of prior sleep restriction on early morning and mid-afternoon driving simulator performance.

Figure 1.3 The effects of sleep loss, alcohol and their combination on the occurrence of driving incidents
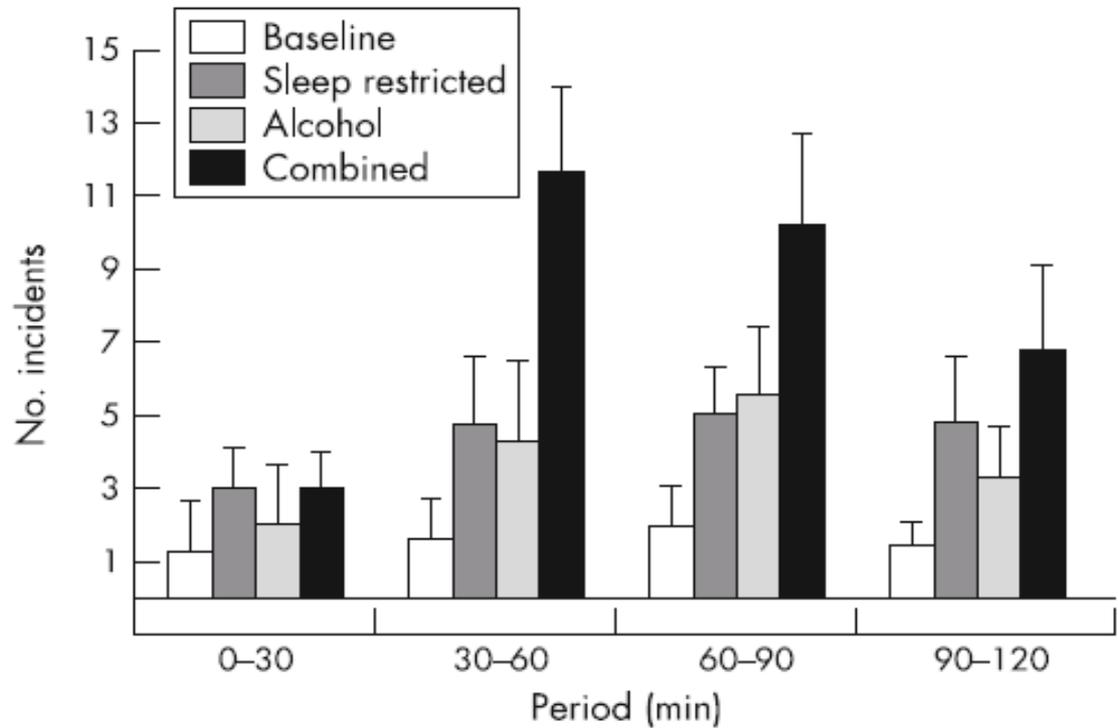
Reproduced with permission of BMJ Publishing Group Ltd, from Horne et al, Occup Environ Med, 2003, 30;10: 1334-40 (78). Mean (SEM) of sleep related driving incidents (lane drifting) over four consecutive 30 minute periods of simulated driving under baseline, sleep restriction (5 hours time in bed), alcohol (0.038 ± 0.004 g/dL) and combined sleep restriction and alcohol (0.032 ± 0.004 g/dL) conditions.

The majority of driving simulator research has focused on young subjects, presumably due to the known higher incidence of sleep and alcohol related MVAs in this age group (341-345). Greater tolerance to sleep restriction and better hazard perception following alcohol in older compared to younger drivers may further explain this over representation (233, 346-348). More laboratory-based research is needed to elucidate the separate and combined effects of alcohol and sleepiness on driving performance, perception of sleepiness hazard and the risk of MVAs in younger versus older subjects. It is also important to investigate the impact of sleep deprivation and alcohol alone and in combination on driving performance in individuals with intrinsically higher levels of sleepiness as a result of a sleep disorders such as OSA, as the effect of these additional stressors may be more detrimental to driving performance in these patients compared to healthy individuals.

In summary, sleepiness and alcohol are important contributing factors to MVAs worldwide. It is apparent from both epidemiological and experimental studies that the basal level of sleepiness/alertness (which is subject to circadian/homeostatic variation) is a critical determinant of what further sleepiness and performance impairment may result from alcohol. The neural correlates of the interactive relationship between sleepiness and alcohol are unclear but it appears that sleepiness and alcohol impact upon common neural circuits and brain regions.

1.3.3.3   Actions of alcohol on sleep/wake neural pathways and neurotransmitter systems

It is apparent that sleepiness and alcohol interact to produce qualitatively similar yet greater decrements in cognitive and driving performance than is observed for sleepiness or alcohol alone. A possible explanation for this interactive effect may be that alcohol and sleep restriction operate through common, or similar neural pathways and neurotransmitter systems involved in the regulation of sleep and wakefulness.

The basal forebrain is thought to be an important brain region governing sleep and wakefulness, through its widely projecting cholinergic, glutamatergic and GABAergic neuronal systems (63, 64, 67). Other brain regions involved in the maintenance of wakefulness and induction of sleep include the posterior and lateral hypothalamus, tegmentum and pons nuclei and preoptic/anterior hypothalamic areas (64). Factors known to have the greatest impact on neuronal activity in sleep/wake promoting brain regions are the glutamate neuroreceptor NMDA (N-methyl D-aspartate), neurotransmitter GABA (γ-Aminobutyric acid) and the homeostatic neuromodulator adenosine (63, 64, 67).

Glutamate is the most abundant excitatory neurotransmitter in the brain, with many glutamate-releasing neurons projecting to the cerebral cortex, basal forebrain and the brainstem. Glutamate-containing neurons make up a large part of the ascending reticular activating system and release most glutamate during wakefulness (63, 64, 67). GABA is the main inhibitory neurotransmitter in the brain

and most GABA is released during NREM sleep (63, 64, 67). Adenosine is both a neuromodulator and a key by-product of energy metabolism resulting from the breakdown of adenosine triphosphate. Adenosine accumulation is indicative of energy depletion and may act as an important sleep "homeostat" within the central nervous system since adenosine increases in the basal forebrain and the cortex during wakefulness and sleep deprivation, and decreases during subsequent recovery sleep (63, 64, 67).

The interaction of alcohol with these main sleep/wake promoting neurotransmitters, receptors and neuromodulators may be responsible for greater sedation and poorer driving performance observed when alcohol and sleepiness are combined. The inhibitory action of GABA (which promotes sleep) is enhanced by low doses of alcohol in a similar way to hypnotic drugs (e.g. barbiturates and benzodiazepines) (64, 66, 67). The excitatory action of glutamate is dampened by low doses of alcohol through its inhibition of the glutamate receptor NMDA, thus effectively promoting sleep (66). The sleepiness associated with prolonged wakefulness and sleep deprivation is thought to be due to rising adenosine levels in sleep promoting regions of the basal forebrain (64, 65). Alcohol may promote adenosine's sleep-inducing properties in three ways; 1) by enhancing adenosine synthesis, 2) by increasing adenosine receptor function and 3) by inhibiting adenosine re-uptake into cortical and basal forebrain neurons (66, 67).

To sum up, there is a large body of evidence demonstrating that alcohol and sleepiness have negative and interrelated impacts on driving performance, increasing the risk of MVAs in healthy subjects. Alcohol should not be evaluated

without due consideration to the time of day, since there are important circadian and homeostatic influences that cause levels of sleepiness to vary throughout the day. Although drinking small quantities of alcohol prior to driving is legal (e.g. up to a BAC 0.05 g/dL in Australia) the variable effect of alcohol at different times of day or following sleep loss may lead to a greater MVA risk even if the BAC is within legal limits. Indeed it has been shown that alcohol-related accident rates are highest and driving simulator performance is at its worst at times of peak sleep pressure.

Driving is a complex task critically dependent on a number of different components of neurocognition including vigilance, attention, visual-spatial coordination, tracking and selective inhibition. The evidence summarised above suggests that sleep restriction and alcohol (or their combination) have the potential to negatively impact the function of brain regions and neurotransmitter systems important for sleep/wake regulation.

1.3.3.4 Comparison of behavioural impairments due to sleep loss, alcohol and OSA

After the work by Dawson and Reid (333), which showed equivalent decrements in psychomotor performance after 17 hours of wakefulness and 0.05 g/dL alcohol, several investigators compared the performance impairing effects of sleep loss and alcohol (274, 275, 349-351) and OSA (167, 352). Comparing the performance decrements due to sleep disturbance and alcohol is a useful way to highlight the magnitude and importance of such impairments, as alcohol levels can be easily

measured and have recognised legal thresholds. In contrast to Dawson and Reid, who demonstrated equivalent impairments in psychomotor function following 24 hours of wakefulness and 0.1% BAC, Falleti et al. (349) found that 24 hours of wakefulness impaired cognitive performance (speed of continuous attention and memory and learning, and complex matching accuracy) more than that produced by a BAC of 0.05 g/dL. Maruff et al. (350) demonstrated similar findings using a more rigorous statistical approach to account for intra-individual and within-group variability not accounted for in previous similar studies. Using a driving simulator to compare the effects of sleep loss (acute total sleep deprivation or chronic 2 hour reduction in sleep over 7 days) and alcohol, Powell et al. (351) found equivalent driving performance decrements with sleep loss compared to alcohol (BAC of 0.089%).

In addition to comparing the effects of sleep loss/wakefulness and alcohol, some authors have also compared performance impairments observed in patients with OSA with performance at various BACs (167, 352). Powell et al. (352) demonstrated that in middle-aged patients with mild to moderate OSA, performance on a reaction time task was worse than in healthy subjects who had BAC levels that were above the legal limit of 0.08%. More recently, Hack and co-workers (167) also compared driving performance impairments as a result of 24 hours of sleep deprivation, 0.071 g/dL of alcohol ingestion and impairments associated with OSA. The authors found that driving simulator performance impairments in OSA patients were between those seen with one night of sleep loss and those seen with alcohol in a healthy control group, but resembled more the

effect of sleep loss since performance progressively deteriorated throughout the drive, which was not the case following alcohol.

Thus, sleep loss, alcohol and their interaction have deleterious effects on neurobehavioural performance, with OSA having a somewhat similar affect on cognitive and driving performance. OSA is a common condition and these patients already experience poor sleep, EDS, cognitive deficits and heightened MVA risk at baseline. However, given the potential for interactive effects and that lifestyle choices around alcohol consumption and sleep restriction are likely to be similarly or perhaps more prevalent in OSA patients as in the general population, an important clinical question concerns what effect additional sleep loss and alcohol may have on patients with OSA who may be more vulnerable to performance deficits and associated risks. In order to build a theoretical framework to help address this question the following sections will discuss the potential mechanisms contributing to neurobehavioural abnormalities associated with OSA and examine how these factors may lead to a greater patient vulnerability to performance deficits with additional central nervous system stressors such as sleep restriction and alcohol.

1.4   Potential mechanisms of neurobehavioural abnormalities in OSA

1.4.1   Daytime sleepiness and intermittent hypoxia

OSA is characterised by repeated UA occlusion, sleep fragmentation (from frequent arousals from sleep) and intermittent blood oxyhaemoglobin desaturation (hypoxia).

The literature is divided on the relative contributions of sleep fragmentation and hypoxia to neurobehavioural abnormalities in OSA. Some studies report relationships between neurobehavioural outcomes and the degree of sleep fragmentation (353-355), others with the degree of hypoxia (19, 47, 143) and some report associations with both sleepiness and hypoxia (18, 20). It appears likely that both factors are important and contribute differently to various cognitive domains. Animal models of OSA and human brain imaging studies provide insights into how sleep fragmentation and hypoxia may impact on brain areas such as the pre-frontal cortex (PFC) that govern daytime cognitive functions. The following section summarises the literature on the contributions of the main clinical features of OSA (e.g. sleep fragmentation and intermittent hypoxia) to daytime abnormalities in performance and brain function.

Sleep fragmentation leads to EDS (353, 356, 357), which in turn has been found to correlate with poor neurobehavioural performance (12, 29, 32, 353, 354, 356-361). Intermittent hypoxia (IH), a major nocturnal manifestation of OSA, has received considerable attention over the last two decades. Some studies have shown associations with deficits in neurocognitive function (22, 362, 363), but study findings are often inconsistent. For instance, while some authors attribute cognitive deficits to the degree of hypoxaemia (143, 364), others relate deficits to daytime sleepiness (18, 27). Such disparities in the literature may partly reflect large variations in the patient populations studied (e.g. in age, OSA severity), the measures of sleep fragmentation/hypoxia used (e.g. AHI, arousal index, average O_2 desaturation, minimum O_2 desaturation, sleep time with O_2 below 90 or 80%) and differences in types of cognitive tests and the cognitive domains they actually

measure (363). For example the Trail B task is viewed by different investigators as either an executive task (18), an attention/concentration task (143) or a visual-motor task (20). Consequently, different interpretations of tests and what they measure may contribute to discrepant conclusions across studies.

Despite some discordance between study findings, the cognitive domains consistently found to be significantly impaired in OSA patients are attention/vigilance and executive function (22, 23, 362). Both cognitive domains are important for real-life performance tasks such as driving. In a recent review (362), it was found that out of 7 studies assessing attention/vigilance, 2 related the OSA impairment to nocturnal measures of sleep fragmentation, 1 to hypoxaemia and 4 found an association between both nocturnal factors. It is likely that both factors have an important synergistic role in cognitive abnormalities associated with OSA. Most studies have employed correlation analysis to explore relationships between nocturnal sleep/respiratory measures, however the associations are often moderate at best (r values ranging between 0.3-0.4). Alternatively, some studies have directly compared cognitive function in groups of patients either with or without hypoxia (143) or sleep fragmentation (365). Findley and colleagues (143) compared cognitive function in OSA patients with and without associated hypoxia matched for age, education and sleep measures (sleep time, sleep stages, sleep efficiency, limb movement, etc). Hypoxic patients performed worse (considered abnormal by neuropsychological assessment) than non-hypoxic patients on tests of attention, concentration, complex-problem solving and short-term recall. Furthermore, across all patients, hypoxia correlated with overall cognitive impairment. However, hypoxic patients had higher BMI (47 versus 32 kg/m^2) compared to non-hypoxic patients

and it was unclear if AHI and respiratory related arousal indices were matched between the groups. Roehrs and co-workers (365) attempted to evaluate the impact of sleep fragmentation in OSA independent of hypoxia effects by comparing a group of OSA patients with chronic obstructive pulmonary disease (COPD) patients who typically experience significant hypoxia but without severe sleep fragmentation. OSA patients were more impaired on tasks of sustained attention/vigilance, while COPD patients were impaired on motor skill tasks. The authors attributed the attention/vigilance deficits in OSA to sleep fragmentation, which was not present in the COPD group. However, comparisons between OSA and COPD patients are problematic as hypoxaemia experienced in each condition is fundamentally different (intermittent hypoxia in OSA versus sustained hypoxia in COPD) such that matching patient groups is impossible and interpretation of these data is difficult. On the other hand, experimental sleep fragmentation in healthy subjects has a negative effect on performance (353, 366), supporting that sleep fragmentation effects are nevertheless potentially important in explaining neurocognitive task performance deficits in OSA.

Although it appears that sleep fragmentation and hypoxia in OSA can both influence daytime function, the relative contributions of these two factors to daytime cognitive deficits and the mechanisms by which these factors impair performance are unclear. Animal models provide the means to directly assess the impact of experimental sleep fragmentation and hypoxia on performance and brain structure.

1.4.1.1 Animal models of OSA

Rat and mice models of OSA have been developed to evaluate the separate effects of sleep fragmentation (367, 368) and intermittent hypoxaemia (13-17, 21, 369-375) on the animal's brain and neurobehavioural function. Experimentally induced sleep fragmentation for 24 and 72 hours in rats resulted in impaired acquisition of spatial learning in a water maze test, and was explained by the absence of hippocampal long-term potentiation (a long-lasting change in synaptic efficiency thought to underlie declarative memory formation) compared to control rats (368). In a more recent study (367), hippocampal long-term potentiation was associated with reduced excitability of CA1 pyramidal neurons following 24 hours of fragmented sleep.

In experiments in which rats were exposed to IH, Gozal and colleagues (13) found a marked increase in apoptosis (cell death) in CA1 hippocampal regions and the cortex 1-2 days after IH, which was accompanied by significant impairments in cognitive performance. Veasey and colleagues (14) showed that mice exposed to a longer IH protocol exhibited increased sleep times, decreased sleep latencies, elevated isoprostane (a marker of free radical oxidation), protein carbonylation and nitration, and induction of antioxidant enzymes in wake promoting regions of the basal forebrain and brainstem. Other researchers have also observed significant increases in brain antioxidants suggestive of considerable oxidative and inflammatory stress (14-17).

Although animal models provide the means to assess the effects of sleep fragmentation and IH on cognition and brain function, the levels of sleep fragmentation and hypoxia are often more severe than those generally observed in human OSA, thus making it difficult to translate these findings to human outcomes. Also, there have been no attempts to date in IH experiments to replicate the corresponding changes in arterial PCO_2 that occur during upper airway obstructive events in human OSA. While it is impossible to directly evaluate the impact of sleep fragmentation and IH on the human brain as has been done in animals, several investigators have employed brain imaging techniques to examine brain morphological changes in OSA.

1.4.1.2 Magnetic resonance imaging (MRI) in OSA

A number of recent investigations (11, 12, 24-33, 113) have used MRI to assess the effects of OSA on the brain, although the results to date have been somewhat inconclusive. Macey and colleagues (25), using T1-weighted MRI and voxel-based morphometric analysis, found that compared to controls, OSA patients had a significant grey matter loss in many brain regions, including the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum. The same investigators also recently showed that in patients with OSA, axonal fibre (white matter) integrity is significantly compromised in many brain regions including the pre-frontal cortex (31). This is consistent with findings from animal studies, and suggests that hypoxia and/or sleep fragmentation causes significant cortical damage that may lead to cognitive deficits associated with OSA.

However, a more recent investigation (26) using a similar imaging approach to Macey et al. (25), found no direct associations between regional grey matter volume and OSA, suggesting that hypoxia does not cause structural brain damage. These discrepancies in results may arise from differences in the number of OSA patients studied and their OSA severity, and differences in patient recruitment inclusion and exclusion criteria. O'Donoghue and colleagues (26) argued that using strict criteria for recruitment, such as excluding OSA patients with significant co-morbidities (e.g. heart disease and depression) and carefully matching control subjects, yields data of greater validity. Another uncertainty in the imaging literature is to what extent hypoxia or sleep fragmentation contributes to the cognitive deficits in OSA as, unlike in the animal literature, more direct analysis of brain damage in humans is very difficult. More controlled studies are required to tease out the relative contributions of sleep fragmentation and hypoxia to cognitive deficits in OSA patients (32), but it is likely that both factors are important and differentially contribute to various sub-components of neurocognitive deficits in OSA.

1.4.1.3 Functional magnetic resonance imaging (fMRI) in OSA

In addition to using structural imaging techniques to assess OSA brain morphology, a number of investigators have used functional MRI (fMRI) to examine cortical activation in OSA patients in response to specific cognitive tasks, including verbal learning (113), sustained attention (11) and working memory (29). These studies have revealed that there are differential cortical responses depending on the difficulty and type of cognitive task used. For example, Ayalon et al. (113)

examined cerebral activation responses in OSA patients during the performance of a verbal learning task, and demonstrated increased cerebral activation compared to controls. Patients showing this augmented cerebral response had intact performance on the verbal learning task. Similarly, Archbold et al. (28) showed increased cortical activation in patients with OSA during a working memory task. Interestingly, greater activation was associated with increased OSA severity. From these results the authors concluded that increased cortical activation and the ability to maintain performance in patients with OSA is reflective of an adaptive brain response (compensatory recruitment) whereby additional brain capacity is recruited to maintain performance. Compensatory recruitment is an example of brain plasticity in response to external stressors and has been demonstrated during verbal learning tasks in healthy subjects exposed to a night of total sleep deprivation (see section 1.3.1.2) (259, 260, 262). In general these separate findings in sleep deprived healthy subjects (259, 262) and OSA patients (28, 113) suggest similar compensatory mechanisms during learning and memory tasks. However, cortical responses to attention tasks in OSA patients are somewhat different, with a decrease in activation (failure of compensatory recruitment) and reduced performance (29), compared to intact compensatory recruitment in sleep deprived healthy subjects (376).

Vigilance and attention are critical to maintaining safe driving; therefore tasks that assess these cognitive domains are more relevant to driving performance than verbal learning or memory tasks. Observations regarding cortical responses during attention tasks in OSA patients versus control subjects suggest that there is insufficient compensatory capacity in OSA patients to maintain performance. The

prevailing theory is that this is due to long-term sleep fragmentation and/or nocturnal hypoxaemia.

1.4.2 Current theories regarding attention and vigilance abnormalities associated with sleep loss, alcohol and OSA

Vigilance and attention are complex psychological constructs that in part influence almost all aspects of cognition (239). They are crucial for maintaining performance on real-world tasks such as operating machinery, flying a plane and driving a train or a motor vehicle. Based on evidence from both animal and human studies (241, 377-385), there are a number of theories for the neural underpinnings of attention/vigilance systems.

Posner and Paterson (386) proposed a model of the cortical attention network with two sub-systems. The "posterior attention system" involved in orienting to visual locations sub-served by the posterior parietal lobe, superior colliculus and thalamic regions and the "anterior attention system" which involves target stimuli detection and requires the function of the anterior cingulate (386). Mesulam (387) proposed a somewhat similar model of attention, including parietal brain regions in the sensory representation of space, lateral frontal regions in motor responses to stimuli and the anterior cingulate in determining if stimuli are motivationally salient. LaBerge (388) recently extended these earlier theories of attention and proposed a triangular circuit of attention including three main forms of attention, namely, brief selective attention (identification and selection of information), preparatory attention (sustained for period of time in anticipation of a stimulus) and maintenance

attention (sustained for a longer period of time in order to process ongoing activity). Each of these theories of attention incorporate the reticular activating system, which importantly underlies the maintenance of vigilance and acts upon all levels of the attention system (389).

The complex neural networks of attention are popularly conceptualised as cognitive "top-down" factors (i.e. knowledge, expectations and current goals in regards to a relevant stimulus) and sensory "bottom-up" factors reflecting sensory stimulation (i.e. characteristics of the stimulus) interacting with other factors, such as novelty and unexpectedness, reflecting the interaction between cognitive and sensory influences (239, 241, 380, 390). Thus, "top-down" mechanisms enhance the neural processing of relevant sensory input and facilitate the discrimination between signal and 'noise' (distracting stimuli) (380), while "bottom-up" processes rely on the salience of the target and its ability to trigger attentional processing by recruiting 'higher' cortical brain regions in a bottom-up manner (e.g. processing of visual information in the primary visual cortex followed by temporal regional processing of visual stimulus identification and parietal regions for location). Using driving as a practical example, top-down control might include prior knowledge of the nature and meaning of traffic light signals with corresponding enhancement of information processing and bias (filtering irrelevant information) preferentially directed toward relevant stimuli (e.g. traffic lights), so that when approaching an intersection an appropriate response is coordinated according to changing stimuli (e.g. change from green to red requiring the driver to stop). Bottom-up control in this scenario would be influenced by the novelty and sensory distinctiveness of stimuli (e.g. lights changing from green to red would be a novel and distinct stimulus in the visual field

and would attract attention) with constant interaction with higher order cognitive top-down processes enabling goal-directed identification, filtering and an appropriate response to stimuli.

It is important to note that these are, however, overlapping and interrelated theoretical concepts that do not necessarily represent anatomical systems of afferent and efferent projections (380). Importantly, these mechanisms interact to maximise performance during attention and vigilance tasks (380, 391). Top-down processes have been theorised to be mediated via the frontal cortex and involve the so called anterior and posterior attention systems that function to detect target stimuli and bias orientation of attention towards the target source, respectively (386). These theories of attention are substantiated by human imaging and animal studies that demonstrate sequential activation of frontal-parietal-sensory brain regions, modulation of activity in sensory and sensory-associational brain regions and decreased activation of task-irrelevant brain regions (239, 380, 392, 393). This frontal-parietal-sensory system is thought to be innervated by cholinergic projections from the basal forebrain, which controls arousal and wakefulness, and is a major component of top-down processes that help mediate sustained attention (vigilant attention) (380). During sustained attention the cholinergic projection system is activated via direct connections from the PFC to the basal forebrain. Cholinergic inputs terminate in all cortical brain regions and facilitate all aspects of sustained attention performance including enhancement of sensory processing of target stimuli, filtering of irrelevant stimuli (distracters) and optimisation of decisional strategies (380).

Sturm and Willmes (394) have proposed yet another multi-component model of attention. These investigators have classified attention as having "intensity" (tonic) and "selection" (phasic) aspects. The intensity (tonic) aspects of attention include sustained attention and alertness/vigilance, while the selection (phasic) aspects include higher order orienting and cognitive attention (394). In this model, as in the "top-down" and "bottom-up" concepts, there is co-activation of frontal-parietal-thalamic and brainstem networks in response to alerting and orienting attention demands. There is an emphasis of a vigilance component of attention in this model, which is said to be functionally distinct from the selection aspects and have a more fundamental role in maintaining attention performance over time (394). This model has been adopted by sleep deprivation researchers as it implies that vigilant attention (sustained attention) becomes unstable (state instability) over time. This instability is evident within very short periods of time (i.e. seconds) while on task (68, 70, 253) rather than over longer periods (hours) as previously thought (395), and coincides with momentary lapses in attention.

1.4.2.1   Behavioural and neural correlates of lapses in attention

Behaviourally, instability in attention over time causes increased errors and slower reaction times to the point that the stimulus can be completely missed. In a real-world operational sense such as driving this can lead to catastrophic performance failures such as MVAs. A simple and sensitive measure of attention and vigilance is the psychomotor vigilance task (PVT), which has been extensively used in chronic sleep restriction studies (243, 271, 272). The standard task takes 10 minutes and

requires subjects to continuously monitor for and rapidly respond with a button press to a target stimulus which appears unpredictably between 2-10 sec. Reaction time and attention lapses (reaction times slower than 500 msec) are the main measures with the latter shown to be highly sensitive to sleep loss and extended wakefulness (62, 238, 243). Attention lapses occur spontaneously in rested individuals performing psychomotor tasks such as the PVT, but markedly increase in frequency and duration when the attention systems are stressed by extended wakefulness/sleep deprivation (236, 238, 243), or the administration of alcohol (296, 396).

Imaging studies have evaluated brain activation during attention tasks in a trial-by-trial manner comparing brain activation during attention lapses compared to normal non-lapse responses (68, 71, 376). Drummond and co-workers (376) used fMRI to evaluate cortical activation during fastest and slowest reaction times on the widely used PVT task in 20 healthy adults following normal sleep and after 36 hours of sleep deprivation. Following normal sleep, fast reaction times were characterised by greater activation within the cortical sustained attention network and associated motor regions. Attention lapses, especially following sleep deprivation, were associated with greater activation within the "default mode network" (which is normally deactivated by stimuli) made up of frontal and posterior midline regions (376). The concept of a "default mode" brain activity comes from observations by Raichle and colleagues (397, 398) and refers to the pattern of brain activity during the resting state (i.e. laying down awake with eyes closed) in the absence of any stimulus. These basally active regions are usually rapidly deactivated when a stimulus is presented and attention systems are engaged. Using a different

global/local attention task Weissman et al. (71) found, in agreement with Drummond et al. (376), that attention lapses were associated with less deactivation in the "default mode" network, with decreased stimulus evoked (bottom up) sensory activity and increased activity in the frontal and parietal cortex. Furthermore, mechanisms for recovering from attention lapses were evident by increased stimulus evoked activity in the right inferior frontal gyrus and the right temporal parietal junction which was associated with better performance on the next (post lapse) trial. As with sleep deprivation, ingestion of alcohol by healthy subjects also leads to an overall slowing of information processing and suppressed activation of the frontal-parietal, cerebellar, occipital and motor regions. This leads to behavioural impairments such as slower response speed and increased errors (283, 303, 304, 399). A very recent study by Ayalon et al. (29) demonstrated that compared to controls, patients with OSA showed reduced sustained attention performance and reduced activation in the frontal-parietal and cingulate regions involved in attention, with slower reaction times (lapses) related to decreased activation in the these brain regions.

In summary, attention lapses can occur spontaneously in well rested healthy subjects, but are markedly exacerbated by prior extended wakefulness/sleep loss, ingestion of alcohol or sleep disorders such as OSA, and are characterised by altered brain activity in attention and "default mode" brain regions just prior to each lapse.

1.4.3 Special role of the pre-frontal cortex (PFC) in the effects of sleep restriction, alcohol and OSA on performance

The human PFC is the largest brain region, comprising ~29% of the cortex, and has vast afferent and efferent connections with all other brain regions (400, 401). The PFC is involved in mediating and organising, to variable degrees, all higher order cognitive functions (402, 403). The dorsolateral PFC, orbital cortex and cingulate cortex work together to enable planning of actions, working memory and maintenance and focusing of attention/vigilance (through mechanisms described in the preceding section) to allow appropriate and intentional responses to stimuli (403). Kane et al. (404) suggest that the dorsolateral PFC is one of the critical structures in the anterior and posterior "attention control" brain network having an executive role in processing stimulus-related information in a goal-directed manner and inhibiting distraction from irrelevant stimuli. Although simple psychomotor reaction time tasks (designed to assess basic attention/vigilance processes) may rely little on higher order function of the PFC and its influence on attention brain circuits, in real-life complex behaviours such as driving, there would almost certainly be a more critical role for the PFC in maintaining goal-directed inhibitory influences, particularly during attention/vigilance demanding conditions. It is therefore likely that damage to the PFC will impact on performance during complex cognitive tasks such as driving.

Horne and colleagues (69) have suggested that the PFC is the most active area of the brain during wakefulness, and therefore requires the greatest recovery during sleep. As such, the PFC is potentially more vulnerable to central nervous system

stressors than other brain regions. Numerous experimental observations in healthy subjects suggest that the PFC is highly sensitive to sleep deprivation (or sleep fragmentation) and alcohol (69, 256, 259, 260, 262, 263, 405-408). Although hypoxia has been shown to affect many brain regions, it has been implicated as an important factor impairing PFC related cognitive functions (13-21, 369), with some evidence suggesting that the PFC may be more prone to hypoxic damage than other brain regions (369). Thus, it seems that the human PFC is of central importance to complex behavioural task performance and attention/vigilance, and sensitive to central nervous system stressors such as sleep loss, alcohol and hypoxia. Consequently, the cognitive and attentional deficits after sleep loss, alcohol and hypoxia, particularly those observed during higher order executive/attention functions, may reflect their impact on the PFC and the downstream brain regions sub-served by the PFC. A combination of these stressors, e.g. alcohol in the presence of sleep deprivation, may be particularly deleterious to PFC function and the performance of tasks requiring sustained attention/vigilance (55, 78, 79). This might also apply in OSA patients (who have a background level of sleep disruption) who are exposed to further sleep loss or alcohol.

1.5   Summary and aims of thesis

OSA is associated with impairments in driving simulator performance, increased risk of MVA and a variety of neurocognitive deficits that may not "normalise" following CPAP treatment. Common "lifestyle" factors such as moderate sleep restriction and low-dose alcohol, separately and together, have been shown to

impair cognitive function and driving performance and increase MVA risk in healthy subjects. The behavioural impairments observed in OSA patients and healthy, sleep deprived or alcohol affected subjects are similar and involve deficits in the activity of attention/vigilance-controlling brain regions sub-served by the PFC. The PFC is known to be sensitive to the stress of sleep loss, alcohol and OSA related sleep fragmentation/hypoxaemia. Although, sleepiness and alcohol have been shown to interact and cause greater performance decrements when combined, possibly via their affects on common neural circuitry, the impact of additional sleep loss and alcohol on driving and cortical activation in patients with OSA remains unclear. The effectiveness of CPAP treatment in normalising driving simulator performance and cortical activation is also unresolved. These are important clinical and basic research questions with significant further implications for community education, accident prevention and traffic safety. Therefore, the aim of the studies presented in this doctoral thesis was to compare the effects of moderate sleep restriction and low-dose alcohol on driving simulator performance and evaluate cortical activation in OSA patients before and after CPAP therapy relative to responses in appropriately matched healthy subjects.

1.5.1 Specific aims and hypotheses

The aim of the first study, presented in Chapter 2, was to compare the effects of low-dose alcohol and acute partial sleep deprivation on driving simulator performance in untreated OSA patients versus healthy age/gender matched control subjects. The specific hypothesis was that OSA patients would be more vulnerable to the effects of sleep restriction and alcohol and thus would experience

significantly greater decrements in driving performance compared to healthy matched controls.

The aim of the second study, presented in Chapter 3, was to measure the effects of ~3 months of CPAP treatment on driving simulator performance under alcohol, restricted and normal sleep conditions in patients with severe, previously untreated OSA, compared with healthy age/gender matched controls over an equivalent follow-up period without treatment. It was postulated that CPAP treatment would improve driving simulator performance in OSA patients under all conditions thereby reducing OSA dependent vulnerability to sleep deprivation and alcohol, but CPAP would not normalise driving performance compared to healthy controls.

The aim of the final study, presented in Chapter 4, was to compare the effects of ~3 months CPAP treatment on cortical activation by examining early and late auditory event related potentials in severe OSA patients and healthy age/gender matched controls. The hypothesis was that auditory event related potentials would be abnormal in severe OSA patients, would improve following CPAP treatment, but remain abnormal in comparisons to healthy controls.

CHAPTER 2. EFFECTS OF ALCOHOL AND SLEEP RESTRICTION ON PERFORMANCE DURING SIMULATED DRIVING IN UNTREATED PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

2.1 Introduction

Obstructive sleep apnoea (OSA) causes excessive daytime somnolence and reduced vigilance, concentration and neurocognitive function (22, 409). The risk of motor-vehicle accidents is increased between 2 and 7 fold, particularly amongst OSA patients with moderate to severe disease (34-40, 166). Community surveys have shown that approximately 7% of the middle-aged population have at least mild OSA (i.e. more than 10 obstructive events per hour of sleep) (1, 2, 4) with as many as 80% undiagnosed (3, 7, 100). For those patients who are diagnosed, delays in instituting treatment are common (410) and between 46-83% fail to adhere to treatment over the long term (46). The many undiagnosed or untreated OSA sufferers are a serious public health concern with respect to road safety. OSA-related accidents have been estimated to result in 1,400 road fatalities and cost 15.9 billion dollars annually in the United States alone (411). Improving access to diagnosis and treatment may help reduce this public health burden but even with improved sleep medicine services there will likely remain many unidentified or untreated OSA sufferers that remain at increased risk of motor vehicle accidents. A

better understanding of the factors contributing to motor vehicle accidents amongst OSA sufferers is therefore needed to develop cost-effective prevention strategies.

This study was designed to compare the effects of two common "lifestyle" factors, low-dose alcohol and acute partial sleep deprivation on driving simulator performance, between untreated OSA patients and healthy matched control subjects. We postulated that because of prior chronic sleep disruption and possible hypoxia-induced brain damage (13, 14, 24-26, 47, 54, 409), OSA patients would be more vulnerable to the effects of these two common, mild central nervous system stressors and would experience significantly greater decrements in driving performance.

2.2   Methods

The study was approved by the Human Research Ethics Committees of the Repatriation General Hospital, University of South Australia and University of Adelaide. Subjects were introduced to the study objectives and protocol during an introductory session, gave written informed consent and were remunerated for their participation.

2.2.1   Study design

OSA patients and control subjects underwent driving simulator assessments under three different conditions that were presented in random and counter-balanced order, namely: 1) after a normal night-time sleep, 2) after a single night of sleep

restriction (4 hours time in bed from 2:00-6:00 am) and 3) after acute administration of low-dose alcohol (target blood-alcohol concentration 0.05 g/dL). All driving simulator sessions began at 2:00 pm and were conducted at least 5 days apart to avoid carry over effects from prior interventions.

2.2.2   Subject selection

Thirty eight untreated OSA patients of varying disease severity were recruited following diagnostic polysomnography. Neither they nor their referring physician had specific concerns about their driving. To minimize selection bias, patients were told the study was to investigate general neurocognitive performance and were unaware that the trial measured driving performance until after they agreed to attend an introduction session. Twenty healthy control subjects matched for age and gender were recruited from the general population through newspaper advertisements, which provided only a general description of the study and made no mention of driving performance measures.

Exclusion criteria were as follows: professional driver or shift worker; history of driving <2yrs or <2hrs per week; significant medical co-morbidities (e.g. cardiac or respiratory failure), periodic limb movement disorder (periodic limb movement arousal index >5/hr), past head injury or depression; use of alertness altering prescription medications that may alter neurocognitive function (e.g. antihistamines, opiates, antidepressants); history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they obtained higher than normal

scores on sleep quality (Pittsburgh Sleep Quality Index > 5) and daytime drowsiness (Epworth Sleepiness Scale > 10) questionnaires.

2.2.3   Baseline measures

Prior to driving simulator assessment, all participants completed questionnaires assessing general health (medical conditions, medication, alcohol, caffeine and drug use), sleep quality/habits and daytime drowsiness using the Pittsburgh Sleep Quality Index (412), and the Epworth Sleepiness Scale (125). All participants had overnight standard diagnostic polysomnography with the following recordings: electroencephalography (C3/A2, C4/A1 lead placements), left and right electro-oculograms, submental electromyogram, nasal cannula to measure nasal pressure, limb movement sensors, inductive plethysmography for thoraco-abdominal motion, lead II electrocardiography and arterial oxygen saturation (finger pulse oximetry). All signals were digitized and stored using a Compumedics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardised methods (413, 414). Apneas and hypopnoea were scored according to internationally agreed criteria (414). All studies were scored by one staff member certified by the Board of Registered Polysomnographic Technicians.

2.2.4   Main outcome measures

The main outcome measures were driving simulator performance parameters including lateral steering deviation, braking reaction time, crash frequency and pre-crash electoencephalography/electro-oculography measurements. Driving

performance was assessed using the AusEd driving simulator which ran on a purpose-built Windows 2000 workstation, 19-inch BENQ FP937s monitor with Logitech MOMO steering wheel and pedals used to assess the driving parameters.

Steering deviation was measured from the average deviation in centimetres from the driver's median lane position sampled at 30 Hz. Subjects were instructed to maintain speed within 60-80 km/h, but to apply the brakes as quickly as possible whenever a slow moving truck was presented ahead in the driving lane. Truck presentations occurred a total of 7 times during the drive and the mean braking reaction time was computed for the 7 truck-ahead incidents. Crashes occurring throughout the driving task were defined as: car deviating from the road (all 4 wheels completely off the road), collision with a truck, or if the car was stationary for >3 seconds.

The main outcome measure for crashes was the number of controls and OSA patients who experienced at least one crash incident. A secondary crash analysis was undertaken to determine if crashes were associated with brief fall-asleep episodes and prolonged eye closures. Fifteen second epochs of electroencephalography, electro-oculography and synchronized video (head and shoulders) prior to each crash (crash epoch) were scored for the presence of prolonged eye closure (>2 sec) and microsleeps (>2 sec continuous electroencephalographic theta activity) within each crash epoch. A random sample of an equal number of 15-second non-crash epochs were selected and matched within subjects and condition to be compared with the crash epochs.

The simulated driving task used in the present study consisted of a 90-minute country night-time drive on a predominantly straight dual-lane road with bends occurring at 5 minute intervals, each taking approximately 10 seconds to negotiate. There was no oncoming traffic or traffic lights. Driving simulator studies have been shown to correlate reasonably well with on road driving (223, 337) and the AusEd simulator has been previously validated and shown to be sensitive to fatigue in a range of experimental settings (55, 73, 77, 79, 415).

2.2.5   Detailed experimental procedures

For all three conditions subjects' sleep patterns and duration were monitored throughout the study using actigraphy monitors (Actiwatch, Mini-Mitter Co, Inc, Model-AW64, Oregon, USA) worn from at least 5 days prior to beginning the experiments until study completion to estimate sleep/wake timing, to ensure compliance with the sleep restriction protocol and to ensure patients did not nap in the 24 hours prior to the experiments (416). In addition, during the night of sleep restriction, participants left a message on a time/date stamped answering machine at bedtime (2:00 am) and wake time (6:00 am), again to ensure compliance with the protocol. Subjects were instructed to abstain from alcohol, caffeinated beverages, not to nap for 24 hours prior to each experimental session and to consume breakfast before 9:00 am on the day of each experiment. Subjects were transported by taxi to and from the laboratory.

Upon arrival at the laboratory at 12:00 pm, each subject's blood-alcohol concentration was estimated using a calibrated breathalyzer (Dräger

Alcotest7410[Plus]), sleep diaries were collected, activity monitor data downloaded and the answering machine checked for compliance with the sleeping regime. Subjects consumed a standardised lunch with a glass of water at 12:15 pm before electrode application for electro-encephalographic monitoring (C3/A2, C4/A1, O1/A2, O2/A1 and EOG) of drowsiness throughout the driving test. At 1:30 pm all subjects consumed either 375 ml of sugar-free, non-caffeinated control soft drink (in the normal and restricted sleep conditions) or a volume of 40% Vodka calculated to achieve a target blood-alcohol concentration of 0.05 g/dL mixed with the same soft drink. Target blood alcohol concentrations were achieved using doses of alcohol derived from the mathematical formulae below (79, 284), where total body water (TBW) is first calculated using age, height and weight, before alcohol dose estimation from TBW and the target BAC.

TBW = 2.447-(0.09516 x age [yrs]) + (0.1074 x height [cm]) + (0.3362 x weight [kg])

Alcohol Dose (g)　　=　　$\dfrac{\text{Target BAC (grams) x 0.8}}{\text{TBW}}$

2.2.6   Data analysis and statistics

Steering deviation data, excluding the first minute of acceleration and initial lane positioning, were divided and averaged into 18 intervals for the remaining 89 minutes of the drive. Linear mixed model analysis was used to examine fixed effects of condition (normal sleep, sleep restriction and alcohol), group (patients vs. controls) and time on task (18 intervals), with each subject considered to have a random intercept assumed constant across conditions, and using an autoregressive covariance structure (AR1) to adjust for serial correlation across time (SPSS Inc, Version 16.0, Chicago). The fully saturated model was run first, followed by removal of the non-significant three-way (group x condition x time) interaction term such that the final model included the main effects of group, condition, time and all two-way interaction terms. Significant interaction effects were explored via custom contrasts within the mixed model. Mixed model analysis was also used to examine braking reaction time with fixed effects of condition (normal sleep, sleep restriction, and alcohol) and group (patients vs. controls), subject as a random intercept assumed constant across conditions, and using a diagonal covariance structure. Satterthwaite approximated degrees of freedom are reported rounded to the nearest whole number.

Binary Logistic Regression (GEE for longitudinal/repeated measures data, clustering on subject) (417, 418) was conducted to investigate group and condition effects on the presence of at least one crash [no/yes] (Stata v9.0). Given only one crash in the control group, group by condition effects could not meaningfully be examined in this analysis. Condition effects were therefore examined only in OSA

patients with condition specified as a predictor variable [normal sleep/sleep-restriction/alcohol] and each patient appearing in the model three times (one observation per condition).

A second model was used to investigate if the presence of microsleeps (>2 sec theta) or eye closures (>2 sec) in the preceding 10 seconds was predictive of crash. This model included all OSA patient crashes, with crash epochs matched with randomly selected non-crash epochs from the same driver in the same condition (one observation per epoch). Due to this matching of crash and non-crash epochs it was not appropriate to assess the effect of condition in this model as different subjects contributed differently to the three conditions. Values are means (SD) or [95%CI] unless otherwise indicated and adjusted odds ratios (OR). $p < 0.05$ was considered statistically significant.

2.3   Results

Thirty-eight OSA patients and twenty control subjects were recruited. Subject's anthropometric characteristics, sleep study results, caffeine and alcohol consumption and medication use are shown in Table 2.1. The estimated sleep time (actigraphy) during normal and restricted sleep, average alcohol ingested and blood-alcohol concentrations before and after the driving task are shown in Table 2.2. All subjects complied with the sleep restriction protocol and had a blood-alcohol concentration of 0.0 g/dL upon arrival to the laboratory on each experimental day.

Table 2.1 Participant anthropometric characteristics, polysomnography and questionnaire results, and medication use

	Controls (n=20)	OSA (n=38)
N Males/Females	15/5	28/10
Age (yrs)	50.6 (10.1)	52.0 (10.4)
Body-Mass Index (kg/m^2)	24.5 (2.5)	33.9 (8.1) †
Apnea Hypopnoea Index (AHI: events/hour)	8.3 (4.0)	46.4 (21.7) †
% of sleep time with SaO_2<90%	0.07 (0.31)	6.7 (14.7) †
Average SaO_2 desaturation (%)	2.4 (0.8)	4.1 (1.8) †
Pittsburgh Sleep Quality Index	2.9 (1.0)	9.4 (4.9) †
Epworth Sleepiness Scale	5.0 (3.0)	9.3 (5.3) †
Driving History (kilometers/year)	11,450 (5,762)	13,983 (7,906)
Education (years completed)	12.9 (2.8)	11.7 (2.7)
Caffeine Consumption (cup or equivalent/day)	2.7 (1.3)	3.6 (1.9) †
Smoking (cigs/day)	0.2 (0.9)	1.5 (4.0)
Habitual Alcohol Intake (Std Drinks/week)	8.8 (5.8)	7.4 (10.2)
Medication Consumption (# of people by condition)		
Hypertension	0	11
Hyperlipidemia	0	6
Diabetes	0	2
Gastro-Esophageal Reflux Disease	0	5
Arthrititis	0	4
Thyroid Disease	0	4
Asthma	0	2
Gout	0	2
Hay fever	0	1

Values are mean (SD), † = significant difference from controls, p<0.05.

Table 2.2 Actigraphy estimated sleep time, average alcohol consumed and blood alcohol concentration before and after the driving task

	Controls	OSA
Estimated Sleep Time (mins)		
Normal Sleep	468 (42)	456 (48)
Restricted Sleep	222 (24)	228 (60)
Alcohol consumed during study (grams)	41.6 (8.5)	48.6 (8.7) †
Blood Alcohol Concentration (g/dL)		
2:00 pm (start of driving task)	0.045 (0.011)	0.048 (0.016)
3:30 pm (end of driving task)	0.023 (0.01)	0.023 (0.01)

Values are mean (SD), † = significant difference from controls, $p < 0.05$.

2.3.1 Driving performance

2.3.1.1 Steering deviation

Steering deviation in OSA and control groups over the course of the drive in each condition is shown in Figure 2.1. The group x condition x time interaction term was not statistically significant in the fully saturated model and was removed for the remaining analyses. In the final model there were statistically significant effects of group $(F_{[1,56]}=10.6,$ p<0.01), condition $(F_{[2,325]}=16.1,$ p<0.001) and time $(F_{[17,1937]}=6.8,$ p<0.001) and statistically significant group x time $(F_{[17,1967]}=1.8,$ p=0.02) and group x condition $(F_{[2,533]}=3.4,$ p=0.04) but not condition x time interaction effects. Averaged across all time points, OSA patients showed statistically significantly greater steering deviation than control subjects under all conditions (Mean [95%CI] over all conditions; OSA 50.5 [46.1 to 54.9], controls 38.4 [32.4 to 44.4], mean OSA versus control group difference; normal sleep 9.5 [1.8 to 17.4] cm, p=0.02, sleep restriction 14.4 [6.7 to 22.1], p<0.001, alcohol 12.2 [4.5 to 20], p<0.01). Changes in steering deviation over time were also greater in OSA patients compared to control subjects (group x time interaction). An increase in steering deviation averaged across the whole drive in the sleep restriction compared to the normal sleep condition was statistically significantly greater in the OSA compared to the control group (difference from normal sleep; OSA 8.5 [6.1 to 10.9] cm, p<0.001, controls 3.7 [0.5 to 6.9] cm, p=0.02, difference between groups 4.8 [1.1 to 8.5] cm, p=0.01). The change in steering deviation averaged over time in the alcohol versus normal sleep condition was not different between groups. However, there was a statistically significant increase in steering deviation

averaged over time in the alcohol compared to the normal sleep condition in OSA patients, but not in controls (difference from normal sleep; OSA 5.4 [2.8 to 8.1] cm, p<0.001, controls 2.8 [-0.7 to 6.3] cm, p=0.12, difference between groups 2.6 [-1.6 to 6.9], p=0.23).

Figure 2.1 Effects of sleep restriction and alcohol on steering deviation
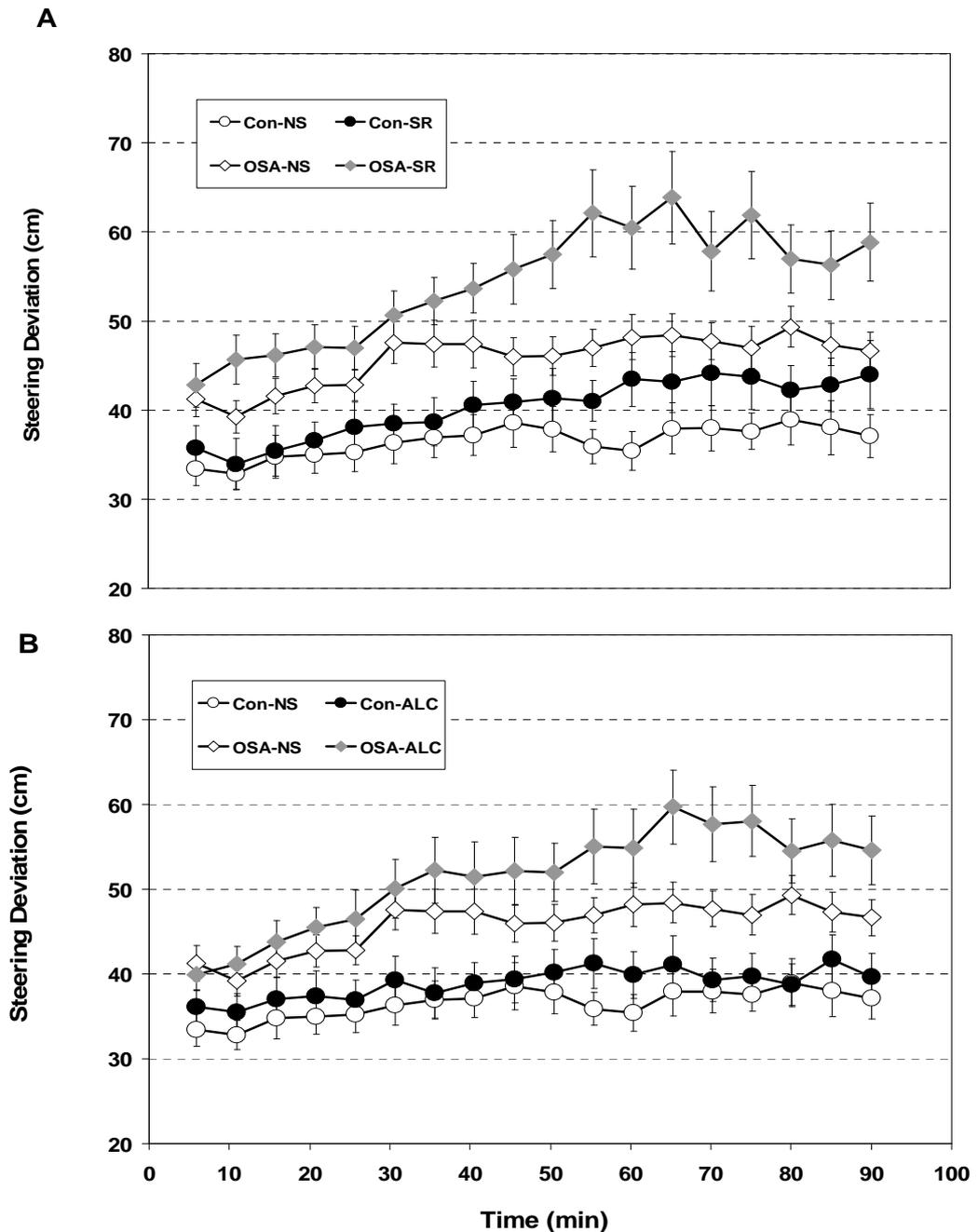
Steering deviation at 4.9 min intervals throughout 90 min simulator driving in OSA patients (n=38) and control participants (n=20) under (A) normal sleep (NS) versus sleep restriction (SR) conditions and (B) normal sleep (NS) versus low-dose alcohol (ALC). Values are mean (SEM).

2.3.1.2 Braking reaction time

There was a significant main effect of condition on braking reaction time ($F_{[2,77]}$=4.0, p=0.02). Braking reaction time was statistically significantly slower following sleep restriction 1.39 [95%CI 1.28 to 1.59] sec compared to normal sleep 1.22 [1.14 to 1.30] sec, p<0.01), but not following alcohol 1.34 [1.21 to 1.46] sec, p=0.175). There were no significant group differences in braking reaction time or interaction effects between groups.

2.3.1.3 Crashes

The number and proportion of subjects in the patient and control groups who experienced at least one crash during the simulator drives are shown in Table 2.3. OSA patients were approximately 25 times more likely to have at least one crash (OR [95%CI]=25.4 [1.3 to 500.1], p=0.03). The high odds ratio and CI in this model likely reflect that only a single crash occurred in the control group. OSA patients were significantly more likely to have at least one crash in the sleep restriction condition (OR=4.0 [1.8 to 8.8], p<0.01) and the alcohol condition (OR=2.3 [1.0 to 5.1], p<0.05) compared to the normal sleep condition (p<0.01).

2.3.1.4 Pre-crash analysis

Only one control subject had a single crash under the normal sleep condition and was excluded from this analysis. In OSA patients, there were a total of 125 individual crashes. The vast majority (96%) of crashes were off-road events, with

the remainder truck collisions of stopping events. When examining the contribution of microsleeps and prolonged eye closure to having at least one crash under any condition, microsleeps (OR=19.2 [9.1 to 40.7], p<0.01), and eye closures (OR=7.2 [3.3 to 15.7], p<0.01) were significant predictors of having at least one crash (p<0.01).

Table 2.3 Proportion and percentage of participants exhibiting crashes

	Controls	OSA
Baseline	1/20 (5%)	4/38 (10.5%)
Sleep Restriction	0/20 (0%)	12/38 (32%)
Alcohol	0/20 (0%)	8/38 (21%)

2.4   Discussion

This study shows that performance on a driving simulator is impaired in OSA patients compared with healthy age matched controls, and supports previous studies showing reduced driving simulator performance (34, 36, 166) and increased risk of motor vehicle accidents (35, 37-40) amongst OSA patients. The important new findings are that a single night of partial sleep restriction caused more steering impairment and a higher crash rate during a monotonous driving task in OSA patients than healthy control subjects, and that low dose alcohol similarly increased the crash rate in OSA patients. The deterioration of steering in OSA patients was also more influenced by time on task compared to healthy subjects. The level of experimental acute sleep restriction that was used is commonly experienced by shift workers (419) and others in the community (420). Similarly, the level of blood alcohol concentration achieved just prior to the drive (BAC$\leq$0.05 g/dL), and which we found to impair driving simulator performance, equates to "responsible" social drinking and is currently legal with respect to driving in almost all legislatures. Thus, the finding that OSA patients had more marked driving impairment than healthy subjects as a result of both partial sleep deprivation and low dose alcohol consumption has broad and direct clinical relevance.

This study did not address specific mechanisms for the increased vulnerability to sleep restriction and alcohol observed in OSA patients. However, recent evidence suggests that changes in the pre-frontal cortex may play an important role. The pre-frontal cortex appears to be particularly vulnerable to the effects of sleep deprivation and alcohol (256, 259, 263, 408, 421), and is the brain region primarily

responsible for executive function and vigilance (22). Driving simulation can be thought of as a global test of executive function as it comprises a number of different aspects of neurocognition including vigilance, attention, visual-spatial coordination, tracking and non-target related stimulus inhibition. Recent brain imaging studies suggest that functional changes in the pre-frontal cortex may be responsible for many of the neurobehavioural deficits observed in untreated OSA patients (22, 23, 113, 222) and in healthy subjects after sleep deprivation (256, 259, 263).

A literature search using the PubMed data base and the key words sleep apnoea, driving performance, driving simulation, traffic accidents, sleep restriction and alcohol uncovered only two previous reports directly relevant to the present study. Using the same driving simulator, but with a 30-minute driving task, Desai and colleagues (73) found that after one night of total sleep deprivation there were no significant differences in steering performance between mild OSA patients, and control subjects. Similarly, Wong and colleagues (415) from the same group found no significant difference between moderate to severe OSA patients and control subjects during a 30-minute driving simulator task after 40 hours of constant wakefulness. These results contrast with our findings after partial sleep restriction and could be due to a time-dependence of performance decrements, as the driving task was an hour longer in our study. We found that after sleep restriction and alcohol, deviations from control condition driving simulator performance appeared to emerge only after approximately 30 minutes on task. To explore this further we repeated the statistical analysis of steering deviation, using the same mixed model approach but on data from the first 30 minutes only of the driving task. No

significant condition or group x condition differences were found in keeping with the findings of previous studies. Thus, the shorter driving task used by Desai et al. and Wong et al. may have been insensitive to detect condition-dependent performance decrements between OSA patients and healthy control subjects.

Steering deviation is generally found in driving simulator studies to be highly sensitive to sleepiness in monotonous driving environments (336). It is not surprising therefore, that this parameter was adversely affected in patients with OSA, and more so after both sleep restriction and alcohol. Perhaps surprising was that alcohol, unlike sleep restriction, did not result in a greater steering decrement in OSA patients compared to control subjects. This may reflect the fact that blood-alcohol concentrations decreased during the alcohol-condition drive, in contrast to increasing homeostatic sleep pressure during the sleep restriction drive. Interestingly, while there were no group differences in steering after alcohol, steering deviation progressively increased over time on a background of falling blood-alcohol concentrations. A persistent depression of driving performance following alcohol administration and when blood-alcohol levels have returned toward zero has been observed by others (287) and may warrant advice to OSA patients regarding potential additional driving risks associated with alcohol. The increased crash rate in OSA patients following alcohol and sleep restriction appeared to be due principally to inattention and steering failure. "Off road" episodes accounted for 96% of crashes and prolonged eye closures and microsleeps were more frequent in crash versus non-crash epochs supporting that sleepiness and falling asleep during the driving task importantly contribute to the more frequent simulator crashes (performance failures) observed in OSA patients.

In contrast to steering performance and crash incidence, which was differentially impaired by sleep restriction and alcohol in OSA patients, braking reaction time was not different between OSA patients and control subjects under any of the conditions. Thus, it would seem that OSA patients may not be able to sustain concentration as well as healthy subjects during monotonous tasks, particularly when additionally stressed by alcohol or sleep restriction, but can equally and relatively rapidly activate critical areas of the pre-frontal cortex and engage alerting responses when suddenly presented with novel stimuli (e.g. truck ahead).

Some caution needs to be exercised in extrapolating the findings of this driving simulation study to on-road driving. Nevertheless, driving simulators do measure the main aspects of real driving, including visual tracking and coordination, attention, reaction and vigilance (223, 336). In direct comparison studies, while tending to overestimate some driving abnormalities, simulator results correlate well with on-road driving performance (223). Simulators offer the advantage of assessing driving performance in a safe and controlled environment, particularly in studies such as this where the effects of experimental interventions are unpredictable and potentially severe (i.e. fall asleep crash).

A potential limitation in interpreting the results of this study is that the OSA patients were on average heavier than the control subjects reflecting that obesity is a major cause of OSA, and it is very difficult to find BMI-matched control subjects who do not have sleep disordered breathing. The different body mass indices of the two groups nevertheless raise the possibility that over-weight or obesity rather that

sleep apnoea was responsible for the driving impairments observed in the OSA group. While obese subjects without sleep apnoea have been reported to have disturbed sleep at night and to be more sleepy in the day compared with normal weight subjects (422), we think it is highly unlikely that obesity was responsible for the driving impairments observed amongst the OSA patients in our study. First, obesity *per se* is not known to be a risk factor for motor vehicle accidents and second, a secondary analysis comparing the 10 lightest OSA patients in our study (BMI 26.1 ± 2.0) to the control subjects (BMI 24.5 ± 2.5) showed, as with the main results, significant group, condition, time and group x condition interaction effects on steering deviation (mixed model analysis, all $p<0.05$).

Clinical and public health implications

With a prevalence of OSA of 7% or more amongst the middle-age population, these findings have potentially important implications for patient and public safety (1, 2, 4). It is known that patients with OSA are at increased risk of motor vehicle accidents (34-40, 166). Many patients though, even those with severe OSA, deny symptoms of daytime sleepiness or falling asleep during routine driving. The present study results suggest that some of the increased motor vehicle accident risk observed amongst OSA populations may be attributable to common behaviours such as alcohol consumption and sleep restriction (56, 281, 419, 423) that seem to amplify driving impairment and induce micro-sleeps. Thus, in sleep clinics where there exist substantial waiting lists or delays between diagnosis and treatment it would seem prudent to not only warn patients of the increased risk of

driving accidents, but also the potential additional risks of consuming even small quantities of alcohol, and of restricting their sleep.

The prevalence and severity of OSA are linked to ageing and obesity, both of which are on the increase globally (2, 10). Most OSA patients remain undiagnosed and untreated (3, 100, 410). Reducing the accident risk due to OSA in the general population will therefore be challenging but may ultimately be assisted by public health and self-help campaigns that warn of the likely additional risks of alcohol and sleep loss in people at high risk for OSA such as in obese, middle-aged or elderly snorers. Future epidemiological or case control studies of accidents and OSA should pay specific attention to the possible interactive effects of alcohol and prior sleep time.

In conclusion, we have shown that compared to healthy individuals, OSA patients are more vulnerable to the deleterious effects of low dose alcohol and one night of moderate sleep restriction on various driving performance parameters. Thus, it may be advisable for untreated OSA patients diagnosed with, or showing symptoms of OSA, to avoid even legal doses of alcohol and sleep restriction prior to driving or potentially, before performing other tasks where safety is a factor.

CHAPTER 3. DRIVING SIMULATOR PERFORMANCE REMAINS IMPAIRED AFTER CPAP TREATMENT IN PATIENTS WITH SEVERE OSA

3.1   Introduction

Obstructive sleep apnoea (OSA) is linked to a 2-7 fold increased risk of motor-vehicle accidents, particularly amongst patients with moderate to severe disease (34-40, 166, 424). Community surveys have shown that OSA affects approximately 7% of the middle-aged population (1, 2, 4) with as many as 80% of those affected being undiagnosed (3, 7, 100). Thus, OSA presents a serious public health concern with respect to road safety. These concerns are further increased by recent evidence that OSA patients are more affected by sleep restriction and low dose alcohol than are healthy subjects (425) (see CHAPTER 2).

An important clinical question is to what extent treatment of OSA improves the driving abnormalities and reduces the accident risk associated with OSA. Several studies and a recent meta-analysis (426) support that continuous positive airway pressure (CPAP) treatment improves driving simulator performance (199, 201-204, 427) and reduces accident risk (205-210, 426). Two studies found that CPAP treatment of OSA patients returned driving simulator performance to the level of healthy control subjects (201, 427), while another clinical observational study

reported that CPAP therapy reduced motor vehicle accident rates to the background rate of the general population (208). However, in our view these studies suffered from several important methodological limitations. Short (20 min), divided attention driving simulator tasks were used (201, 427), which may underestimate the driving risk of patients in more ecologically relevant situations, i.e. highway or country road driving. Retrospective comparisons of driving accident rates pre- and post-OSA treatment (426) do not control for other factors such as changes in driving exposure, changes in driver behaviour by virtue of being in a study and other medical treatments. The remaining driving simulator studies did not compare the results in CPAP-treated patients with non-apnoeic control subjects, and thus do not address if CPAP treatment completely corrects driving disturbance in OSA patients. Several recent studies suggest that CPAP treatment may be only partially effective in restoring cognitive function (47, 50, 54, 211, 428), cortical activation (51, 54) and daytime somnolence (52, 53) even for subjects who comply optimally with therapy (53).

The purpose of the present study was therefore to measure the effects of ~3 months of CPAP treatment on driving simulator performance in patients with severe, previously untreated OSA. OSA subject results were compared with those of healthy control subjects matched for age and gender. In contrast to previous driving simulator studies using short divided attention driving scenarios (199, 201-204, 427) we chose a relatively long simulated driving task analogous to a monotonous country drive. Since we had previously shown during simulated driving using the same protocol that, compared to healthy subjects, untreated OSA patients exhibit greater vulnerability to the detrimental effects of sleep restriction

and alcohol (425), we also compared the effects of CPAP treatment on driving simulator performance before and after these stressors. We postulated that CPAP treatment would improve but not normalise driving performance in OSA patients. The baseline OSA and control subject data reported in the present study are a sub-group of an earlier, larger report on the effects of alcohol and sleep restriction on simulator driving performance in OSA (425) (see CHAPTER 2).

3.2   Methods

The study was approved by the Human Research Ethics Committees of the Repatriation General Hospital, University of South Australia and University of Adelaide. Subjects were introduced to the study objectives and protocol during an introductory session, gave written informed consent and were remunerated (controls subjects AU $400, OSA patients AU $200) for their participation. This study was an investigator designed and conducted trial funded by the Australian National Health and Medical Research Council (grant #390400).

3.2.1   Study design

This study was designed to test the effects of approximately three months of CPAP treatment on driving simulator performance in patients with severe OSA (apnoea-hypopnoea index >45 events/hr of sleep). All participants were studied under three separate conditions in random order. Driving simulator sessions began at 2:00 pm and were conducted at least 5 days apart to avoid potential carry over effects from prior interventions. The conditions included 1) normal night-time sleep, 2) a single

night of sleep restriction (4 hours time in bed from 2:00-6:00 am) and 3) acute administration of low-dose alcohol (target blood-alcohol concentration 0.05 g/dL). Baseline driving performance measurements were collected in all subjects and repeated after approximately three months follow-up. During the follow-up period OSA patients were treated with CPAP and control subjects continued their normal activities.

3.2.2 Subject selection

Patients with severe OSA who were willing to commence CPAP, and healthy control subjects without OSA, who were all prepared to undertake repeat follow-up experiments, were recruited from an earlier study (425). OSA patients were recruited following diagnostic polysomnography. Neither they nor their referring physician had specific concerns about their driving. To minimize selection bias, patients were told the study was to investigate general neurocognitive performance and were unaware that the trial measured driving performance until after they agreed to attend an introduction session. Control subjects matched for age and gender were recruited from the general population through newspaper advertisements, which provided only a general description of the study and made no mention of driving performance measures.

Exclusion criteria were as follows: professional driver or shift worker; history of driving <2 yrs or <2 hrs per week; significant medical co-morbidities (e.g. cardiac or respiratory failure), periodic limb movement disorder (periodic limb movement arousal index >5 /hr), past head injury or depression; use of alertness altering

prescription and non-prescription medications that may influence sleep and daytime behavioural function (e.g. antihistamines, opiates, antidepressants); history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they obtained higher than normal scores on sleep quality (Pittsburgh Sleep Quality Index > 5) and daytime drowsiness (Epworth Sleepiness Scale > 10) questionnaires.

3.2.3   Subject assessment

Prior to driving simulator assessment, all participants completed questionnaires assessing general health (medical conditions, medication, alcohol, caffeine and drug use), sleep quality/habits and daytime drowsiness using the Pittsburgh Sleep Quality Index (412), and the Epworth Sleepiness Scale (125). All participants had overnight standard diagnostic polysomnography with the following recordings: electroencephalography (C3/A2, C4/A1 lead placements), left and right electro-oculograms, submental electromyogram, nasal cannula to measure nasal pressure, limb movement sensors, inductive plethysmography for thoraco-abdominal motion, lead II electrocardiography and arterial oxygen saturation (finger pulse oximetry). All signals were digitized and stored using a Compumedics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardised methods (413, 414). Apneas and hypopnoea were scored according to internationally agreed "Chicago" criteria (414, 429). The OSA severity cut offs adopted by our laboratory were: normal (AHI<15 events/hour), mild OSA (AHI≥15 events/hour), moderate OSA (AHI≥30 events/hour) and severe OSA (AHI≥45 events/hour) bearing in mind that AHI cut-off values of 15 and 30 events/hour using

Chicago scoring criteria correspond to approximately 5 and 10 events/hour respectively using the recent AASM "Recommended" scoring criteria (429). Diagnostic sleep study variables were calculated for the full night of polysomnography. For the CPAP titration study, AHI, oxygen desaturation and arousal indices were calculated over the period of sleep where the CPAP level was closest (± 1 cmH_2O) to that prescribed by the reporting physician in order to determine AHI under therapeutic pressure. All studies were scored by one staff member certified by the Board of Registered Polysomnographic Technicians.

3.2.4   Treatment protocol

After the baseline experimental driving simulator sessions, subjects with severe OSA underwent a laboratory based CPAP titration polysomnography to establish the therapeutic CPAP setting. All OSA patients were followed up by their referring physician and underwent CPAP education. The education session involved a clinic appointment with a qualified CPAP nurse who provided clinical information regarding the purpose and effectiveness of CPAP therapy and provided comprehensive patient training to facilitate effective and adherent home use. In addition, all OSA patients were fitted with a suitable mask and issued a fixed-setting CPAP machine (ResMed S8 Lightweight, NSW, Australia). OSA patients were encouraged to use their CPAP machines as much as possible and their compliance and clinical treatment were monitored by a CPAP nurse at 1 and ~3 months after commencement of treatment. The average daily compliance with CPAP therapy over ~3 months was downloaded from the inbuilt timer in each CPAP machine at each follow-up visit. To control for regression to the mean and

possible practice effects, control subjects also had repeat driving simulator testing after approximately three months. Control subjects were not issued a CPAP or sham CPAP, but were asked to continue their normal activities during this period.

3.2.5   Main outcome measures

All outcome measures were assessed at baseline and the ~3 month follow-up visit. Driving performance was assessed as previously described (425) using the AusEd driving simulator (Woolcock Institute for Medical Research, Sydney, Australia) which ran on a purpose-built Windows 2000 workstation (Microsoft, Redmond, Washington), 19-inch monitor (BenQ FP937s, Taipei, Taiwan), MOMO steering wheel and pedals (Logitech, Fremont, California). The chosen simulated driving task was a 90-minute country night-time drive on a predominantly straight dual-lane road with bends occurring at 5 minute intervals, each taking approximately 10 seconds to negotiate. There was no oncoming traffic or traffic lights. The main outcome measures were the driving simulator performance parameters of lateral steering deviation, braking reaction time and crash frequency.

Steering deviation was measured from the average deviation in centimeters from the driver's median lane position sampled at 30Hz. Subjects were instructed to maintain speed within 60-80 km/h, but to apply the brakes as quickly as possible whenever a slow moving truck presented ahead in the driving lane. Trucks appeared a total of 7 times during the drive and the mean braking reaction time was computed for the 7 truck-ahead incidents. Crashes occurring throughout the driving task were defined as: car deviating from the road (all 4 wheels completely

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off the road), collision with a truck, or if the car was stationary for >3 seconds. The main outcome measure for crashes was the number of controls and OSA patients who experienced at least one crash incident.

3.2.6 Detailed experimental procedures

Subjects' sleep patterns and duration were monitored using sleep diaries and actigraphy monitors (Actiwatch, Mini-Mitter Co Inc, Model-AW64, Oregon, USA) worn from at least 5 days prior to beginning the experiments until study completion to estimate sleep/wake timing, to ensure compliance with the sleep restriction protocol and to ensure subjects did not nap in the 24 hours prior to the experiments (416). In addition, during the night of sleep restriction, participants left a message on a time/date stamped answering machine at bedtime (2:00 am) and wake time (6:00 am), again to ensure compliance with the protocol. Subjects were instructed to abstain from alcohol, caffeinated beverages, not to nap for 24 hours prior to each experimental session and to consume breakfast before 9:00 am on the day of each experiment. Participants were transported by taxi to and from the laboratory.

Upon arrival at the laboratory at 12:00 pm, each subject's blood-alcohol concentration was estimated using a calibrated breathalyzer (Dräger Alcotest7410Plus), sleep diaries were collected, activity monitor data downloaded and the answering machine checked for compliance with the sleeping regime.

Subjects consumed a standardised lunch with a glass of water at 12:15 pm before electrode application for electro-encephalographic monitoring (C3/A2, C4/A1,

O1/A2, O2/A1 and EOG) of drowsiness throughout the driving test. At 1:30 pm all subjects consumed either 375 ml of sugar-free, non-caffeinated control soft drink (normal and restricted sleep conditions) or a volume of 40% Vodka calculated to achieve a target blood-alcohol concentration of 0.05 g/dL mixed with the same soft drink. Target blood alcohol concentrations were achieved using doses of alcohol calculated as previously described in CHAPTER 2 (425).

3.2.7 Data analysis and statistics

Anthropometric characteristics, sleep study variables, driving experience, caffeine and alcohol consumption were compared between groups using unpaired Student t-tests. Paired t-tests were used to examine within-group differences between baseline vs follow-up evaluation measurements. Steering deviation data, excluding the first minute of acceleration and initial lane positioning, were divided and averaged into 18 intervals for the remaining 89 minutes of the drive. To address the question of whether or not treatment completely resolves steering deviation in OSA patients following 3 months treatment and to account for known time on task effects (425), linear mixed model analysis was used to examine fixed effects of group (OSA vs controls) time on task (18 intervals), follow-up period (baseline vs follow-up) and all possible interactions (SPSS Inc, Version 16.0, Chicago). Subject identity was specified as a random intercept term assumed constant across conditions and an autoregressive covariance structure (AR1) was used to adjust for serial correlation across the 18 time points. To address the question of whether or not treatment reduces OSA patient vulnerability to sleep restriction and alcohol, a similar linear mixed model analysis was used with the addition of condition (normal

sleep, sleep restriction and alcohol) as a fixed effect. Braking reaction time was assessed via linear mixed model analysis with the same model parameters. In all cases, the fully saturated models were run first, followed by removal of non-significant interaction terms. The primary hypotheses were evaluated on the basis of main and interaction effects and, where relevant in the case of statistically significant effects, custom post-hoc contrasts adjusted for multiple comparisons using Bonferroni correction.

Chi^2 tests were used to compare the proportion of control versus OSA participants exhibiting at least one crash at baseline and follow-up in all conditions. Binary logistic regression (GEE for longitudinal/repeated measures data, clustering on subject) (417, 418) was conducted to investigate condition and treatment effects on the presence of at least one crash [no/yes] in OSA patients (Stata v10.0). Given that only one control subject had a crash at follow-up, group effects could not meaningfully be examined in this analysis. Condition and treatment were specified as predictor variables [normal sleep/sleep-restriction/alcohol and baseline/follow-up] and each patient appeared in the model three times (one observation per condition). In addition, a Cox survival model (with data clustered on subject identity) was constructed to investigate the impact of condition and treatment on time to first crash. As there was only one crash in the control group, this analysis also focused on the patients only. The model included predictors of treatment (baseline/follow-up), condition (normal sleep/sleep restriction/alcohol) and a treatment by condition interaction. Values are presented as means (SD) or [95% confidence interval] unless otherwise indicated, with $p < 0.05$ considered statistically significant.

3.3   Results

Eleven subjects with severe OSA and nine control subjects were studied and their anthropometric characteristics, sleep study results, caffeine and alcohol consumption and medication use are presented in Table 3.1. It was not possible to precisely schedule 3 months follow up for each subject. Mean follow-up time was 103 (range 76-129) days after CPAP treatment was initiated in the patient group and 113 (94-152) days after baseline assessments in the control group. Estimated sleep time (actigraphy) during normal sleep, restricted sleep and alcohol conditions, average alcohol ingested and blood-alcohol concentrations before and after the driving task are provided in Table 3.2. All subjects complied with the sleep restriction protocol and exhibited a blood-alcohol concentration of 0.0 g/dL upon arrival to the laboratory on each experimental day. The level of experimentally induced sleep restriction and blood alcohol concentration at baseline and follow-up were not different between groups (Table 3.2). Mean±SD CPAP compliance in the patient group was high at 6.0 ± 1.4 hours/night.

Table 3.1 Participant anthropometric characteristics, polysomnography results, and medication use

Groups	Control (n=9)		OSA (n=11)	
N Males/Females	7/2		10/1	
Age (yrs)	53.2 (9.6)		54.2 (13.0)	
Body-Mass Index (kg/m^2)	24.3 (2.6)		35.9 (9.6) *	
Sleep Parameters	**Diagnostic PSG**	**CPAP Titration**	**Diagnostic PSG**	**CPAP Titration**
Apnea Hypopnoea Index (AHI: events/hour)	6.6 (3.8)	-	69.1 (20.1)*	5.3 (5.7)#
% of sleep time with SaO$_2$<90%	0 (0)	-	13.7 (17.8) *	0.1 (0.3) #
Average SaO$_2$ desaturation (%)	2.2 (0.4)	-	5.2 (2.8) *	2.0 (0.4) #
Respiratory Arousal Index (Arousals/hr)	1.6 (1.1)	-	25.9 (14.9) *	0.5 (0.8) # *
Limb Movement Arousals (Arousals/hour)	4.1 (3.0)	-	3.9 (4.3)	1.8 (2.6)
Arousal Index (Arousals/hour)	13.5 (5.8)	-	39.1 (16.3) *	11.6 (7.3) #
Sleep Stage 1 (min)	26.8 (11.5)	-	65.4 (55.6) *	24.4 (17.6) #
Sleep Stage 2 (min)	171.8 (42.6)	-	167.0 (28.8)	171.4 (37.1)
Sleep Stage 3 (min)	48.6 (23.3)	-	40.0 (23.3)	51.1 (24.7)
Sleep Stage 4 (min)	7.2 (7.8)	-	13.3 (16.6)	21.5 (25.6)
REM Sleep (min)	62.2 (26.2)	-	54.3 (23.7)	72.0 (31.3)
Sleep Efficiency (%)	71.0 (15.6)	-	78.7 (11.3)	80.1 (11.0)
	Baseline	**3 months follow up**	**Baseline**	**3 months follow up**
Epworth Sleepiness Scale	4.9 (2.6)	4.4 (2.2)	9.7 (5.6) *	7.0 (4.0)
Pittsburgh Sleep Quality Index	2.6 (0.9)		9.5 (6.0) *	
Driving History (kilometers/year)	11525 (4912)		18131(4946) *	
Education (years completed)	13.4 (3.1)		11.4 (3.0)	
Caffeine Consumption (cup or equivalent/day)	2.3 (1.1)		3.5 (1.6)	
Smoking (cigs/day)	0.0 (0.0)		2.1 (4.9)	
Habitual Alcohol Intake (Std Drinks/week)	10.7 (4.5)		11.1 (14.6)	
Medication Use (# of people by condition)				
Hypertension	0		4	
Hyperlipidemia	0		1	
Diabetes	0		0	
Gastro-Esophageal Reflux Disease	0		2	
Arthrititis	0		1	
Thyroid Disease	0		0	
Asthma	0		1	
Gout	0		1	
Hay fever	0		0	

Values are mean (SD), *=between group, #=within group p<0.05.

Table 3.2   Actigraphy estimated sleep time, average alcohol consumed and blood alcohol concentration before and after the driving task

Group	Controls		OSA	
Evaluation	**Baseline**	**3 Month Follow-up**	**Baseline**	**3 Month Follow-up**
Estimated Sleep Time (mins				
Normal Sleep	459 (66)	473 (51)	443 (59)	438 (65)
Sleep Restriction	212 (12)	212 (13)	216 (65)	225 (30)
Alcohol	471 (53)	473 (32)	416 (67)	430 (57) *
Alcohol consumed during study (g)	38.7 (4.4)	39.1 (4.9)	45.6 (6.9)*	48.3 (6.2) *
Blood Alcohol Concentration (g/dL)				
2:00 pm (start of driving task)	0.042 (0.009)	0.046 (0.013)	0.045 (0.016)	0.038 (0.013)
3:30 pm (end of driving task)	0.019 (0.006)	0.021(0.010)	0.026 (0.013)	0.016 (0.013)

Values are mean (SD) at baseline and 3 month follow-up evaluations, *=between group difference within the same period of evaluation, p<0.05.

3.3.1   Driving simulator performance

3.3.1.1   Steering deviation

The four way (group x condition x time x treatment) interaction term was not statistically significant in the fully saturated model and was removed for the remaining analysis. In the final model there were several significant main and interaction effects indicating treatment (baseline vs follow-up), condition and time dependent differences between groups in steering deviation responses. The final model showed statistically significant effects of group ($F_{[1,18]}=7.0$, $p<0.017$), condition ($F_{[2,309]}=28.2$, $p<0.001$), time ($F_{[17,719]}=5.8$, $p<0.001$), treatment ($F_{[1,619]}=35.2$, $p<0.001$), group x condition ($F_{[2,309]}=8.2$, $p<0.001$), group x treatment ($F_{[1,619]}=124.0$, $p<0.001$), condition x treatment ($F_{[2,645]}=7.3$, $p<0.01$), group x condition x treatment ($F_{[2,645]}=9.6$, $p<0.001$) and group x time x treatment ($F_{[17,1178]}=1.8$, $p=0.022$).

Between group differences in steering deviation responses over time at baseline and follow-up are shown in Figure 3.1 (averaged across conditions). Given the absence of any further interactions involving time, all remaining contrasts were averaged across time (Figure 3.2). At baseline evaluation, untreated OSA patients demonstrated statistically significantly greater steering deviation compared to controls under all conditions combined (mean over the full drive in all conditions; OSA group, 57.2 [95% CI, 48.4 to 65.9] cm vs control group, 36.0 [26.4 to 45.7] cm, $p<0.01$) and separately (normal sleep, sleep restriction and alcohol; all $p<0.01$). Compared to normal sleep, sleep restriction resulted in a statistically significantly

greater increase in steering deviation in the OSA compared to the control group (mean increase across the whole drive; OSA group, 11.4 [8.8 to 13.9] cm vs control group, 1.2 [1.6 to 3.9] cm, p<0.001). Similarly, alcohol resulted in a statistically significantly greater increase in steering deviation in the OSA group compared to control subjects (mean increase across the whole drive; OSA group, 10.5 [8.0 to 13.0] cm, vs control group 2.2 [0.6 to 5.0] cm, p<0.001).

At follow-up evaluation, CPAP treated OSA patients demonstrated a statistically significant improvement in steering deviation under all conditions combined (mean decrease calculated over the full drive across all conditions, 7.4 [6.2 to 8.5] cm, p<0.01) and in each condition separately (all p<0.01). Steering deviation averaged across each drive in control subjects was not different between baseline versus follow-up under normal sleep or alcohol conditions (p>0.1), but showed minor worsening at follow-up in the sleep restriction condition (baseline evaluation, 36.1 [26.3 to 45.9] cm vs follow-up, 40.2 [30.4 to 49.9] cm, p<0.001).

Despite improvements, steering deviation averaged across each drive remained statistically significantly greater in treated OSA patients compared to controls under normal sleep (OSA group, 46.8 [38.0 to 55.7] cm vs control group, 36.1 [26.3 to 45.9] cm, p=0.025) and sleep restriction (OSA group, 53.4 [44.6 to 62.3] cm vs control group 40.2 [30.4 to 49.9] cm, p=0.048), but not alcohol (p=0.1). At follow-up the increase in steering deviation after sleep restriction and alcohol compared to normal sleep was not statistically significantly different between OSA patients and controls (average increase compared to normal sleep with sleep restriction; OSA group, 6.6 [4.1 to 9.2] cm vs control group, 4.1 [1.2 to 6.8] cm, p=0.176: with

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alcohol; OSA group, 2.4 [0.3 to 5.0] cm vs control group, 2.5 [0.3 to 5.3] cm, p=0.968).

Figure 3.1 Steering deviation at baseline and follow-up evaluations
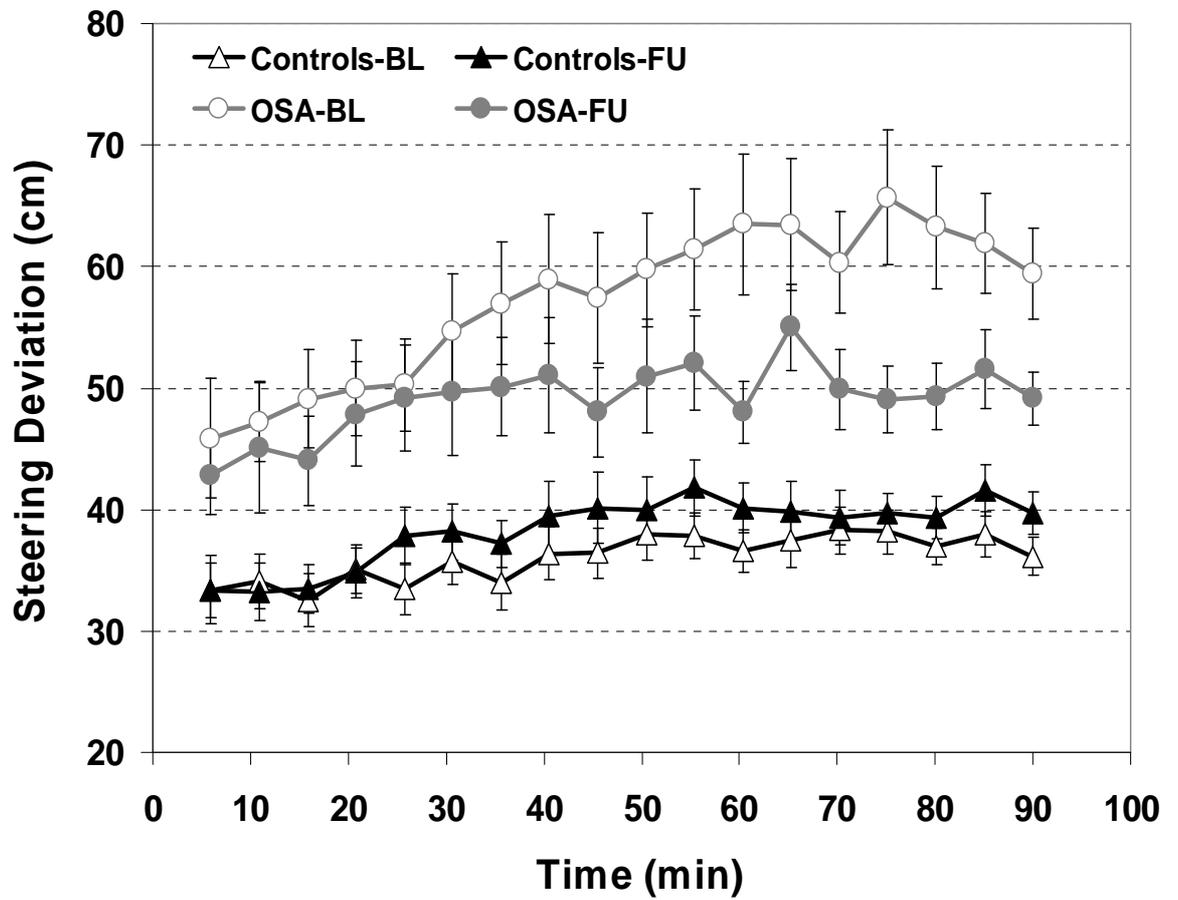
Mean (SEM) steering deviation throughout the 90 minute drive collapsed across the three experimental conditions in control and OSA patients at baseline evaluation (BL) and 3 months follow-up (FU).

Figure 3.2 Steering deviation under the three experimental conditions at baseline and follow-up evaluation
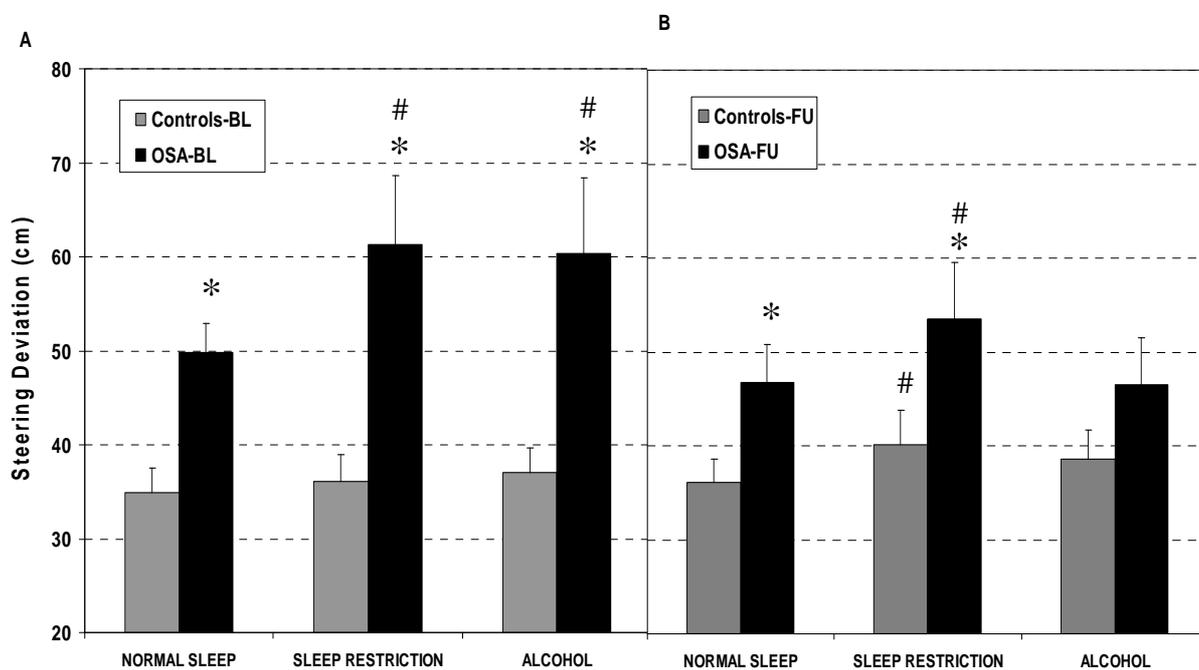
Mean (SEM) steering deviation during 90 minute simulator drives in OSA and control groups under normal sleep, sleep restriction and alcohol conditions at (A) baseline evaluation (BL) and (B) 3 months follow-up (FU). Symbols indicate significant difference, $p<0.05$: * = OSA different from controls, # = Within group difference from normal sleep.

3.3.1.2　　　Braking reaction time and crashes

Braking reaction time was not statistically significantly different between groups, conditions, or treatments and there were no significant interaction effects. The proportion of OSA patients and controls experiencing at least one crash in each condition is shown in Table 3.3. In total there were 90 crashes and all were off-road events. Across all conditions, a statistically significantly higher proportion of OSA patients crashed 1 or more times compared to controls at baseline ($p=0.003$) and after 3 months follow-up ($p=0.028$). Only a single control subject crashed and this was at the 3-month follow-up assessment. Within the OSA group, the proportion of patients exhibiting at least one crash was not different between baseline versus follow-up evaluation. In logistic regression, there were no statistically significant condition or treatment effects in the proportion of OSA patients exhibiting at least one crash. Although survival plots suggested slightly improved crash free survival (ie subjects appeared to drive for longer before experiencing a crash event) following treatment and during baseline compared to sleep loss and alcohol conditions, there were no statistically significant treatment or condition effects on crash free survival.

Table 3.3 Proportion and percentage of participants exhibiting at least one crash during 90 minute simulator driving at baseline and 3 month follow-up evaluations

Group	Controls		OSA	
	Baseline	**3 months follow-up**	**Baseline**	**3 months follow-up**
Normal Sleep	0/9 (0%)	0/9 (0%)	2/11 (18%)	2/11 (18%)
Sleep Restriction	0/9 (0%)	1/9 (11%)	5/11 (45%)	1/11 (9%)
Alcohol	0/9 (0%)	0/9 (0%)	4/11 (36%)	4/11 (36%)

3.4   Discussion

Similar to previous reports (34, 36, 166, 425) this study has demonstrated that driving simulator performance is impaired in subjects with untreated severe OSA compared to healthy control participants. Furthermore, in agreement with the study reported in CHAPTER 2 (425), OSA patients exposed to additional sleep restriction and alcohol prior to CPAP treatment showed greater vulnerability to these stressors compared to controls. The important new findings of this study are that while some aspects of driving simulator performance among OSA patients improved after ~3 months of CPAP treatment, driving ability remained significantly impaired compared with age and gender matched healthy controls. Treatment did appear to reduce the increased vulnerability to sleep loss and alcohol that was observed among OSA patients before treatment. However, CPAP treatment resulted in only partial improvement in steering deviation and there was no significant reduction in the proportion of OSA patients experiencing one or more crashes. There were no significant group, condition or treatment dependent changes in braking reaction time, which may reflect the small number of reaction time measurements collected during the drive (7 truck presentations in 90 min). Alternatively, the lack of differences in reaction time may suggest that controls and OSA patients were similarly able to relatively rapidly activate critical cortical areas needed for alerting responses when suddenly presented with novel stimuli (e.g. truck ahead).

Our study is the first to directly compare prolonged (90 min) driving simulator performance in CPAP-treated OSA patients with age and gender matched control subjects. However, in discussing the results of active versus sham CPAP treatment

in OSA patients, Hack et al. (199) noted that driving performance in the actively treated group (mean CPAP use 5.6 hr/night) did not quite fall to figures obtained previously in the same laboratory in a matched control group using the same simulator (36). Also, several other studies have shown only partial recovery of daytime sleepiness and no significant improvements in neurophysiological function following treatment of OSA (47, 48, 50-54), potentially contributing to persistent driving impairment. One of the latter studies (53) demonstrated that approximately 60% of OSA patients had persistent daytime sleepiness (multiple sleep latency test sleep onset time <7.5 min) despite 3 months of optimal (i.e. >6 hours/night) CPAP treatment. There are several other driving simulator studies (199, 201-204, 427) that have shown improvements in driving performance in OSA patients days to months after initiation of CPAP therapy. However, all but two of these studies (201, 427) failed to include a healthy control comparator group making it difficult to know whether driving simulator performance was normalised by CPAP treatment. One of the simulator studies that did include a healthy control group showed that after a mean of 9.2 months of CPAP treatment, lane position variability during a 20 min driving task was the same in OSA patients as in healthy controls (201). Results from another study that used another 20 min divided attention driving simulator task and included a healthy control group also demonstrated normalisation of driving simulator performance in OSA patients treated for 3 months (427). An important methodological difference that could explain contrasting results with the current study is that we assessed primary vehicle control (steering deviation) during a 90 minute simulation of monotonous country driving in contrast to the 20 min divided attention oriented driving simulator tasks used by George et al. (201) and Mazza et al. (427) The authors of the latter study acknowledged that although deficits in

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driving simulator performance normalised after treatment on a 20 min divided attention task, this may not take into account the effects of cumulative soporific factors associated with longer distance driving where impairments may become more severe. Indeed, we have previously demonstrated that steering deviation continues to deteriorate throughout a 90 minute monotonous driving test, beyond what is evident within the first 30 minutes (425). Therefore, shorter driving tests may miss driving impairment occurring later during a long drive in untreated OSA patients. In addition, residual driving difficulties following CPAP treatment may be masked by alerting effects of divided attention tasks (430). Furthermore, normalisation in driving performance reported by George et al. (201) was observed in mildly sleepy OSA patients (mean multiple sleep latency of 7.2 min before treatment) and partly explained by an improvement in objective sleepiness in treated subjects. However, the driving performance deficits and improvements with CPAP observed by Mazza et al. (427) were in OSA patients who were not objectively sleepy on the Oxford sleep resistance test (OsleR). Although objective sleepiness was not assessed in the present study, subjective sleepiness before and after treatment was generally within normal limits in our OSA patients, raising the importance of our finding of residual driving simulator impairment in relatively non-sleepy OSA patients.

There are several possible explanations for residual driving simulator performance abnormalities observed amongst OSA patients after CPAP treatment in our study. Perhaps most likely is that OSA produces some irreversible effects on neurocognitive function, or that genetic factors simultaneously influence OSA propensity and sensorimotor systems involved in driving. Alternative explanations

include that the treatment period may have been too short, CPAP compliance inadequate to show full benefits, or there may be effects of co-morbidities or perhaps obesity *per se* in OSA compared to control participants. Sub-optimal treatment appears unlikely given that the AHI of OSA patients during CPAP titration was not different from the AHI of control subjects without CPAP, and previous data showing that benefits of 3 months of CPAP treatment on the percentage of subjects achieving normal objective (Multiple Sleep Latency) sleepiness scores plateau at adherence rates of 6hrs/night (53). One small uncontrolled study found that residual sleepiness after 7 weeks of CPAP treatment was not evident when affected subjects were re-studied ~4 years later (431), perhaps supporting that more than 3-months of CPAP therapy is needed for full reversal of neurocognitive deficits induced by OSA. Some evidence suggests that obesity without OSA is associated with excessive daytime sleepiness (422), but we are not aware of any data suggesting that obesity *per se* or the types of co-morbidities present in our OSA patients, or their treatments, impact on driving performance. We were careful to exclude patients with co-morbidities and medications known to effect driving such as anti-depressants and opioids. Some studies show that hypoxia may play an important role in causing persistent cognitive performance impairments in treated OSA patients independent of sleepiness (47, 432). This is further supported by recent studies showing structural changes in central nervous system white and grey matter among OSA patients (25, 31), suggesting that some neurocognitive deficits observed in OSA patients may be irreversible by the time of diagnosis. While these mechanistic questions remain unresolved, we believe, based on current clinical research experience (46, 53), that the average CPAP adherence of 6 hrs/night achieved by subjects in the present study is relatively high, and likely

the most that can be expected in this patient group given the current state of CPAP technology and practices. Therefore, our data showing residual driving impairment after 3 months of CPAP is highly pertinent to practitioners in this field. However, further studies are needed to confirm these findings and establish mechanisms.

Several epidemiological studies recently reviewed in a comprehensive meta-analysis (426) have reported reduced motor vehicle accident rates among CPAP treated OSA patients by comparing accident rates before and after treatment (205-210). Only two of these studies included a concurrently assessed control population to allow assessment of the degree of normalisation of accident rates in CPAP-treated subjects (205, 208). These studies reached somewhat different conclusions, with one study (208) showing accident rates reduced among CPAP treated patients to the level of controls, while the other (205) observed accident rate reductions in both treated patients and re-evaluated controls. The authors of the latter study (205) concluded that a period of CPAP treatment was associated with reduced accidents in the OSA group, but that this could not necessarily be attributed to CPAP *per se*. OSA patients may modify their driving or other behaviours by virtue of being in a clinical study examining accident risk (i.e. the Hawthorne effect) (426). This potentially important confounding factor is shared by all retrospective epidemiological studies. Thus, these clinical epidemiological studies suggest that CPAP is associated with a significant reduction in accident risk but whether this is the result of CPAP therapy *per se* or other treatments or behavioural changes associated with OSA diagnosis and management is not known. Whether there remains an increased accident risk after CPAP therapy

particularly in situations conducive to fall asleep accidents also remains unknown, although the data from this study suggest it may remain increased.

3.4.1 Study limitations

There are some limitations that need to be considered when interpreting the findings of this study. The sample size was relatively small, but was nevertheless sufficient to detect residual between group differences at follow-up with the repeated–measures design. However, a larger sample would be required to assess relationships between various clinical factors such as self-reported sleepiness and medical co-morbidities versus residual driving performance impairment after CPAP treatment.

Some caution needs to be exercised in extrapolating the findings of this driving simulation study to on-road driving. Driving simulators measure the main aspects of real driving, including visual tracking and coordination, attention, reaction and vigilance (223, 336). In direct comparison studies, while tending to overestimate some driving abnormalities, simulator results correlate well with on-road driving performance (223-226). It is difficult to know if the AusEd simulator is able to predict real world motor vehicle accident risk and further studies are required to address this important question. However, the AusEd driving simulator is not fundamentally different to other research driving simulators and has been previously validated and shown to be sensitive to fatigue and alerting/sedating substances (e.g. caffeine, alcohol and benzodiazepines) in a range of experimental settings (55, 73, 77, 79, 415, 425). Ours is the first study in OSA to use such a

lengthy driving simulator task. It is possible therefore that our results may have been due to poor subject motivation or co-operation in completing the 90-minute monotonous driving simulator task, but we found no evidence of this. Patients appeared to co-operate fully with the procedures and none requested the task be terminated early because of boredom, fatigue, motion sickness or any other factor. Simulators offer the advantage of assessing driving performance in a safe and well controlled environment, particularly in studies such as this where the effects of experimental interventions are unpredictable and potentially severe (i.e. fall asleep crash). Furthermore, we believe that prolonged monotonous driving tasks that simulate country driving are likely to be more relevant when assessing crash risk in OSA than relatively short divided attention tasks.

3.4.2   Clinical and public health implications

Most studies, including our own, conclude that CPAP treatment of OSA results in an improvement in driving performance and reduction in accident risk. Taken together with other studies showing persistent sleepiness and neurocognitive deficits after several months of apparently optimal CPAP treatment, the findings of this driving simulator study suggest that driving impairment during long drives persists in severe OSA patients optimally treated with CPAP. Further similar controlled studies are needed to confirm these findings and to explore whether persistent driving simulator abnormalities in CPAP-treated OSA patients are associated with increased on-road motor vehicle accident risk.

CHAPTER 4. EARLY AND LATE AUDITORY EVENT RELATED POTENTIALS REMAIN ABNORMAL DESPITE OPTIMAL CPAP TREATMENT IN PATIENTS WITH SEVERE OBSTUCTIVE SLEEP APNOEA

4.1   Introduction

Obstructive sleep apnoea (OSA) affects up to10% of middle aged adults (1, 4) and has been consistently linked to deficits in executive function (23, 362), driving performance (34, 166) and heightened motor vehicle accident risk (39, 40). In addition, the study reported in CHAPTER 2 (425) found that compared to controls, driving simulator impairments in OSA patients are further exacerbated by additional sleep loss or alcohol. Until recently, it was thought that neurobehavioural effects of OSA could be reversed completely by OSA treatment. For example, a number of reports suggest that excessive daytime sleepiness (433, 434), cognitive function (50, 435) and driving simulator performance (201, 427) return to normal levels in CPAP treated OSA patients. However, a growing body of more recent evidence suggests that sleepiness (52, 53) and cognitive executive function (50, 211, 428) do not return to the level of healthy controls, even when OSA patients are optimally treated with CPAP (53).

Event related potentials (ERPs) provide objective markers of cortical information processing (144, 145) and are sensitive to the state of arousal, attention and vigilance (148, 436), as well as cognitive deficits in many neurological conditions (144, 151) and sleep deprivation/fragmentation (152, 437). Several studies have demonstrated ERP abnormalities in OSA patients (51, 54, 136-142), particularly the P3 component which is believed to reflect the timing and efficiency of higher order cognitive information processing required to detect and respond to target stimuli (144, 146). Persistent P3 abnormalities in CPAP treated OSA patients have been reported in several studies (51, 54, 136-138), suggesting a component of irreversible neurocognitive deficit in OSA. However, the interpretations of these findings and across study comparisons are problematic due to a number of methodological differences and limitations. For example, CPAP adherence is generally not reported (51, 136-138), making it hard to exclude inadequate treatment as the cause of persistent ERP abnormalities in CPAP treated OSA patients. Also, there are inadequate control data in previous studies. None report nocturnal polysomnographic measures or sleep duration prior to ERP testing for the control group (51, 54, 136-138), and three studies (51, 54, 137) relied on historical control ERP data from separate studies. In three studies (51, 54, 136), it was unclear if the time of ERP recording was matched between patients and controls, and in another if the controls were age matched (137). These factors are important given recent evidence showing that ERPs vary with increasing age (156, 438) and time of day (139, 144). In recent reviews, Polich et al. (144, 145) highlight that P3 is influenced by many exogenous and endogenous biological determinants (e.g. age, circadian factors, fatigue, food/drink intake and prior sleep), supporting that

matching of groups and experimental conditions is important when comparing ERPs in patient and control populations.

Very few studies have examined the effects of OSA treatment on early ERP components that precede the P3, such as N1 (automatic stimulus detection) (154, 155), P2 (classification/identification and inhibition processes) (156, 157) and N2 (mismatch detection processes) (154, 159). Available evidence suggests that ERP components, although representing distinct stages of information processing (157, 160), are all part of a complex chain of interdependent cortical information processing events that should be considered as a whole rather then in isolation (157). These early components have been found to be sensitive to an individual's state of arousal (155) and sleep deprivation (152), and abnormalities have been reported in untreated OSA (139, 141). However, only two early studies (136, 137) have examined the effects of OSA treatment on early ERP components, and the adequacy of control data remains unclear in both.

Thus, this study aimed to assess the effects of ~3 months of optimal CPAP treatment on the N1, P2, N2 and P3 components of auditory ERP (AERP) waveforms in severe OSA patients compared to age and gender matched controls. Both OSA patients and controls were studied at baseline and after ~3 months, with OSA patients treated with CPAP during this period, and with follow-up measurements in the control group to allow evaluation of possible practice or time effects that may confound inferences regarding treatment. We postulated that compared to controls, the N1, P2, N2 and P3 AERP waveforms would be significantly delayed and reduced in amplitude in severe OSA patients before

CPAP treatment, and would improve but not normalise to the level of healthy matched controls following optimal CPAP treatment.

4.2 Methods

The study was approved by the Human Research Ethics Committees of the Repatriation General Hospital, University of South Australia and University of Adelaide. Subjects were introduced to the study objectives and protocol during an introductory session, gave written informed consent and were remunerated for their participation. This study was an investigator designed and conducted trial funded by the Australian National Health and Medical Research Council (grant #390400).

4.2.1 Subject selection and screening

OSA patients were recruited following diagnostic polysomnography at the Adelaide Institute for Sleep Health laboratory. Control subjects matched for age and gender were recruited from the general population through newspaper advertisements. Exclusion criteria for both groups were as follows: professional drivers, shift workers; history of driving <2 yrs or <2 hrs per week; significant medical co-morbidities (e.g. cardiac or respiratory failure), periodic limb movement disorder (periodic limb movement arousal index >5 /hr), past head injury or depression; use of alertness altering prescription or non-prescription medications that may influence sleep and ERP (e.g. antihistamines, opiates, antidepressants); history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they obtained higher than normal scores on sleep quality (Pittsburgh Sleep Quality

Index > 5) and daytime drowsiness (Epworth Sleepiness Scale > 10) questionnaires. The subjects in the current study were part of a previously reported study that investigated driving simulator performance in OSA patients (425) (see CHAPTER 2). Only patients with severe OSA were invited to participate in the present study. Results are reported for OSA and control subjects who agreed to have ERP measurements at baseline and 3 months later and, in the case of OSA patients, who also agreed to use CPAP treatment during the follow-up period.

Prior to AERP assessments, all participants completed questionnaires assessing general health (medical conditions, medication, alcohol, caffeine and drug use), sleep quality/habits and daytime drowsiness using the Pittsburgh Sleep Quality Index (412), and the Epworth Sleepiness Scale (125). Approximately 1-2 weeks prior to the baseline protocol, all OSA and control subjects had overnight standard diagnostic polysomnography with the following recordings: electroencephalography (C3/A2, C4/A1), left and right electro-oculograms, submental electromyogram, nasal cannula based pressure, piezo-electric limb movement sensors, inductive plethysmography for thoraco-abdominal motion, lead II electrocardiography and arterial oxygen saturation (SaO_2, finger pulse oximetry). All signals were digitized and stored using a Compumedics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardised methods (413, 414). Apneas and hypopnoeas were scored according to internationally agreed Chicago criteria (414, 429), with hypopnoeas scored on the basis of a 10 sec or more reduction in airflow of ≥50% or a reduction in airflow associated with an oxygen desaturation of >3% or an arousal. The Chicago scoring criteria result in higher Apnoea Hypopnoea Index (AHI) values than if other scoring criteria are used (429).

We therefore chose the following OSA severity cut-off values for this study: normal (AHI<15 events/hour), mild OSA (AHI 15-30 events/hour), moderate OSA (AHI 30-45 events/hour) and severe OSA (AHI≥45 events/hour). All diagnostic sleep study variables were calculated over the full night. For the CPAP titration, AHI, SaO_2 variables and arousal indices were calculated at the closest available pressure to that prescribed by the reporting physician ±1 cmH_2O to estimate AHI at or near the therapeutic pressure. All studies were scored by one staff member certified by the Board of Registered Polysomnographic Technicians.

4.2.2   Experimental protocol

The experimental protocol was the same at baseline and follow-up evaluation. Subjects' sleep patterns and duration were monitored using sleep diaries and actigraphy monitors (Actiwatch, Mini-Mitter Co, Inc, Model-AW64, Oregon, USA) worn from at least 5 days prior to the experimental session to estimate sleep/wake timing and to ensure comparable sleep obtained by both controls and OSA patients. Subjects were instructed to maintain a regular sleep pattern and habitual sleep duration, abstain from alcohol, caffeinated beverages, not to nap for 24 hours prior to the experimental session and to consume breakfast before 9:00 am on the day the experiment.

Upon arrival at the laboratory at 12:00 pm, each subject's blood-alcohol concentration was estimated using a calibrated breathalyzer (Dräger Alcotest7410Plus) to ensure sobriety, sleep diaries were collected and activity monitor data downloaded. Subjects consumed a standardised lunch with a glass of

water at 12:15 pm followed by a set-up for electroencephalographic recordings using the international 10-20 system. Subject assessment started at 2:00 pm beginning with driving simulator assessments (data reported in CHAPTER 2 and CHAPTER 3). At 4:00 pm all subjects commenced auditory odd-ball ERP assessment.

4.2.3   Treatment protocol

After the baseline AERP assessments, subjects with severe OSA underwent a laboratory based CPAP titration polysomnography to establish the therapeutic CPAP setting. All OSA patients were followed-up by their referring physician and underwent CPAP education. The education session involved a clinical appointment with a qualified CPAP nurse who provided the clinical information regarding the purpose and effectiveness of CPAP therapy and provided crucial patient training necessary for home use. In addition, all OSA patients were fitted with a suitable mask and issued a fixed-setting CPAP machine (ResMed S8 Lightweight, NSW, Australia). OSA patients were encouraged to use their CPAP machines as much as possible and their compliance and clinical treatment were monitored by a CPAP nurse at 1 and ~3 months after commencement of treatment. The average daily compliance with CPAP therapy over ~3 months was downloaded from the inbuilt timer in each CPAP machine at each follow-up visit. Control subjects were not issued a CPAP or sham CPAP, but were asked to continue their normal activities during this period.

4.2.4   Auditory event related potential recording

An auditory odd-ball paradigm was used to record AERP data in all participants and N1, P2, N2 and P3 components of AERP elicited by target stimuli were the main outcome measures of the study. During the odd-ball task, all subjects were seated in a comfortable chair in a sound attenuated room and instructed to focus their gaze on a designated area keeping their eyes open and avoid excessive eye, head and neck movements. Electroencephalographic recordings were obtained from gold-cap electrodes affixed using the 10-20 system at Fz, Cz and Pz midline scalp sites referenced to like mastoids and using a ground electrode on the right collarbone. Left and right electro-oculograms were recorded referenced to a forehead electrode. All electroencephalographic signals were high pass filtered at 0.15 Hz and recorded at 512 Hz. The odd-ball tone paradigm was administered binaurally using ear-insert headphones (EA-R-Tone, Cabot Safety Corporation/Auditory Systems Division, IN) and consisted of 100 msec pure 1 kHz non-target tones occurring with 80% probability, and 100 msec pure 2 kHz odd-ball target tones occurring with 20% probability. Participants were instructed to ignore non-target tones and to attend to target tones by pushing a hand-held button as quickly as possible with their dominant hand. Tones were delivered in random order with an inter-stimulus interval of 2,000-3,000 msec randomised on each tone. Two odd-ball trials each lasting approximately 10-15 minutes were conducted separated by ~10 minutes to prevent AERP habituation (439).

4.2.5 Data processing and analysis

Single AERP trials were rejected if eye movements (electro-oculogram exceeding ±50 µV) or artifact (clipping, amplifier drift) intruded into the 1,200 msec AERP window. Following rejection of individual artifact contaminated AERP trials, the remaining target and non-target tones AERP trials were separately ensemble averaged to minimise non-stimulus related background electroencephalographic activity (noise). From averaged target tone responses, the N1 component was identified as the greatest negative peak between 70-140 msec from stimulus onset, the P2 as the greatest positive peak between 120-300 msec, the N2 as the greatest negative peak between 150-350 msec and P3 the greatest positive waveform occurring 260-500 msec from stimulus onset. The AERP latencies were calculated as the time from stimulus onset (in msec) taken to reach the peak of the component and the amplitude was measured (in µV) as the difference between peak amplitude and the averaged baseline 200 msec pre-stimulus onset.

4.2.6 Statistical analysis

Paired student t-tests were used to compare anthropometric, sleep study characteristics and questionnaire results between the two groups and between baseline and follow-up evaluations within each group. Linear mixed effects model analysis was used to examine fixed effects of group (OSA vs control) and treatment (baseline vs follow-up) on AERP latencies and amplitudes using a scaled identity covariance structure, with subject specified as a random intercept term (PASW, SPSS Inc, Version 18.0, Chicago, IL). Statistically significant interaction effects

were examined via custom post-hoc contrasts within each linear mixed model. Values are means (SD) unless otherwise indicated with p<0.05 considered statistically significant.

4.3   Results

9 severe OSA patients and 9 controls completed the study. Subject's anthropometric characteristics, sleep study results, sleep duration prior to assessments, caffeine and alcohol consumption and medication use are shown in Table 4.1. Prior to baseline AERP assessment, diagnostic sleep study results showed that compared to controls, severe OSA patients had significantly greater body mass index, AHI, average oxygen desaturation, respiratory related arousal frequency, amount of stage one sleep, and were subjectively sleepier on ESS and PSQI scores (Table 4.1). Control subjects were free of any medications, while 3 OSA patients were taking medication for hypertension, 1 for hyperlipidimia, 2 for gastro-esophageal reflux, 1 for arthritis, 1 for gout and 1 for asthma, consistent with known links between OSA and other medical co-morbidities. Follow-up measurements were made as close to 3 months as practical, on average 102 (range 76-129) days after CPAP treatment was initiated in the OSA patients and 113 (94-152) days after baseline assessment in the control subjects. Estimated average sleep time (actigraphy) 5 days and 24 hours prior to assessments at baseline and follow-up were not statistically significantly different between groups or time of assessment (Table 4.1). CPAP compliance was high at 6.0 (1.6) hours/night. All subjects could differentiate between standard and target tones in

the auditory odd-ball paradigm during the introduction sessions and all subjects exhibited greater than 95% accuracy for correct target detection.

4.3.1   Auditory event related potentials

The number of artifact free target AERP available for averaging was not statistically significantly different between OSA and control subjects at baseline (62±5 vs 65±8) or follow-up evaluations (54±7 vs 72±5). The grand average AERP waveforms at Fz, Cz and Pz are shown in Figure 4.1. The N1, P2 and N2 were maximal at Cz, while P3 was maximal at Pz. Average peak latencies and amplitudes for N1, P2, N2 and P3 waveforms from the AERP at maximal electrode sites for control and OSA patients are shown in Table 4.2.

Table 4.1 Participant anthropometric characteristics, polysomnography results at baseline and after 3 months follow-up, questionnaire results and medication use

	Controls		OSA	
N Males/Females	7/2		8/1	
Age (yrs)	53.2 (3.2)		59.0 (7.7)	
Body-Mass Index (kg/m²)	24.3 (0.9)		33.2 (2.0) †	
Sleep Parameters	Diagnostic PSG	CPAP titration	Diagnostic PSG	CPAP titration
Apnea Hypopnoea Index (AHI: events/hour)	6.6 (3.8)	-	64.5 (19.3)††	5.6 (6.3) #
% of sleep time with $SaO_2 < 90\%$	0.0 (0.0)	-	10.6 (14.9)	0.1 (0.3)
Average SaO_2 desaturation (%)	2.2 (0.4)	-	4.8 (2.9) †	2.1(0.4) #
Respiratory Arousal Index (Arousals/hour)	1.6 (1.1)	-	25.8 (15.1)	0.5(0.9) #
Limb Movement Arousals (Arousals/hour)	4.1 (3.0)	-	4.7 (4.4)	2.0 (2.7)
Arousal Index (Arousals/hour)	13.5 (5.8)	-	40.0 (16.1)	11.0 (7.0) #
Total Sleep Time (min)	405.9 (32.5)	-	423.2 (37.0)	402.6 (42.1)
Sleep Stage 1 (min)	26.8 (11.5)	-	70.3 (59.4) †	28.4 (16.9)
Sleep Stage 2 (min)	171.8 (42.6)	-	161.4 (28.8)	176.0 (34.9)
Sleep Stage 3 (min)	48.6 (23.3)	-	36.0 (24.1)	49.8 (26.8)
Sleep Stage 4 (min)	7.2 (7.8)	-	10.4 (16.4)	17.6 (26.9)
REM Sleep (min)	62.2 (26.2)	-	54.9 (20.6)	70.8 (30.9)
Sleep Efficiency (%)	71.0 (15.6)	-	76.3 (11.1)	80.5 (10.3)
	Baseline	Follow-up	Baseline	Follow-up
Epworth Sleepiness Scale	4.9 (2.6)	4.4 (2.2)	11.1 (5.3) †	7.7 (4.1) †
Average Actigraphy Estimated Sleep Time				
5 days before experimental session (min)	459 (66)	473 (51)	446 (66)	431 (69
24 hours prior to experimental session (min)	464 (71)	472 (52)	459 (90)	432 (66)
Questionnaire Measures				
Pittsburgh Sleep Quality Index	2.6 (0.9)		10.2 (6.5) †	
Driving History (kilometres/year)	11525 (4912)		16894 (4548)	
Education (years completed)	13.8 (3.1)		10.3 (2.1) †	
Caffeine Consumption (cup or equivalent/day)	2.3 (1.1)		3.6 (1.9)	
Smoking (cigs/day)	0.0 (0.0)		0.1 (0.3)	
Habitual Alcohol Intake (Std drinks/week)	10.8 (4.5)		11.4 (15.7)	

Values are means (SD), † $p < 0.05$. †† $p < 0.001$ - between group difference within the same period of evaluation, # <0.05 - between evaluation difference within the same group. For OSA patients, sleep measures are presented separately for diagnostic PSG and CPAP titration

Figure 4.1 Grand average auditory event related potentials at baseline and follow-up evaluation
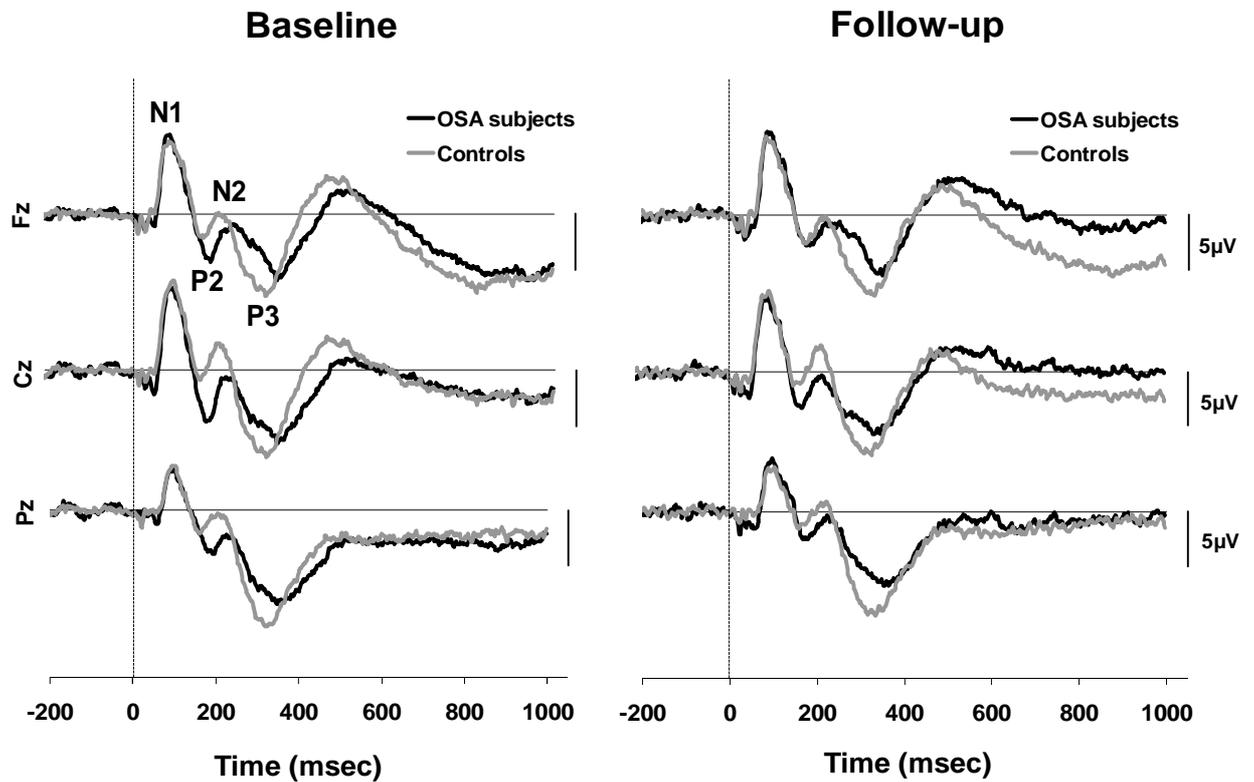
Grand average waveforms (positive down) from AERP at Fz, Cz and Pz electrode sites in control (n=9) and OSA patients (n=9) assessed at baseline and follow-up illustrating persistent abnormalities in the P2, N2 and P3 components. Different AERP components are labelled on the Baseline (Fz) trace.

Table 4.2 Auditory event related potential latency and amplitude data

Evaluation	Baseline		Follow-up	
Group	Controls	OSA	Controls	OSA
Subject N	9	9	9	9
AERP Latency (msec)				
N1 - Maximal at Cz	99.0 (3.2)	101.0 (4.3)	96.4 (3.6)	102.5 (5.4)
P2 - Maximal at Cz §	169.4 (4.5)	182.4 (4.8)	164.0 (3.8)	182.4 (8.6)
N2 - Maximal at Cz §	211.7 (5.2)	239.0 (7.5)	216.0 (5.2)	236.2 (10.3)
P3 - Maximal at Pz	323.4 (6.4)	376.2 (9.8)††	323.0 (7.2)	355.1 (10.9)†#
AERP Amplitude (µV)				
N1 - Maximal at Cz	-9.2 (0.9)	-8.4 (0.9)	-8.2 (0.5)	-8.0 (0.9)
P2 - Maximal at Cz §	1.8 (1.0)	5.3 (1.2)	2.2 (0.9)	5.2 (1.1)
N2 - Maximal at Cz	-3.7 (1.6)	-1.1 (1.4)	-3.5 (1.3)	-1.3 (0.9)
P3 - Maximal at Pz §	11.7 (0.9)	9.3 (0.8)	10.7 (1.0)	8.5 (0.6)

Values are means (SEM). Data presented at maximal sites of activation for control and OSA patients at baseline and follow-up evaluations, § $p<0.05$ – Main group effect (controls different from OSA), † $p<0.05$, †† $p<0.01$ - Difference between groups within the same evaluation, # $p<0.05$ - Between evaluation difference within the same group.

At baseline evaluation OSA patients demonstrated significantly delayed P2 (main group effect, $F_{[1,16]}=4.6$, $p=0.047$), N2 (main group effect, $F_{[1,50]}=4.2$, $p=0.03$) and P3 latencies (group difference at baseline, $F_{[1,21]}=17.9$, $p<0.001$), increased P2 amplitude (main group effect, $F_{[1,16]}=5.5$, $p=0.032$) and decreased P3 amplitude (main group effect, $F_{[1,16]}=4.6$, $p=0.047$) compared to controls (Figure 4.1 and Table 4.2). P3 latency showed a statistically significant reduction post-treatment in OSA patients (group x treatment interaction, $F_{[1,16]}=5.3$, $p=0.035$), but remained statistically significantly delayed compared to controls (group difference at follow-up, $F_{[1,21]}=6.6$, $p=0.018$) while the control group showed no change in P3 latency between baseline and 3 month follow-up (Figure 4.1and Table 4.2). There was no statistically significant treatment or group by treatment interaction effects in any other AERP component to indicate within or between group changes with time or treatment.

4.4   Discussion

This carefully controlled study demonstrated that, compared to age and gender matched controls, most AERP components are abnormal in severe untreated patients with OSA, and only P3 latency showed some, but incomplete recovery following 3 months of CPAP treatment with high adherence (average of 6 hours of CPAP use per night). Why CPAP did not alter the early AERPs and only resulted in a partial improvement in P3 in treated OSA patients is unclear, but is consistent with some previous studies (54, 138). These findings may reflect irreversible cortical damage associated with years of sleep fragmentation and/or hypoxaemia

experienced in severe OSA, or perhaps neuronal differences that simultaneously predispose individuals to OSA and neurocognitive abnormalities.

Although possible, type II error appears very unlikely to explain the lack of treatment effects in early AERP components given the repeated measures design, high test-retest reliability of ERP measures (440), presence of large between group differences in several AERP measures and that a ~20 msec reduction in P3 latency was detected with CPAP treatment in the OSA group. Based on within-subject standard deviations of repeated latency and amplitude measures in the order of 7 msec and 1.4 µV respectively, we estimate that 9 subjects per group was sufficient to detect time or treatment changes in the order of 7 msec and 1.5 µV, and between group differences in the order of 10 msec and 2 µV respectively.

In agreement with most previous studies, we found no abnormalities in the N1 component in OSA patients before or after CPAP treatment (136, 137, 139). In apparent contrast, one study in which participants were selected based on a questionnaire rather than sleep studies, reported a more negative N1 peak in OSA patients compared to controls (141). However, a reduction rather than an increase in N1 amplitude would be expected in individuals with lower arousal and attention such as in OSA, as has been shown in sleep deprivation (437) and sleep inertia (436) studies. Consequently the current study and most other available data appear to support that the neural generators of the N1 are not affected by even severe OSA.

The current study, like 3 previous studies (136, 139, 141), showed that P2 was larger and delayed in severe OSA patients compared to controls, suggesting an abnormal stimulus classification response (154, 156, 157). Only one early investigation (136) has evaluated the effect of CPAP treatment on the P2 component showing, in agreement with our findings, that P2 latency did not change following 6 weeks of CPAP treatment, but that P2 amplitude measured as peak to peak amplitude (N1-P2 complex) normalised in treated patients. Some investigators have speculated that the larger P2 in OSA patients may reflect "over processing" of sensory information with inefficient inhibitory processes attempting to compensate for OSA related deficiencies (141). This hypothesis stems from brain imaging and ERP studies showing increased activation and exaggerated P2 in sleep deprived subjects (262, 263, 437). Increased cortical activation has also been observed by Avalon et al. (113) in OSA patients during verbal learning and was considered to most likely reflect compensatory cortical recruitment.

Similar to the P2 response, the N2 AERP component was delayed in severe OSA patients. Although N2 amplitude appeared to be lower in OSA patients, this was not statistically significant. The N2 is usually seen only in response to target stimuli and is thought to reflect endogenous mismatch detection processes, or the discrimination between target and non-target stimuli (154, 159). The current findings are in agreement with an earlier study by Wasleben et al. (137), which also showed delayed N2 latency that did not improve following 2 days of CPAP treatment. In contrast, using a 6 week CPAP treatment protocol, Rumbach et al. (136) reported a shortening of N2 latency, which remained abnormal in comparison to controls. While it is difficult to compare these previous studies in which the

severity of OSA and treatment effectiveness are unclear to the current findings, our data suggest that N2 stimulus mismatch responses in severe OSA patients remain abnormal despite 3 months of effective CPAP with good treatment compliance.

The P3 is the most widely studied ERP component as it is thought to reflect higher order cognitive information processing more readily related to behavioural abnormalities than shorter latency ERP responses. In the present study, P3 latency was significantly delayed and amplitude significantly decreased in OSA patients compared to healthy controls, suggesting overall impairments in higher cortical information processing. Two other studies (136, 137) have found similar decrements in both P3 latency and amplitude. Following CPAP treatment P3 latency in the OSA patients was shortened in this study, but remained significantly longer than in controls, a finding consistent with other studies (51, 54, 138), including one evaluating longer-term (6 months) treatment (54). Recent behavioural studies demonstrating residual performance impairments in treated OSA (50, 211, 428) further support treatment persistent cortical information processing deficits in OSA. Although, some studies have found a correlation between P3 and sleep efficiency (441), apnoea-hypopnoea index (441) and percent time with oxygen saturation below 90% (138), the neural substrate for irreversible abnormalities in early ERP components in OSA remains unclear. It is possible that both sleep quality and hypoxaemia are important, with partial improvements in P3 perhaps reflecting improved sleep quality but persistent hypoxic damage. Our AERP findings in severe OSA patients suggest only limited scope for treatment improvements, but given the small sample, do not allow for a meaningful

exploration of relationships between sleep parameters and AERP measures. It is however, an area that warrants further systematic investigation.

There are other factors that may be important to consider in the current study. OSA patients had a significantly higher BMI and more medical co-morbidities compared to normal weight controls, reflecting the close association between body mass, OSA and co-morbid disease (7). It is possible that co-morbidities and/or obesity *per se* may have contributed to differences in AERP responses between OSA patients and controls before and/or after treatment. Although there is some evidence suggesting that obesity may be associated with abnormalities in frontal lobe function (442), such studies have not controlled for OSA, despite the known high prevalence of OSA in obese (BMI>30) individuals (7). Studies of auditory, somatosensory and visual evoked potentials have also found no evidence for an effect of obesity *per se* on these responses (443, 444). Thus, while it remains theoretically possible that some of the differences in AERP observed between patients and controls may be the result of group differences in BMI, we consider it more likely that the abnormal AERP responses observed in OSA patients, which in the main did not improve with CPAP treatment, were the consequence of permanent cortical damage caused by nocturnal respiratory abnormalities.

Fewer years of completed education in OSA patients compared to controls could also influence ERP responses and is a risk factor for obesity and OSA. Few data are available to evaluate the impact of education status on ERP responses, but there is some evidence that this is unlikely to have impacted our main findings (445, 446). Furthermore, two control subjects with greater than 16 years of

education contributed to the difference in education level between control and OSA patients in this study and removal of these patients from the analysis did not alter the main ERP findings of the study (i.e. greater P2 amplitude, delayed N2 and P3 latency in the OSA vs control group remained).

We studied a relatively small group of patients with severe OSA alone, such that it is unclear what effect CPAP treatment may have in milder OSA, and comparisons with previous studies where OSA severity is often unclear are difficult. In addition, although CPAP adherence was high in the present study (~6 hours per night), and likely the most that can be expected over 3 months of treatment, it is possible that longer-term treatment and/or greater nightly use may have improved AERP responses in these patients. It is also possible that although the OSA patients adhered well to treatment, the amount of sleep or the quality of sleep was less in patients than controls. Our results showed no difference in the amount of actigraphy-determined sleep in the 5 days prior to testing between patients and control subjects, but the average period of CPAP treatment in patients (6 hours) was less than the 7.2 hours of total sleep recorded by actigraphy. Thus some residual sleep disturbance in the OSA patients may have contributed to persistent abnormalities at least in P3. However, this seems an unlikely explanation for our overall findings since not even a partial improvement with treatment was evident in the early AERP components. To address this question more fully, future studies should ideally document sleep by PSG in the experimental groups and attempt to match the quantity and quality of sleep in CPAP-treated patients and controls.

CPAP is the gold standard treatment for OSA and its consistent use improves many of the negative consequences associated with OSA. However, this study adds to existing evidence that CPAP treatment does not normalise cognitive and behavioural abnormalities associated with severe OSA, such as sleepiness, executive function and the performance of complex, safety critical tasks such as driving. Larger studies are needed to further examine the persistence of deficits, preferably collecting both behavioural and neurophysiologic data before and after CPAP treatment in order to elucidate the factors contributing to persistent neurobehavioural impairment in OSA. ERPs provide a sensitive tool for assessing cortical information processing that may be a useful tool for differentiating patients at risk of safety critical performance deficits or failures in complex tasks such as driving.

In conclusion, this study demonstrates significant abnormalities in auditory event related potentials associated with severe untreated OSA, with no changes in early AERP components and only limited improvements in P3 latency following 3 months of optimal CPAP treatment. These findings support the hypothesis that severe OSA has lasting effects on cortical function that may place these patients at continued risk for residual daytime performance deficits despite treatment.

CHAPTER 5.   SUMMARY AND CONCLUSIONS

OSA is a common sleep disorder affecting up to 10% of the middle aged population. It is characterised by repeated collapse of the upper airway, intermittent hypoxaemia and sleep fragmentation. These nocturnal pathophysiological events are thought to be the major cause of excessive day time sleepiness, cognitive abnormalities and increased motor-vehicle accident risk observed in patients with OSA. Similar neurobehavioural abnormalities have been observed in healthy individuals exposed to mild central nervous system stressors such as sleep restriction and low dose alcohol. For example, experiments in healthy young subjects have shown that these two common "life-style" factors impact negatively on driving simulator performance (e.g. approximately 5-fold increase in lane drifting incidents compared to baseline) (78), with even greater decrements observed when they were applied simultaneously (~10-fold increase in lane drifting incidents) (78). In Study 1 (CHAPTER 2) it was postulated that because of months to years of prior sleep disruption and intermittent nocturnal hypoxia OSA patients would exhibit even greater decrements in function when challenged with these lifestyle factors compared to healthy non-apnoeic controls.

Treating OSA with CPAP has been shown to significantly improve the negative consequences of OSA. Indeed, it has been generally believed that CPAP treatment, used regularly, can normalise daytime sleepiness, neurobehavioural function and driving performance in OSA. However, more recent evidence suggests that these functional abnormalities do not necessarily normalise in

patients with moderate to severe OSA, even in those who appear to comply optimally with treatment. Many early studies failed to include a suitable healthy comparator group, making it difficult to ascertain whether or not improvements observed amongst OSA patients after treatment represented a return to normal functioning. Also, in previous driving simulator experiments the tasks used were relatively short, potentially masking residual functional impairments that only become apparent on long monotonous drives where sustained attention demands are particularly relevant to fall-asleep accidents, and more challenging. The question regarding the effectiveness of CPAP treatment in improving driving simulator performance in severe OSA patients and reducing OSA patient vulnerability to sleep restriction and alcohol when compared to a healthy matched control group was examined in Study 2 (CHAPTER 3). The effectiveness of CPAP treatment in improving cortical sensory processing in severe OSA patients compared to healthy matched controls using auditory event related potentials was examined in Study 3 (CHAPTER 4).

In Study 1 (CHAPTER 2) 90-minute driving simulator performance was compared between OSA patients and healthy controls under three different experimental conditions: (1) usual sleep (baseline condition); (2) moderate sleep restriction (4 hours time in bed); and (3) low dose alcohol (targeting the Australian legal blood alcohol concentration limit of 0.05 g/dL). As expected, under the baseline condition, OSA patients demonstrated more steering deviation and had a higher propensity to crash. However, in addition, OSA patients showed a *greater deterioration* in their steering deviation and crash behaviour after sleep restriction and alcohol. Interestingly, steering impairment became statistically significant only after

approximately 40 minutes on task. The majority of crashes also occurred in the second half of the drive and were associated with sleepiness and attention failures (prolonged eye closure and microsleeps). These findings are potentially of major clinical and public health importance. To the extent that driving simulator results such as these are indicative of real driving performance, greater vulnerability to sleep loss and low-dose alcohol observed amongst OSA patients in this study, implies that a portion at least of the known increased motor vehicle accident rate associated with OSA may be attributable to these common life-style factors. Sleep clinicians may need to advise their patients of the potential for even modest levels of sleep restriction and relatively-low, legally-acceptable levels of alcohol consumption to increase the risk of driving accidents.

Study 2 (CHAPTER 3) assessed the effectiveness of ~3 months CPAP treatment in improving 90-minute driving simulator performance and reducing vulnerability to further performance deficits with sleep loss and alcohol in patients with OSA. A sub-group of 11 severe OSA patients and 9 healthy controls, matched for age and gender, who completed Study 1 repeated the protocol at 3 months follow-up. Patients were treated with CPAP during this 3-month period and were highly compliant with therapy, using CPAP an average of 6.0 ± 1.4 hours/night. Control subjects did not use CPAP and were not treated in any other way during the follow-up period. At baseline, untreated OSA patients demonstrated worse driving simulator performance compared to controls under all conditions, and showed greater steering decrements following sleep restriction and alcohol than control subjects. At 3-months follow-up, CPAP-treated OSA patients demonstrated a significant improvement in steering deviation under all conditions. However, despite

improvement, OSA patients' steering deviation performance did not reach the level of control subjects under normal sleep and sleep restriction conditions, and crash frequency remained significantly elevated following CPAP treatment. OSA patient vulnerability to sleep loss and alcohol was reduced. These findings suggest that CPAP treatment improves but does not normalise driving performance in patients with severe OSA during long monotonous driving scenarios. These findings challenge conclusions drawn from previous driving simulator studies that employed shorter drives and showed normalisation of driving simulator performance, and supports other studies showing residual neurobehavioural abnormalities in CPAP-treated patients. Further larger prospective studies are clearly warranted to investigate the relationship between residual driving simulator impairment and on-road motor vehicle accident risk. In the meantime, it may be prudent for sleep clinicians to suggest to OSA patients that they exercise particular care when undertaking long distance driving, even if patients are apparently optimally treated.

Study 3 (CHAPTER 4) assessed the effectiveness of ~3 months CPAP treatment on brain function in OSA patients using sensitive electrophysiological methods of cortical auditory event-related potentials. With this method positive and negative deflections in the electroencephalogram occurring in response to an auditory signal provide markers of cortical information processing. Cortical event-related potential studies in OSA patients have demonstrated several abnormalities, particularly in later components such as the P3, which occurs 300-400 msec from stimulus onset, with some studies reporting persistent abnormalities after OSA treatment. Earlier components of event-related potentials had not been systematically investigated in OSA populations previously, despite important complementary information on the

integrity of sensory pathways projecting to the cortex. Study 3 used an auditory odd-ball paradigm (non-target tones to be ignored interspersed with rarer target tones requiring an attentional response) to examine brain sensory processing in 9 patients with severe OSA and 9 healthy age- and gender-matched controls at baseline and after ~3 months. Patients were treated with CPAP during this 3-month period and were highly compliant with therapy, using CPAP an average of 6.0 ± 1.6 hours/night. Control subjects were not treated and continued their normal routine during the follow-up period. Compared to controls early and late auditory target event related potentials were abnormal in severe OSA patients at baseline. Specifically N2 and P3 peaks were smaller and delayed in latency, and P2 amplitude was larger. At follow-up, P3 latency was the only measure to improve following CPAP treatment, but remained prolonged compared to control subjects, despite a high level of CPAP compliance in OSA patients. The abnormalities observed in earlier components of auditory event-related potentials in OSA patients did not change after CPAP treatment. These findings add to existing evidence of residual neurobehavioural abnormalities from previous studies, and complement the findings of driving simulator performance deficits reported in Chapter 3. These data suggest the possibility of permanent (irreversible) alterations to brain function in patients with severe OSA as a result of years of prior sleep fragmentation and hypoxaemia. Alternatively, the limited effectiveness of CPAP could be due to inherited genetic factors in OSA patients simultaneously predisposing them to developing OSA and cognitive/neuro-physiological abnormalities. A further possibility is that co-morbid conditions, such as hypertension- or diabetes-related vascular disease and obesity may independently cause cognitive and neuro-physiological abnormalities.

The experiments reported in this thesis do not directly address the pathophysiological pathways or mechanisms responsible for increased vulnerability to deficits associated with sleep loss and alcohol, and persistent functional abnormalities after CPAP treatment in OSA patients. There are, however, some potential explanations worthy of discussion. Vigilant attention performance is crucial for driving and depends on activation of brain networks involving the frontal-parietal-thalamic and brainstem regions such as the thalamus, anterior cingulate gyrus, middle prefrontal gyrus and inferior parietal lobes (70, 394). If the neural circuitry of this attention system is damaged (possibly permanently) as a result of a disorder such as OSA, or compromised by factors such as sleep loss or alcohol, it could reduce the systems efficiency to appropriately compensate, leading to more frequent attention lapses.

Some support for permanent neural deficits as a result of OSA comes from studies on animal models of OSA. These have shown evidence for direct and substantial oxidative damage affecting brain morphology and behaviour from experimental hypoxaemia and sleep fragmentation (22). In addition, some evidence suggests that damage to particular brain regions such as the pre-frontal cortex (which is important for higher order cognitive function and a crucial part of the attention network) may be more neurobehaviourally detrimental than damage to other brain regions (69). Indeed, the PFC appears to be particularly sensitive to sleep loss (either sleep restriction or fragmentation), alcohol and hypoxaemia (259, 405, 408). Therefore, it is plausible that similar mechanisms produce permanent deficits in the brains of human OSA patients, leading to neurobehavioural abnormalities

associated with OSA and greater vulnerability to further impairments in the presence of additional central nervous system stressor such as sleep restriction and/or alcohol.

Although the direct examination of brain damage in humans is difficult, there is indirect support from animal data and from structural brain imaging studies in human OSA patients showing a more focal, localised loss of grey matter (447) and more recently metabolic disturbances in white matter, including in the PFC (24, 448). White matter abnormalities appear to persist despite CPAP treatment, and this may contribute to irreversible neurobehavioural abnormalities in CPAP treated patients. The white matter "skeleton" is made up of myelinated axons and represents the interconnectedness between widespread cortical regions (235). The degree of white matter interconnectedness in healthy subjects has recently been shown to differentiate between individuals who are vulnerable vs resistant to performance decrements following sleep deprivation (235). This finding may be key for explaining increased vulnerability to performance deficits with sleep loss in OSA patients (as white matter is already compromised in these patients), although this hypothesis remains to be tested. Sufficiently large and appropriately controlled brain imaging studies are needed in OSA patients to elucidate the structural neural correlates of OSA dependent neurobehavioural deficits and their vulnerability to additional central nervous system stressors such as sleep loss and alcohol, and persistent abnormalities post-treatment.

Further convincing evidence for inefficient brain function as a result of sleep deprivation and OSA comes from functional imaging studies. These studies

demonstrate recruitment of additional brain regions in sleep deprived healthy subjects during memory and verbal learning tasks, where increased activation is interpreted as protective compensation for the stress of sleep loss. Similar increased activation has been observed in non-sleep deprived OSA patients, and potentially reflects a protective compensatory mechanism for deficits associated with sleep fragmentation and hypoxaemia in OSA. Importantly, when compensatory recruitment is observed, performance is usually maintained at normal or near normal levels, while the absence of compensatory recruitment or a decrease in cortical activation are generally associated with poorer performance (28, 113). It is likely that there is a limit to the amount of stress that can be effectively compensated. Therefore, in individuals where excessive sleepiness is an issue, such as in patients with OSA, maintaining cognitive performance may be compromised due to limited compensatory "reserve". Thus, exposing OSA patients to any additional stress (such as sleep loss or alcohol) could result in greater vulnerability to deficits associated with this stress (as the cortical "threshold" for maintaining performance is lower), resulting in poorer performance compared to a healthy sleeper. Thus, in addition to future structural imaging studies, functional brain imaging studies are needed to identify the pattern of brain activity that occurs during task performance (perhaps during driving simulation) in OSA patients that are subjected to additional central nervous system stressors.

With the identification of the neural correlates of OSA dependent (and possibly irreversible) neurobehavioural abnormalities and greater vulnerability to additional stressors, it would be prudent from a practical, patient-care and traffic safety perspective to determine if and how these correlates, in conjunction with

neurobehavioural measures (such as driving simulation), are related to real-world accident risk in OSA.

In conclusion, this thesis presents new findings with important clinical implications. Patients with OSA demonstrate greater vulnerability to driving simulator performance impairments following moderate sleep restriction and low and legal alcohol consumption, far beyond deficits observed in healthy individuals subjected to these common life-style factors. To the extent that these observations can be translated to real on-road driving, this suggests that patients should be cautious when sleep opportunity is reduced or even small quantities of alcohol are consumed to reduce motor vehicle accident risk, particularly during long distance monotonous country driving. Although CPAP treatment reduced the vulnerability to further driving simulator performance impairments with sleep loss and alcohol in severe OSA patients, performance impairments persisted suggesting that treated OSA patients may remain at increased motor vehicle accident risk. Residual abnormalities in treated OSA patients are not limited to behavioural function of driving simulator performance but are also evident in persistent abnormalities in cortical information processing. Further studies examining the mechanisms (both neural and behavioural) underlying persistent neurobehavioural abnormalities and increased vulnerability to additional stressors in OSA patients are warranted.

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