

**An Exploratory Study of Neuropsychological Impairment, Driving Performance,
and Sleepiness in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary
Disease.**

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ABSTRACT

Obstructive Sleep Apnoea (OSA) and Chronic Obstructive Pulmonary Disease (COPD) are both medical conditions clearly associated with cognitive impairment. Impaired performance on tasks measuring reaction time, concentration, learning, memory, and driving ability have been observed. These deficits result in a higher risk of accidental injury for people who are diagnosed with such disorders. In patients with OSA, impaired performance on these measures may reflect the sleep fragmentation associated with multiple arousals during sleep, and/or the degree of hypoxemia and oxygen desaturation. In contrast, the level of impairment seen in COPD is related to the degree of hypoxemia both during sleep and during waking hours. The major aim of this study was to compare driving performance and neuropsychological function in OSA and COPD patients with healthy control participants, and to also compare OSA patients to COPD patients. The second aim was to determine the contribution of sleep fragmentation and hypoxaemia to poor performance and neuropsychological decline. Experiment 1 compared fourteen patients with OSA to eleven healthy control participants on measures of driving performance, subjective and objective sleepiness, and neuropsychological functioning. Experiment 2 compared the same variables in a group of fourteen COPD patients and eleven control participants. OSA patients were also compared to COPD patients using the same measures (Experiment 3). Experiment 1 demonstrated that OSA patients reported significant subjective daytime sleepiness and decreased levels of alertness when compared to control participants. On a simulated driving task, there were no significant differences noted between the groups. However, OSA patients demonstrated vigilance impairment, and impaired performance on immediate and delayed verbal memory. Experiment 1 demonstrated that measures of sleepiness were related to visual attention, immediate visual memory, procedural memory and cognitive flexibility. Hypoxaemia was related to immediate and delayed visual memory, and median reaction times. The COPD patients in Experiment 2 demonstrated impaired vigilance and reaction times, reduced immediate and delayed verbal memory, and difficulty maintaining the vehicle in the appropriate lane on the driving simulator. There were no firm conclusions drawn regarding the impact of hypoxaemia on cognitive, vigilance, or driving performance tasks. While Experiment 3 indicated no significant difference between the OSA and

COPD patients on cognitive tasks or driving simulator, trends indicated that COPD patients demonstrated poorer performance on the driving simulator. A major finding of Experiment 3 was that although COPD patients did not subjectively report the same level of sleepiness as OSA patients, objective measures indicated a greater level of sleepiness while performing the driving simulator. This study emphasised the importance of detecting impairments so that physicians can alert patients to the potential dangers of driving while sleepy, as well as the cognitive deficits that may impact on daily functioning. The current study also highlighted the use of cognitive testing to identify those patients with OSA or COPD who may be more at risk of accidental injury due to poor attention, memory, or executive functioning.

DECLARATION

“I, Daniela De Fazio, declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled “An Exploratory Study of Neuropsychological Impairment, Driving Performance, and Sleepiness in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary Disease” is no more than 40,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work”.

Signature:

Date:

DEDICATION

This thesis is dedicated to my parents, Anthony and Elena De Fazio. Their unconditional love, support and encouragement has allowed me to pursue my studies. I will be forever grateful for the sacrifices they have made and for their unlimited patience.

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INTRODUCTION

Motor vehicle traffic accidents are a major cause of death and injury in Australia, and are also very costly in terms of damage to vehicles, property and loss of goods. Road safety has continued to improve since the early 1970's, but road trauma continues to inflict an enormous burden on the Australian community. Based on a study by the Bureau of Transport Economics in 1999, the Australian Transport Safety Bureau (ATSB) estimated that the annual economic cost of road crashes in Australia in 2005 was \$18 billion. This estimate does not even begin to convey the additional burden of pain, suffering and loss incurred by road crash victims, their families and friends, and of the wider community. Since vehicle accident records commenced in 1925, there have been in excess of 164,190 lives that have been lost overall.

In 2006, the ATSB conducted its nineteenth survey into Australian community attitudes to road safety (Pennay, 2006). The purpose of this research was to monitor attitudes to a variety of road safety issues, including speed, drink driving, mobile phone use, and driver fatigue. From the total of 1,644 individuals aged over 15 years interviewed, 16% reported having at some time fallen asleep while driving with almost half of these reporting falling asleep more than once. In 10% of those who had fallen asleep while driving, the most recent episode had resulted in a road accident. This survey also investigated the factors that people perceive contribute to road crashes. When examining community perception as far back as 1993, the most significant changes include an increased mention being made of driver fatigue and inattention/lack of concentration as a contributing factor in road crashes.

The causes of motor vehicle crashes are varied and include factors such as road and vehicle design, traffic volume, and human fallibility. Recent road safety research indicates that human error is a major contributing factor in explaining up to 75% of all roadway crashes (Medina, Lee, Wierwille & Hanowski, 2004). The overall contribution of medical conditions to motor vehicle crashes is unknown, but it is reasonable to assume that a number of medical conditions may impair human information processing which, in turn, negatively affects driving performance.

Obstructive sleep apnoea (OSA) and chronic obstructive pulmonary disease (COPD) are both chronic medical conditions which may be associated with impaired function, including sensory, motor, and cognitive impairment. The chronic effects of these conditions can result in measurable performance decrements that may assist in the assessment of an individual's ability to drive based on individual performance, rather than on estimates of risk. Research on individuals with OSA has demonstrated that sleep fragmentation and nocturnal hypoxaemia are associated with impaired cognitive functioning, and that the disease is associated with a higher risk of motor vehicle accidents. Patients with COPD have similarly been shown to have cognitive impairment, which is purported to result from chronic hypoxaemia. However, there is a paucity of research examining driving performance in these patients nor are there data on risk of motor vehicle accidents in this group.

The major aim of this study was to compare driving performance and neuropsychological function in both OSA and COPD patients with healthy control participants, and to also compare OSA patients to COPD patients. The second aim was to determine the differential roles sleep fragmentation and hypoxaemia may

have in contributing to poor performance and neuropsychological decline. This study aimed to contribute to evaluating the effects of these medical conditions on driving competence by using direct performance measures, rather than relying only on relative risk data.

CHAPTER 1

1.1. Obstructive Sleep Apnoea

OSA is a breathing disorder that occurs during sleep and is associated with repetitive airway obstruction. It was clinically recognised in 1976 and defined as the repeated obstruction of the upper airway despite ongoing respiratory efforts (Guilleminault, Tilkian, & Dement, 1976). Since then, due to the considerable insights gained into the serious clinical implications of the disorder, it has become one of the most frequent conditions studied in sleep clinics.

Presenting symptoms of OSA include loud snoring, and daytime hypersomnolence particularly in sedentary situations (including driving). Testing also reveals nocturnal oxyhaemoglobin desaturation. OSA is strongly associated with the leading causes of mortality in adults, including hypertension, cardiovascular, and cerebrovascular diseases (Douglas & Polo, 1994; Tangugsorn, Krogstad, Espeland, & Lyberg, 2000). In addition, several neurobehavioral morbidities that are of potentially great public health and economic importance are linked with OSA. These include daytime sleepiness, and impaired concentration and memory, which, in turn, are known to contribute to motor vehicle crashes and work-related accidents (Douglas & Polo; Leger, 1994; Tangugsorn et al.).

1.1.1. Prevalence of OSA

Population based, longitudinal studies of OSA have resulted in well-established epidemiological characteristics of the condition. Although OSA prevalence increases steadily with age in midlife, trends in children, adolescents, and the elderly indicate a number of other factors contribute to OSA rather than it being simply due to age.

In 1993 Young and colleagues reported the prevalence of OSA in a sample of men and women aged thirty to sixty years old from the Wisconsin Sleep Cohort Study. Based on the results of overnight polysomnography, the authors estimated the prevalence of polysomnographically defined OSA to be nine percent for women and twenty-four percent for men. They estimated that two percent of women and four percent of men in the middle-aged work force met the diagnostic criteria for OSA (OSA on polysomnography in association with excessive sleepiness). Similarly, Bearpark and colleagues (1993) investigated the incidence of sleep disordered breathing in the Australian town of Busselton, and found that 8.5% of men and 4.7% of women in a community sample had evidence of sleep disordered breathing.

1.1.2. Aetiology and Pathophysiology of OSA

OSA is characterised by repeated episodes of complete cessation of breathing both nasally and orally (apnoea) that, by definition, usually last for at least 10 seconds or more (Bassiri & Guilleminault, 2000). It can also include partial reductions in ventilation volume to less than 50% of baseline (hypopnoea). Hypopnoeas may also be associated with desaturation in arterial oxygen levels for ten seconds or more (Bassiri & Guilleminault). In a case of symptomatic OSA,

there is an occlusion in the upper airway, which may involve the nose, palate, and base of the tongue, resulting in the cessation of airflow (Bradley & Phillipson, 1985; Shochat & Pillar, 2003). This occlusion is part of a repetitive series of events that usually occurs many times each night during sleep (Bradley & Phillipson).

Pharyngeal collapse results in a tendency to increase inspiratory efforts, and as a result, the airway collapses and pressure within the thorax becomes increasingly negative (Pepperell, Davies, & Stradling, 2002). Consequently, oxygen levels fall and carbon dioxide levels rise (Bradley & Phillipson, 1985). The person usually rouses to a lighter stage of sleep or wakefulness and muscular tone is restored in the upper airway, terminating the apnoea and restoring airflow. With obstruction overcome and ventilation restored, the person usually returns to sleep or deeper sleep promptly and their blood gases also return to normal, only to have the obstruction recur and the progression of events repeated, often up to hundreds of times, leading to significant disruption of sleep.

In humans, the upper airway is not a rigid structure, so its patency depends on transmural pressure and the resistance of the walls to collapse (Orr, 1997). In healthy individuals, there is a natural airflow limitation during sleep that occurs as a result of an increase in upper airway resistance and narrowing (Pepperell, Davies, & Stradling, 2002; Orr). This physiological activity is particularly apparent during the rapid eye movement (REM) stage of sleep, most likely explaining the tendency for OSA to first progress in, and to be most severe during this particular stage of sleep (Bradley & Phillipson, 1985).

Airway narrowing is limited in normal individuals by reflex increases in upper airway tone, and increased inspiratory effort (Horner, Innes, Murphy, &

Guz, 1991). In those with OSA, these reflexes are inadequate and airflow limitation is more prominent. The arousal to wakefulness that terminates an apnoea increases the activation of dilator muscles so that airway patency is restored (Chadwick, Crowley, Fitzgerald, O'Regan, & McNicholas, 1991). Both abnormal anatomical and physiological changes contribute to altering the balance of forces that maintain either airway patency or collapse (Bradley & Phillipson, 1985; Pepperell, Davies, & Stradling, 2002).

Physiological factors contributing to OSA include the important role the central nervous system plays in modulating abnormal changes in pressure (Bradley & Phillipson, 1985; King, O'Donnell, Smith & Schwartz, 2000). There has been considerable research into the neural mechanisms that have an effect on the upper airway, and how changes in sleep might affect the control of these muscles (White, 2006). Histaminergic, serotonergic, noradrenergic, and cholinergic neurons play a role in maintaining wakefulness (White). The firing frequencies of these neural systems decrease with the transition from wakefulness to non rapid eye movement sleep (NREM), and mostly cease activity during REM sleep (White). Hence, investigations have sought to determine how changes in these neural systems that are induced by sleep, affect the activation of the upper airway muscles.

In patients with OSA, the regions behind the soft palate and the tongue are the major sites of airway collapse (Bradley & Phillipson, 1985; White, 2006). Imaging studies have examined this section of the airway and have found that the cross-sectional dimensions of the airway are invariably diminished in patients with OSA compared to healthy subjects (Bradley & Phillipson). Consequently, when sleep induces physiological changes in upper airway muscle function, and

this is superimposed on a structurally small pharynx, the tendency for the airway to collapse is increased (Bradley & Phillipson). Several mechanisms have been proposed to account for the small airway lumen in patients with OSA. Firstly, an important anatomical factor often related to the development of OSA is the dimensions of the lower face, which tend to be smaller in patients with the condition (Bradley & Phillipson; Miyamoto, et al. 1999). The second major finding is of the important role obesity plays in accounting for a small lumen (Bradley & Phillipson; Richman, et al. 1994; Tangugsorn, Krogstad, Espeland & Lyberg, 2000).

From robust epidemiological studies, the general consensus is that there is a strong association with being male and the presence of OSA, and most population-based studies have estimated a two to three fold greater risk for men compared to women (Davies & Stradling, 1990; Strohl & Redline, 1996). Davies and Stradling analysed twelve studies of OSA prevalence in Western populations and estimated that 1-5 % of adult men have OSA. However, its presence in women is increasingly recognised with a focus on the role of sex hormones being an important factor. This has been a fruitful area of investigation, since OSA is relatively uncommon in premenopausal women, with a rise in prevalence noted after menopause (Bixler et al., 2001; Kristal, Edinger, Wohlgemuth & Marsh, 1998). However, administration of oestrogen and progesterone to men (or postmenopausal women) has not been shown to reduce the incidence of apnoeas or hypopnoeas (Shaver & Zenk, 2009).

Obesity is another major risk factor for OSA and is probably the single most predictive factor involved. In prosperous societies, obesity is a major health problem and is observed in 60% of patients with OSA (Richman, et al., 1994;

Strobel & Rosen, 1996). Elevated body mass index (BMI) is a major risk factor for OSA (Dagan, Doljansky, Green, & Weiner, 2006; Strobel and Rosen). Tangugsorn et al. (2000) performed skeletal and upper airway tissue morphology analyses on obese and non-obese patients and found different features that cause airway obstruction in the two groups. The obese patients displayed more abnormalities relating to upper airway soft tissue morphology and head posture. Specifically, the soft tissue of the upper airway was larger in obese patients, particularly that involving the tongue and soft palate. In contrast, the non-obese group showed deviations in the anatomy of cervico-craniofacial structures. These findings were also supported by research by Paoli et al. (2001).

Horner, et al. (1989) examined the sites and sizes of fat deposits around the pharynx in obese patients with OSA compared to healthy control patients. Their investigations used magnetic resonance imaging (MRI) and found that more fatty deposits were evident in areas surrounding the collapsible portions of the pharynx in the OSA patients. It was suggested that the presence of such fat deposits might compromise the function of the upper airway muscles by causing the narrowed airspace to be more dependent on the muscle activity for patency (Horner et al.).

1.1.3. Diagnosis of OSA

The main symptoms suggestive of OSA include loud snoring, nocturnal apnoeic spells, waking at night fighting for breath or with a feeling of choking, dry throat and morning headache, and daytime somnolence (Mendelson, 1987; Bearpark et al., 1993). However, the definitive diagnosis of OSA depends on full polysomnographic studies. Polysomnography involves recording multiple

variables during sleep, including the electroencephalogram (EEG), blood oxygen saturation, and nasal airflow and/or chest movements.

OSA is defined by the number of obstructive apnoea and hypopnoea episodes per hour of sleep (apnoea–hypopnoea index, AHI). Also important when determining the severity of sleep apnoea are the number of sleep disruptions or arousals and the frequency and degree of desaturation of blood oxygen levels. An AHI greater than 5-10 is commonly considered abnormal and reflects a departure from the normal physiology of breathing during sleep. The American Academy of Sleep Medicine (1999) recommends that mild sleep apnoea be defined as an AHI of >5 and ≤ 15 episodes per hour; moderate sleep apnoea, $AHI > 15$ and ≤ 30 episodes/hour; and severe sleep apnoea, $AHI > 30$ episodes/hour.

Another index that is used to measure sleep apnoea severity is the respiratory disturbance index (RDI). The respiratory disturbance index is similar to the apnoea-hypopnoea index, however, it also includes respiratory events that disrupt sleep, but that do not technically meet the definitions of apnoeas or hypopnoeas (American Academy of Sleep Medicine, 1999).

1.1.4. Treatment of OSA

Treatment of OSA has evolved over the past decades to now include weight loss, postural therapy, pharyngeal surgery, mandibular advancement splints, continuous positive airway pressure (CPAP), and more recently medication. Weight loss has been shown to be relatively effective in decreasing the number of apnoeic events, and in reducing arterial oxygen desaturation and sleep fragmentation. Weight loss has been found to result in a decrease in adipose tissue surrounding the upper airway, which, in turn, results in improved upper

airway function and less frequent pharyngeal collapse (Shelton, Woodson, Gay, & Suratt, 1993). Education, behavioural modification and therapeutic follow-up are important in aiding weight loss maintenance and need to be encouraged as part of weight loss programs for those with OSA. Other lifestyle factors such as smoking cessation and avoidance of alcohol are also recommended.

Patients with OSA demonstrate structural abnormalities of the upper airway that can occur at multiple sites. These abnormalities can now be successfully detected using imaging techniques such as cephalometric radiographs, computerized tomography (CT) scans, and MRI (Hsu & Brett, 2001) and can be the focus of surgery when other non-surgical interventions have been exhausted or are not tolerated. However, a significant limitation of surgical correction of the upper airway is the lack of long-term outcome studies providing evidence for long-term efficacy.

The most effective and most frequently prescribed treatment for OSA in adults is CPAP. CPAP uses positive pressure delivered via a nasal mask to pneumatically splint the upper airway thus preventing collapse usually associated with OSA (Massa, Gonzalez, Lavery, Wallis, & Lane, 2002). A mask placed over the nose (or nose and mouth in mouth breathers) is used every night throughout the night, to keep the upper airway open by continuously blowing air from a flow generator at a titrated pressure through the upper airway. The necessary pressure is titrated when patients undergo a CPAP implementation polysomnography sleep study usually in a laboratory setting. A Cochrane review assessing the effects of CPAP on treating OSA in adults revealed that for people with moderate to severe levels of the disease, CPAP was effective in reducing symptoms of sleepiness, cognitive dysfunction, and improved quality of life (Lim et al., 2006). It was also

shown to be more effective than oral appliances (i.e., mandibular advancement splints) in reducing respiratory disturbances.

Since CPAP is not a curative treatment, it must be prescribed indefinitely. Thus, non-compliance is a major limiting factor hampering utility of the treatment. There are probably many reasons that patients find it difficult to adhere to CPAP therapy. For example, poor adherence can be related to side effects such as nasal irritation and congestion. This idea was supported by Lewis, Seale, Bartle, Watkins, and Ebden (2004), who found that patients reporting 'initial problems' with CPAP were less likely to show good long-term adherence. They also found that those who 'lived alone', and/or those who had experienced 'recent life events' also reported lowered adherence rates to CPAP therapy. Lewis et al. found no association between initial anxiety and depression scores and long-term CPAP therapy.

Given that CPAP therapy is quite intrusive, it might be assumed that an alternative treatment, for example drug therapy, may improve treatment compliance. Hudgel and Thanakitcharu (1998) suggested that pharmacological agents may improve sleep-disordered breathing by "changing sleep stage distribution, increasing the relative activity of upper airway muscles during sleep to enhance upper airway patency, and altering the control of breathing in order to improve or stabilize the pattern of breathing" (p. 697). Various pharmacologic options include ventilatory stimulants, psychotropic agents, and antihypertensive agents. However, the paucity of randomised control trials means that the efficacy of these pharmacological agents is unproven. Nonetheless, researchers hold hope that a medication may be discovered that will be a complete treatment for OSA.

1.1.5. Hypoxia

A major hallmark of OSA is the occurrence of intermittent hypoxia (IH) and hypercarbia during sleep (Beebe & Gozal, 2002). IH can be defined as repeated episodes of hypoxia combined with periods of normoxia (Neubauer, 2001). It has been well demonstrated that these repeated episodes of on and off bouts of hypoxia elicit changes in a variety of cellular and molecular processes and physiological responses (Chavez, Pichuile, Boero, & Arregui, 1995; Semenza, 2000). These include intermittent blood gas abnormalities, pulmonary hypertension, and increased incidence of cardiovascular and cerebrovascular disease (Beebe & Gozal). Beebe and Gozal describe intermittent blood gas abnormalities as not only disrupting cellular and chemical processing, but also as “altering the restorative processes occurring during sleep” (p. 2).

When discussing the effects of hypoxia on the human body, research has focused on two clinically relevant points of discussion. Firstly, it has become apparent that there are physiological adaptations that combat the chronic effects of hypoxia. These adaptations prove beneficial in protecting against disease and maximizing the efficient use of oxygen for metabolic demand, particularly for improving athletic performance (Neubauer, 2001; Ridgway & McFarland, 2006). The second point of discussion focuses on the long-term detrimental consequences of more chronic IH, such as that seen in OSA.

Ridgway and McFarland (2006) examined the effects of repeated acute and chronic hypoxaemia in healthy individuals who were apnoea (breath-hold) divers. The results were discussed in relation to implications for clinical conditions such as OSA. The authors reported that breath holders appeared to demonstrate relatively intact physiological and cognitive functioning, which gives

insight into how the brain and body adapt to conditions of low oxygen. However, the clinical pathology of the IH associated with OSA suggests that there may be long-term adverse consequences of chronic IH, with chronicity most likely determining whether the body's responses change from providing protection from disease to creating pathology. Serious consequences of IH are elevation of pulmonary artery pressure, heart rate, and sympathetic nerve activity, and development of pulmonary hypertension (Okabe et al., 1995; Bradley & Phillipson, 1985). Another potentially serious consequence of IH may involve its long-term deleterious effects on neuronal and intellectual function.

Patients with severe OSA have a pattern of IH that consists of repetitive periods of deoxygenation followed by reoxygenation. They may experience apnoeic periods that exceed 60 seconds (Pack, 2006; Ridgway & McFarland 2006). The subsequent ischaemia followed by reperfusion results in oxidative change and production of free radicals (Pack). This repetitive cycle has been studied in rodents, and has been associated with significant increases in neuronal apoptosis and reduced functionality within brain regions that mediate learning and memory. Specifically, IH has been found to kill rodent brain cells in the hippocampus, and interferes with the long-term potentiation process that strengthens neural connections (Goldbart, Row, Kheirandish, Brittan, & Gozal, 2004). Hippocampal damage most likely contributes to the learning impairments noted in OSA. Damage has also been noted in regions of the brain responsible for sleep and wakefulness, thus possibly contributing to the persistent sleepiness noted in OSA (Row, Liu, Xu, Kheirandish, & Gozal, 2003; Veasey et al., 2004).

1.1.6. Sleepiness

Sleepiness is referred to as the probability of falling asleep at a particular time (i.e., sleep propensity) (Johns, 2001). At the end of the apnoea-hypopnoea episodes characteristic of OSA, sleep fragmentation occurs along with arousals, with changes on EEG representing returns to wakefulness that may last from <5sec to >20sec (Pepperell, Davies, & Stradling, 2001). This results in excessive daytime sleepiness (EDS) in patients and an inability to stay awake during the day is one of the most common complaints made by those who experience OSA (Bedard, et al. 1991). The consequences of such excessive sleepiness include decreased cognitive function and poorer quality of life, as well as an increased risk of industrial and motor vehicle accidents.

As a means of measuring the functional consequences of sleepiness, particularly falling asleep during standard wakefulness, the Multiple Sleep Latency Test (MSLT), or a variant such as the Maintenance of Wakefulness Test (MWT), is often applied (Strohl et al., 1994). This is an electrophysiological test that correlates with different degrees of sleepiness and measures functional consequences of sleep disruption at 2-hour intervals across waking portions of the day. It has dominated the literature for many years (Strohl et al.). Tests such as these are expensive and time-consuming, take all day to administer, and are therefore not always carried out (Johns, 1993).

Johns (1991) devised the Epworth Sleepiness Scale (ESS), which is a simple questionnaire, to subjectively measure general levels of daytime sleepiness. It asks the subject to rate the chance of falling asleep in eight different situations (Johns, 1991, 1993). Johns (1993) reported that sleepiness, measured by the ESS, was related to both the severity of OSA, and to snoring. It was found

that ESS scores increased with the severity of OSA, and that these patients were distinguishable from primary or simple snorers. Furthermore in 2000, Johns also showed that the ESS was more accurate than the MSLT at distinguishing excessive daytime sleepiness of narcoleptics from the sleepiness of normal individuals. While the ESS measures subjective sleep propensity, it does not measure the particular feelings and symptoms of sleepiness. The Karolinska Sleepiness Scale (KSS) is a quick and simple way to estimate sleepiness. It requires participants to simply rate feelings of sleepiness on a nine-point scale ranging from “very alert” to “very sleepy” (Akerstedt, 1990).

Excessive daytime sleepiness in OSA appears to result from recurrent arousal from sleep, rather than from intermittent hypoxia. The number of apnoea events per hour of sleep is the most common way in which the severity of OSA is measured (the apnoea-hypopnoea index – AHI). Some authors consider the AHI to be the best predictor of daytime sleepiness (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991; Guilleminealt et. al, 1988; Tangugsorn et. al, 2000). Other factors that have been measured and thought to influence EDS include, the degree of oxygen desaturation, gender, and being overweight, however the importance of these factors in affecting EDS have been variable.

A number of studies have sought to determine the relative contribution of both sleep fragmentation and hypoxaemia to EDS. Orr et al., (1979) compared patients with OSA who were either hypersomnolent or asymptomatic for sleepiness. The authors found no difference between the two groups in terms of the degree of sleep disturbance but did find that oxygen desaturation during apnoeic events in somnolent patients was greater and persisted for longer durations than in the non-somnolent patients. This finding strongly suggested that hypoxaemia was

mainly responsible for the EDS. However, a limitation of the Orr et al. study was that sleepiness was assessed by subjective complaints rather than via objective measures. This limitation, along with the small sample size, raises concerns about the validity of these findings.

In 1989, Roehrs et al. used the arousal index as well as measures of hypoxaemia in 466 OSA patients to determine predictors of daytime sleepiness, as measured with the Multiple Sleep Latency Test. This tests measures the number of minutes it takes a patient to fall asleep (Carskadon & Dement, 1977). Using multiple regression analysis, they found that the arousal index was the single best predictor of sleepiness, and that hypoxaemia added little predictive information to the explained variance when arousal index was included in the regression model. Similarly, Colt, Haas and Rich (1991) studied the effects of intermittent hypoxaemia on EDS in seven patients with OSA. Patients were examined under three conditions: baseline (where fragmentation and hypoxaemia were apparent), optimal CPAP pressure (which corrected fragmentation and hypoxaemia), and on CPAP with induced episodic hypoxaemia (no fragmentation). The significant finding of this study was that in both experimental conditions, sleepiness was improved compared to baseline, lending support to the hypothesis that hypoxaemia, on its own, does not cause EDS.

Studies have investigated both sleep disruptions and nocturnal hypoxaemia, and the relative contribution they make to daytime somnolence (Poceta, Jeong, Timms & Mitler, 1990). Poceta et al. found that hypoxaemia was likely to be the primary pathogenetic factor for somnolence in more severe cases of OSA. However, in more mild forms of the disorder, sleep disruption contributes more. Consequently, both pathogenetic factors appear to contribute to

vigilance impairment in OSA, with the contribution being dependent on the severity of the disorder (Poceta et al.).

Bedard et al. (1991) also found that measures of hypoxaemia were the best predictors of daytime sleepiness and alertness in moderate to severe OSA. Thus, it appears that in patients experiencing only mild hypoxaemia, the daytime somnolence is due to the number of arousals during sleep, while in those experiencing more hypoxaemia; the primary cause is related to the severity of hypoxaemia.

1.1.7. Drowsiness

Drowsiness or the drowsy state is a term used by some authors to distinguish sleepiness (propensity to fall asleep) from an intermediate state between sleep and wakefulness (Johns, 2001). When falling asleep intentionally, the drowsy state typically lasts for only a few minutes. However, when struggling to stay awake, for example when driving, it can last much longer (Johns). The tendency to become drowsy can result from a number of factors, including, sleep deprivation, time of day, and sleep disorders such as OSA.

When in the drowsy state, fluctuations in awareness and impaired performance are observed. The periods of lack of awareness are sometimes, but not always associated with a 'microsleep'. These are very brief periods of falling asleep that can last from 3-15 seconds and are sometimes evident on EEG recordings (Priest, Brichard, Aubert, Liistro, & Rodenstein, 2001). People who experience excessive daytime sleepiness are at high risk of microsleep episodes, and are often unaware that they have occurred. Williams Lubin and Goodnow (1959) showed that microsleeps increase with sleep deprivation. Microsleeps are

often responsible for failure to respond appropriately to the environment and result in motor vehicle accidents (Williamson, Feyer, Friswell, & Finley-Brown, 2000).

Although subjective measures of sleepiness, such as the ESS and KSS, have been used in order to assess levels of drowsiness, these measures do not correlate well with each other and, moreover, correlate poorly with motor vehicle accident risk (George, Boudreau, & Smiley, 1996). Patients with OSA may be reluctant to disclose daytime sleepiness and its relationship to driving, either due to poor awareness of risk or because of the potential for loss of driving license and employment (Engleman, Hirst, & Douglas, 1997; George et al., 1996; Horstmann, Hess, Bassetti, Gugger, & Mathis, 2000). Given that many studies rely on subjective data, inconsistencies in reporting complicate the ability to accurately predict safety when operating a motor vehicle. More objective measures of drowsiness would be useful for determining the ability of OSA patients to drive safely.

In order to objectively monitor drowsiness and microsleeps, a number of different measures have been used. Traditionally, electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) have been used to monitor sleep in the laboratory. However the impracticality of requiring electrode placement makes it difficult to monitor the drowsiness of drivers. Furthermore, findings have indicated that EEG recordings are not entirely reliable in signaling the onset of drowsiness (Mitler, Miller, Lipsitz, Walsh, & Wylie, 1997).

Increasing frequency and duration of eye closure, as measured by EOG and video monitoring have also been studied as indicators of driver drowsiness (Hakkanen, Summala, Partinen, Tiihonen, & Silvo, 1999). Blink duration should

indicate drowsiness, even before the occurrence of microsleeps, and therefore may be useful in identifying sleepiness-related risks. Various changes to eyelid and eye movement patterns occur in response to sleep loss and have been shown to correlate with sleepiness (Cajochen, Khalsa, et al., 1999; Santamaria & Chiappa, 1987). In particular, slow eye movements (SEM's) have been demonstrated during the drowsy state that precedes sleep onset and are also evident during light sleep (Aserinsky & Kleitman, 1955). Cajochen et al. found an increase in slow eye closure in 10 healthy males, after 16 hours of wakefulness during a 32 hour period of sleep deprivation.

Blink duration and slow eye closure have also been demonstrated with increasing duration on a task. Morris and Miller (1996) conducted a study of ten partially sleep deprived military pilots during simulated flying. Measuring blink rate, blink duration, long eye closure rate, and blink amplitude, they found that error scores increased significantly with increased task duration. Furthermore, blink rate, blink duration, and long eye closure correlated with increased subjective sleepiness and correlated positively with performance errors. Hakkanen et. al (1999) used a video-scanning method and found that bus drivers with OSA showed increased daytime sleepiness in terms of blink frequency duration on a driving task. The findings indicated that blink frequency was associated with feelings of increased sleepiness. Driver drowsiness has also been assessed using video-images of the vehicle operator's face. Drowsiness can be determined based on slow eye closure, as well as characteristics such as rubbing, yawning, nodding and facial tone (Wierwille, & Ellsworth, 1994). However, differences in rater assessments and scoring of drowsiness make it difficult to establish validity using this method.

PERCLOS (the percentage of time that the eyes are more than 80% closed), developed by Wierwille et al. (1994), has been particularly advocated as a useful method for detecting drowsiness and microsleeps. This method involves automatic video scoring of eye closure. Dinges, Mallis, Maislin and Powell (1998) evaluated the system against a number of different performance measures. Relationships were found between eye closure and lapses in attention and performance on a driving simulator.

However, it is known that some sleep deprived participants fall asleep while their eyes are still open, termed 'driving without awareness' (Karrer, Briest, Vohringer-Kuhnt, Baumgarten & Schleicher, 2004). Given that PERCLOS relies on eyelid closure, and does not include an assessment of eye movements, it is possible that by the time a driver's eyes are mostly closed, they have been driving but not necessarily seeing. Chapman, Johns & Crowley (2006) found that on a vigilance test, 53.8% of errors of omission occurred without the eyelids being fully closed, and 26% of the errors while drowsy occurred with the eyes wide open all or some of the time. Video camera methods of detecting eye closure are unable to detect such centrally mediated lapses in attention that occur when the eyes are open (Chapman, et al.). Furthermore, although the PERCLOS method has been used extensively in research settings, unfortunately very little progress has been made in assessing active participants, for example, while actually driving on a roadway.

Sleep Diagnostics Pty Ltd, Melbourne, Australia, has developed and patented a new method to monitor the drowsiness of drivers and to answer the question of when someone is too drowsy to drive. The Optalert™ method consists of small infrared transducers attached to a spectacle frame that allows continuous

monitoring of the eyes while driving on road (Johns, Tucker, Chapman, Crowley, & Michael, 2007). Each movement of the eyelids and eyes is monitored, providing a minute-by-minute measure of drowsiness. A significant strength of this method is that drivers can be warned when they first demonstrate signs of drowsiness, often well before they are aware, and importantly, before their drowsiness reaches a dangerous level. The objective information that Optalert™ provides overcomes the limitations associated with subjective reporting of drowsiness and contributes to minimising the risks associated with drowsy driving (Johns et al., 2007). This should enable individuals to be aware of drowsiness and to implement appropriate management strategies to prevent falling asleep while driving. Several trials have been undertaken to validate Optalert™ including under conditions of sleep deprivation and various blood alcohol concentrations. However, it has not yet been validated in patients with OSA or COPD.

This method has led to the recognition of new parameters of drowsiness, particularly the relative velocity of eyelid movements. This is derived from ratios of the amplitude and maximum velocity of blinks (Johns, 2003). This is termed the amplitude velocity ratio (AVR). Tucker and Johns (2005) showed that each component of a blink (eyelids closing, remaining closed and reopening) increases with drowsiness. However, when correlations between these components of a blink are measured, the relationships are fairly low and not always statistically significant. Similarly, significant correlations are not always found for the relationship between velocities of eyelid closure and reopening, as measured by the AVRs (Johns & Tucker). When considering these weak relationships, Johns and Tucker suggested that depending on one variable to measure drowsiness is not reliable.

The Johns Drowsiness Scale (JDS) was developed to assess drowsiness while taking into consideration many variables. This included the AVRs for closing and reopening of the eyelids, and the durations of the eyelids closing, of remaining closed, and of reopening during blinks (Johns, Tucker & Chapman, 2005). The JDS is calculated every minute on a scale of 0-10, with scores of 0-4 considered normal. In their study Johns et al. found that Optalert™ was effective in monitoring the drowsiness of drivers continuously and could potentially prevent crashes by prompting drivers to implement a drowsiness management strategy before they fall asleep at the wheel and crash. They collected recordings for 8 volunteers who drove in a simulator for 45 min, both when alert and following up to 30 hours of sleep deprivation. They also studied commercial truck drivers who were asked to drive their usual work routes and schedules. In drivers who were alert and who drove without incident, the JDI varied between 0.5 and 4.0. In those who were sleep deprived, a total of 61 off-the-road crashes in the simulator were recorded. These incidents could have been anticipated with a warning when the JDS reached 4.5, and more so when it was greater than 5.0.

1.1.8. Driving Performance

Excessive sleepiness and intermittent hypoxaemia as experienced by those with OSA have been shown to have adverse effects. These include impairments relating to skills that are important when driving a motor vehicle including poor ability to maintain concentration as well as, decreased vigilance and reaction times (Akerstedt, 1988; Dinges et al., 1997; Russo et al., 1999; Williamson, Feyer, & Friswell, 1996). Studies have found that those with OSA are at a higher risk of motor vehicle accidents compared to those who do not have the disorder. Findley

et al (1988) reported that patients with OSA had a seven-fold greater risk of motor vehicle accidents in comparison to control participants. Furthermore 24% of sleep apnoea patients reported falling asleep once per week while driving. Similarly, in the Wisconsin Cohort Study, Young, Blustein, Finn and Palta (1997) found that men with five or more apnoeas and hypopnoeas per hour of sleep compared to those with no evidence of sleep disordered breathing, were significantly more likely to have had at least one accident in the previous five years.

Although those with respiratory disturbance indices as low as five to ten events per hour, have demonstrated an increased rate of motor vehicle accidents (Findley, Unverzagt & Suratt, 1988; Teran-Santos, Jimenez-Gomez, & Cordero-Guevara, 1999), there is also evidence to suggest that those with more severe disease are more likely to be involved in a crash when compared to those with mild disease (Findley, Fabrizio, Thommi, & Suratt, 1989; Shiomi et al., 2002).

Patients with sleep apnoea also perform worse on tasks of simulated driving (George, 2003; Findley et al., 1989; George et al., 1996; Nilson, Nelson, & Carlson, 1997; Turkington, Sircar, Allgar, & Elliot, 2001). While driving, the operator is required to process complex visual, tactile, and auditory information in order to produce a well-coordinated motor output (George et al.). Among the many tasks involved in driving are the important features of vehicle control, which include maintaining the vehicle within the lane (tracking), and visual search, including scanning for pedestrians, other vehicles, traffics signs and lights (George et al.). Attention is constantly divided between these tasks, and therefore, driving performance simulators have been designed to include these kinds of multiple demands of driving.

George et al. (1997) found that patients with OSA performed substantially worse on the divided attention driving test (DADT), that comprised both visual search and tracking, compared to control participants. There was a greater mean difference between the two groups on the tracking task compared to the visual search measure. These findings indicated that patients with OSA were unable to effectively divide their attention between the two tasks. These results strengthen the findings of Findley et al. (1989) who used two separate driving simulator tasks in order to compare the driving performance of subjects with OSA and controls. The first task simulated highway driving, and the second task simulated rural and city driving. The results indicated that the OSA patients performed worse on both driving tasks compared to the control group and hit a greater number of road obstacles.

Although sleepiness is consistently found as an important contributor to crash risk, Risser et al. (2000) suggested that EEG defined attention lapses play a significant role in poor performance on simulated driving. Fifteen OSA patients and fifteen control participants completed a computer-based driving task that recorded lane position variability, speed variability, steering rate variability, and crash frequency. The frequency of attentional lapses (defined as alpha activity or theta activity lasting three seconds or longer) was also recorded using EEG. The OSA group had greater variability in lane position, steering rate, and speed than the control group, as well as more crashes. EEG revealed more attention lapses that were of longer duration. These lapses were positively correlated to lane position variability and crash frequency.

1.1.9. Vigilance and Lapses in Psychomotor Performance

Changes in mental activity and awareness are evident during the drowsy state where important attentional processes are inhibited (Johns, 2001). Impairment of attention parallels the slowing of reaction times, and both skills are important to the ability to drive safely. Visual reaction time (RT) tests have long been used as measures of these skills, where participants are required to push a button as soon as possible after being presented with a visual stimulus. Following sleep deprivation, RTs increase, where participants are noted to take longer to respond, variability in RT's is observed, and sometimes errors of omission occur where there is a failure to respond at all (Dinges & Kribbs, 1991). Although lapses in performance can be partially attributed to the occurrence of microsleeps, Dinges and Powell (1988) found that performance between lapses on a psychomotor vigilance task (PVT) was also impaired.

The PVT is a sustained-attention, reaction-time task developed by Dinges and colleagues in 1988. It has become a standard laboratory tool for the assessment of sustained performance in a number of experimental conditions (Dinges & Powell, 1988, 1989; Van Dongen, Maislin, Mullington, & Dinges, 2003). Dinges et al. (1997) used the PVT to examine the effect of sleep restriction to only 4-5 hours per night on neurobehavioral alertness while awake. Cumulative sleep restriction resulted in slowed reaction times and increased lapse frequency. The impact of sleep deprivation on PVT performance has been compared with the effects of difference blood alcohol concentrations (Powell et al., 1999). Approximately 20 hours of sustained wakefulness is comparable to a blood alcohol limit in excess of 0.05% (Lamond & Dawson, 1999). Such findings have

highlighted the importance of understanding the impact of sleep deprivation on road safety.

Sleep deprived drivers have been studied in order to determine whether they displayed evidence of peripheral visual field neglect (Russo et al., 1999). In this study, participants were evaluated eight times during sixty-four hours of total sleep deprivation and exhibited impairments on a peripheral visual attention task after twenty hours of sleep deprivation. This dysfunction in peripheral visual field attention may be a behavioural manifestation of cerebral hypo-metabolism due to sleep deprivation (Russo et al.). It may explain motor vehicle accidents, particularly single vehicle, involving driving off the road.

Findley et al. (1995) designed a computer program (Steer Clear) that simulated a long and monotonous highway presenting with obstacles. This program was used as a method to determine impaired vigilance in patients with OSA. The results indicated that patients had poorer performance on the test of vigilance compared to control subjects and that vigilance was further impaired as the severity of OSA increased. Impaired vigilance was also associated with higher motor vehicle accident rates, where patients who hit more than 4.5% of obstacles had a significantly greater automobile accident rate than participants with average performance. Therefore, poor vigilance performance in OSA patients may be a predictor of high risk for automobile accidents.

1.1.10. Neuropsychological Deficits Associated with OSA

Although neuropsychological deficits in intellectual performance, memory, attention, learning abilities, and executive functions in patients with OSA are well recognised, the pathophysiology of these deficits is controversial. Some research suggests that excessive daytime sleepiness is the main contributor to neuropsychological deficits, while other suggests the effects of hypoxaemia are responsible. However, more recent research has suggested that these two factors are differentially related to the observed deficits. Specifically, there is an established association between EDS and attention and memory deficits, while deficits in executive and motor functioning are thought to extend beyond the effects of sleepiness and to be related to hypoxaemia (Bedard et al., 1991; Beebe & Gozal, 2002; Decary, Rouleau, & Montplaisir, 2000). A lack of consensus on the most appropriate way to assess these functions is a likely contributor to the difficulty in making conclusions about the pathogenesis of these deficits.

It has been found that in patients with OSA, general intellectual functioning is reduced, with most studies highlighting the negative effects of hypoxaemia on these abilities. In an early study, Berry, Webb, Block, Bauer, and Switzer (1986) investigated nocturnal hypoxia in heavy-snoring males and found that the number of drops in SaO₂ levels of at least 4% below baseline was negatively correlated with WAIS-R IQ scores. However, confounding factors that may impact on cognitive function, such as vigilance or sleep variables did not appear to be controlled for. Bedard et al. (1991) compared 10 controls with 10 moderately and 10 severely apnoeic patients on neuropsychological assessment, while controlling for vigilance, and found that reductions in measures of general

intelligence (as measured by the Wechsler Adult Intelligence Scale – Revised; WAIS-R) were attributable to the severity of hypoxaemia.

When considering the degree of hypersomnolence reported by patients with OSA, it is not surprising that difficulties in attentional functioning and concentration are frequently identified, and that these impairments may play a role in producing a range of neuropsychological deficits. However, the concept of attention is complex and variations in the neuropsychological measures used to assess this domain result in variable interpretations and conclusions about the pathogenesis of these impairments in patients (Decary, 2000). Furthermore, some studies highlight the role of hypoxaemia in producing attentional deficits (Findley et al., 1986) while others attribute them to excessive daytime sleepiness (Bedard et al., 1991; Greenberg, Watson, Deptula, 1987).

The Trail Making Test is considered to be a test of attention, mental flexibility and speed (Strauss, Sherman & Spreen, 2006). Findley et al. (1986) used the Trail Making Test B (connecting encircled numbers and letters on a page in alternating order) to assess attention and concentration and found that non-hypoxaemic OSA patients were within the expected limits on this task, but that OSA patients who were hypoxaemic had performance scores in the impaired range. However, the hypoxaemic group also had daytime oxygen desaturation and hypercapnia, which may be indicative of pulmonary dysfunction. Therefore, the particular contribution of sleep apnoeas to cognitive dysfunction could not be accurately determined. Bedard et al. (1991) considered Trails B to be a measure of executive function, and instead used Trails A (connecting encircled numbers on a page in order) as a measure of attention and concentration. In their study described earlier, deficits in attentional functioning were related to an increase in daytime

sleepiness, and those patients who were more severely affected showed greater impairments.

The assessment of memory is a fundamental component when assessing the cognitive functioning of OSA patients, with the Wechsler Memory Scale (WMS) being the tool most frequently used to measure memory (Decary, et al., 2000). Memory describes the ability to register, store and retrieve information, and is divided into short-term and long-term memory (STM and LTM). STM abilities are decreased in patients with OSA, regardless of whether verbal or visual information is used (Decary et al., 2000; Findley et al., 1986; Naegele et al. 1995). STM can be further defined as Working Memory (WM), which refers to the ability to temporarily store and manipulate information (Nairne, 1996). Naegele et al. investigated short-term memory impairments in patients with OSA using the digit span and Benton Visual Retention Test. Impairment in both of these measures was predicted by sleep fragmentation, however only digit span was found to be predictive of hypoxaemia. Further research is needed to characterise working memory functioning in OSA patients, as it is yet to receive adequate attention.

LTM impairments are also frequently reported in OSA patients with studies finding deficits for both verbal and visual data (Bedard, et al. 1991; Berry, et al. 1986; Naegele et al., 1995). Episodic LTM memory impairments are common in OSA patients, where experiences include things like forgetting conversations with others, or not remembering details of a movie. This is commonly captured in neuropsychological assessments using the Logical Memory subtest of the WMS that involves recalling stories. Although immediate recall has been found to be impaired in hypoxaemic patients, delayed recall of these stories is most commonly reported as being impoverished. On the other hand, increased levels of sleepiness

are associated with poorer performance in recalling word lists (Valencia-Flores, Bliwise, Guilleminault, Cilveti, & Clerk, 1996).

Despite the findings of deficits in LTM, relatively little is known about procedural memory in patients with OSA. Procedural memory is a form of learning that cannot be verbalized and is therefore expressed implicitly. It refers to “the gradual acquisition and maintenance of motor skills and procedures” (Decary et al., 2000, p. 372) and involves complex interactions of the basal ganglia. Given that these brain structures are among those most vulnerable to hypoxaemia, and that a slowing of EEG in frontal regions has been recognized in OSA patients, these patients may retain a lowered capacity for procedural learning (Decary et al.). However, despite this hypothesis, Rouleau, Decary, Chicoine, Montplaisir (2002) found that OSA patients did not demonstrate procedural skill learning impairments when completing the Mirror Tracing and Rotary Pursuit tasks. Although OSA patients demonstrated normal learning on Mirror Tracing, they did have difficulty with initial adaptation to the task. This suggests that OSA patients have difficulty applying efficient strategies when completing tasks of skill learning that require higher cognitive demands (Rouleau et al). Push-button maze-learning tasks, such as the Austin Maze (AM) have been successfully used to assess procedural learning, topographical memory, and executive function in a number of populations (Bowden et al. 1992; Milner, 1965).

Executive functions play a role in controlling and managing a range of cognitive systems. These functions involve processes such as planning, organisation, cognitive flexibility, abstract thinking, and initiation and inhibition of certain behaviours. The prefrontal cortex (PFC) of the brain is important for executive function and is most vulnerable to the effects of intermittent hypoxia as

a result of its high metabolic demands (Harrison & Horne, 2000). Drummond et al. (1999) suggested that the PFC is also sensitive to sleep deprivation. It is not surprising then, that patients with OSA demonstrate significant deficits in executive function on neuropsychological tests. Trails B is considered by some researchers to be a test of conceptual visuomotor tracking and has been found to be related to impairments in executive function. Bedard et al. (1991) found that OSA patients required a significantly greater amount of time to complete this task. Additionally, they demonstrated that OSA patients had planning difficulties on a maze task, and organisational difficulties on the Picture Arrangement subtest of the WAIS-R.

Further research into neuropsychological deficits associated with OSA needs to address the issue of how to best assess cognitive functions and to increase the understanding of the underlying nature of these impairments. Although sleep fragmentation and intermittent hypoxia appear to contribute to these effects, the independent contribution they make continues to be unclear.

1.1.11. Brain imaging

Research using neuroimaging has made important contributions to understanding impairment in brain structure and function in patients with OSA. Structural MRI has been useful in characterising the neuroanatomy in patients and allows investigation of volumetric and morphometric abnormalities. However results have been inconsistent. Macey et al. (2002) were one of the first groups to comprehensively investigate brain morphology in patients with OSA and in appropriately matched control participants using high-resolution T1-weighted magnetic resonance imaging. They found that the morphology of brain areas

between the two groups differed, with OSA patients demonstrating grey matter volume reductions of up to 18% in some regions. As might be expected, the reductions increased with the severity of the disorder. The grey matter volume declines appeared bilaterally in portions of the parietal, frontal, and temporal cortices, hippocampus, anterior cingulate gyrus, and in the cerebellar cortex.

O'Donoghue et al. (2005) conducted a similar analysis in order to attempt to replicate the findings of Macey et al. (2002) However, the use of Macey et al's post data processing technique, as well as their own manual tracing technique, failed to find any evidence of grey matter abnormalities in patients with OSA. Results of both studies highlight the fact that variability in study protocols and different research MRI's may have a significant effect on results obtained. Furthermore, the groups appeared to mutually conclude that brain abnormalities might be relatively small and not evident following conservative statistical techniques (Zimmermann & Aloia, 2006).

More consistent findings have been reported regarding the presence of decreased hippocampal volume in patients with OSA and this is believed to be related to the effects of intermittent hypoxaemia. Gale and Hopkins (2004) investigated the effects of hypoxaemia on the brain and neuropsychological functioning in patients with severe OSA and in patients with carbon monoxide poisoning. Thirty-six percent of patients with OSA had evidence of hippocampal atrophy that was significantly negatively associated with deficits in non-verbal memory and information processing. Furthermore, a statistically significant association was found between baseline oxygen saturation and hippocampal volume in these patients.

Barlett et al. (2004) also found hippocampal dysfunction in patients with OSA following the use of Magnetic Resonance Spectroscopy (MRS). A strength of their study was that metabolic levels and neuropsychological test performance demonstrated a significant association. Other MRS studies have examined brain metabolism in OSA patients and have found white matter impairments, particularly in the frontal lobes. Kamba et al. (2001) adequately controlled for comorbid medical conditions, such as hypertension and diabetes mellitus, to examine cerebral metabolic abnormalities in OSA. The severity of OSA was found to have a significant negative correlation with N-acetylaspartate (NAA)/Choline (Cho) ratio for white-matter, indicating cerebral metabolic abnormalities, such as gliosis, and neuronal impairment.

Neural deficits in OSA have traditionally been assumed to represent a consequence of the disorder. However, more recent research has suggested results that may reverse this earlier thinking. Volume changes in grey matter may have been present before the onset of OSA and may have contributed to the characteristics of the syndrome (Macey et al. 2002). This is because the grey matter losses have occurred in the left frontal cortex of the brain, an area that modulates upper airway motor function. Grey matter loss has also been found in the cerebellum, a structure considered important for cardiovascular and respiratory control (Gozal, Daniel, & Dohanich, 2001). Macey et al. suggest that the characteristics of OSA lend support to damage to neural systems that may maintain the syndrome. For example, the delay in the restoration of muscle airway tone following an obstruction may be indicative of alterations in the normal control systems or afferent systems that respond to airway closure. Similarly, the authors also state that the typical morphology of OSA patients (obese, short and

large neck, small airway) may imply dysfunction of central neuroendocrine or metabolic regulatory systems. Furthermore, the evident range of cognitive and behavioural deficits suggests involvement of neural areas responsible for functions other than respiratory control (Macey et al. 2002).

Methodological challenges exist that hinder the strength of the conclusions made regarding neuroimaging results. Further research should be aimed at controlling for co-morbid medical conditions, using longitudinal rather than cross-sectional designs, and examining the relationship between neuroimaging and cognitive deficits more comprehensively.

1.1.12. Reversal of Cognitive Deficits

Sleepiness, driving performance, and performance on cognitive tests have been shown to improve significantly after treatment with nocturnal nasal continuous positive airway pressure (CPAP) (Borak et. al, 1996; George, 2001; George, Boudreau, & Smiley, 1997). In a study by Borak et al., tests were performed before, after three months and after twelve months of CPAP treatment. The investigation found that after one year of CPAP treatment significant improvements occurred in visual and spatial memory, concentration, speed of processing, and verbal memory, with results of concentration, and memory tests already significantly improved after three months of treatment. Despite this, after one year of treatment, no significant improvement was observed in IQ. Consequently, it can be implied that CPAP treatment may result in early improvement of selected cognitive function.

An important aspect of OSA is whether treatment with CPAP has a positive effect on driving ability and crash risk. Engleman et al. (1996) studied sleep-related driving incidents (accident and near accidents) in OSA patients before and after CPAP treatment. Patients reported 0.93 incidents per 16,000 km before treatment, and 0.14 after treatment. However, the study relied on retrospective self-reports which may have compromised accurate recall of events. George (2001) investigated 210 patients with OSA together with control participants, and evaluated motor vehicle collision (MVC) rates. They used records from the Ontario Ministry of Transportation database before CPAP therapy, and three years following initiation of therapy. There was a three-fold higher rate of MVC'S in OSA patients before treatment compared to control participants. However the rate fell to comparable levels to the control group in the three-year period following the introduction of CPAP therapy. Collision rates for patients not having undergone treatment remained higher than in control participants over the study period. Although one study has suggested an improvement in driving ability following 14 days of CPAP treatment, there is relatively little known about the time course of the improvement with treatment. Future research will be useful to investigate this further.

D'Ambrosio et al. (1999) investigated quality of life in patients with OSA and its response to CPAP. They used the Medical Outcomes Study Short Form-36 questionnaire before and after 8 weeks of CPAP therapy. When compared with an age and gender matched population, eight weeks of CPAP improved subjective feelings of vitality, social functioning, and mental health. The magnitude of improvement was related to the degree of impairment prior to treatment rather than to the severity of OSA.

1.1.13. Quality of Life

The cognitive impairment, excessive daytime sleepiness and medical consequences experienced by those with OSA undeniably affect their quality of life. The sequelae include depressed mood, irritability, personality changes, sexual dysfunction, and decreased vitality. Studies have found that quality of life assessment in obstructive sleep apnoea falls into major areas that include daytime symptoms, nocturnal symptoms, and limitation of activities, emotional function and interpersonal relationships (Lacasse, Godbout Sériès 2002).

Many studies have suggested a relationship between OSA and depression. Guilleminault et al. (1977) were one of the first groups of researchers to report this association and found that 24% of 25 male patients with OSA had previously seen a psychiatrist for anxiety or depression. Similarly, Reynolds et al. (1989) demonstrated that approximately 40% of 25 male OSA patients met the research diagnostic criteria for an affective disorder. Those who demonstrated more excessive daytime sleepiness had a higher risk of depression. Furthermore Ramos Platon & Espinar Sierra (1992) found that patients with OSA demonstrated personality patterns that were characteristic of a neurotic-mixed type, indicating an anxiety reaction with paranoid features. Depression, schizophrenia, and hypochondriasis were the highest scales. In addition, most patients had severe psychosocial maladjustment.

EXPERIMENT 1

The aim of this study was to compare simulated driving performance and subjective and objective sleepiness in patients with obstructive sleep apnoea with that of healthy control participants. A further aim of this study was to assess neuropsychological functioning in these groups, by comparing memory performance, sustained attention, reaction time, and vigilance. In an effort to explore the nature, extent, and source of these impairments this study also aimed to compare polysomnography characteristics of the groups and investigate the relationship between sleepiness, hypoxaemia and performance. The following hypotheses were proposed.

Hypotheses

1. Patients with OSA would weigh more and have a higher BMI and MAPI when compared to control participants.
2. Patients with OSA would experience decreased total sleep time and sleep efficiency, as well as greater number of arousals per hour of sleep, a higher AHI, and more total sleep time where oxygen was below 90% saturation when compared to the control participants.
3. OSA patients would report higher levels of subjective sleepiness in comparison to control participants.
4. Patients with OSA would perform more poorly on tests of simulated driving performance, sustained attention, vigilance, and reaction time, than control participants.
5. OSA patients would demonstrate increased objective sleepiness in comparison to control participants.

6. Patients with OSA would perform more poorly on tests of neuropsychological function than control participants.
7. Higher levels of subjective sleepiness would be associated with slower reaction times on the PVT, and poorer performance on the driving simulator.
8. Higher levels of subjective sleepiness would be associated with poorer performance on neuropsychological tasks.
9. Decreased total sleep time and sleep efficiency, a higher number of arousals, and high AHI would be associated with slower reaction times on the PVT, and poorer performance on the driving simulator.
10. Decreased total sleep time and sleep efficiency, a higher number of arousals, and higher AHI would be associated with poorer performance on neuropsychological tasks.
11. Sleep disturbances and nocturnal hypoxaemia as indicated by polysomnography measures would be associated with increased daytime sleepiness and levels of alertness as measured by the ESS and KSS.

1.2. Method

1.2.1. Participants

The participants were 14 patients who had been diagnosed with moderate to severe OSA (AHI of greater than 20) following an overnight polysomnography sleep study, and 11 closely matched (age and gender) control participants who were recruited from the community via advertisements (See Appendix A). The OSA sample were untreated at the time of the current study, but were planning to proceed with CPAP treatment, and included 12 males and 2 females between the

ages of 39 and 71 years ($M = 54.64$ years, $SD = 10.95$), with a mean Body Mass Index (BMI) of 32.04 ($SD = 8.09$). The control group consisted of 9 males and 2 females between the ages of 26 and 72 ($M = 54.73$, $SD = 12.37$), with a mean BMI of 25.96 ($SD = 3.95$). Control participants were screened for sleep disordered breathing using the Multivariate Apnoea Prediction Index (MAPI) (See Appendix D) and excessive daytime sleepiness using the ESS (See Appendix B). Those with a score greater than 10 on the ESS were excluded.

All study participants were required to be capable of giving consent, be greater than 18 years of age and hold a current drivers licence. Medical records of all OSA patients were examined against the selection criteria and any participant experiencing chronic neurological illness, chronic liver disease, diabetes requiring insulin, renal impairment, pregnancy or breast-feeding, chronic psychiatric illness, visual acuity problems not correctable with glasses, or regular use of medication known to affect cognition were excluded. Participants unable to speak and read English were also excluded.

Upon ethical approval from the appropriate committees, information sheets were given to the participants and they were invited to take part in the study. The purpose of the study was explained verbally and any questions the participants had were answered.

1.2.2. Materials

Plain Language Statement. The purpose of this statement was to explain as openly clearly as possible the nature of the research, requirements of the participants, and the possible risks and inconveniences associated with participation (see Appendix C).

Consent Form. The form used was the standard version of the Austin Health consent form for participation in psychological/medical research (see Appendix C).

Demographics Questionnaire. This questionnaire was designed to obtain demographic information relating to age, gender, height, and weight, and medications.

Multivariate Apnoea Prediction Index (Maislin et al., 1995). This is a questionnaire that predicts apnoea risk using a score between 0 and 1, 0 representing low risk and 1 representing high risk. Potential control participants with a score >0.5 were excluded. (See Appendix D)

Epworth sleepiness scale (ESS) (Johns, 1991). This scale is a self-reported questionnaire providing a subjective measure of daytime sleepiness. Participants were asked to rate how likely they would be to fall asleep in eight situations related to everyday activities. Such situations included sitting and reading, watching TV, and in a car while stopped for a few minutes in traffic. A scale ranging from 0 = never, to 3 = high chance was used to rate the likelihood of falling asleep. Possible scores ranged from 0 to 24, with more disordered sleep associated with higher scores. A score between 0 and 10 is considered to be within the normal range (Johns and Hocking, 1997). The scale has high internal consistency and test re-test reliability. Pearson's r correlation coefficient was found to be .82 in a group of healthy participants when tested and re-tested following five months (Johns, 1992).

Karolinska sleepiness Scale (KSS) (Gillberg, Kecklund, & Akerstedt, 1994). This scale consisted of a single item that used a nine-point Likert scale in order to measure subjective sleepiness. Participants were required to place a cross next to the point that best described how sleepy they were feeling at that moment. The items range from 1 to 9, with even numbers having a word descriptor i.e., 1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy), but no difficulty remaining awake, and 9 = extremely sleepy-fighting sleep. Therefore, possible scores ranged from 1 to 9 with high scores representing high subjective sleepiness. KSS scores that reach 7 or higher correlate well with changes in drowsiness noted on EEG and EOG, demonstrating high validity (Akerstedt & Gillberg, 1990). (See Appendix E)

Alertness Questionnaire (AQ). This questionnaire was used to measure participants' assessments of eleven symptoms of sleepiness. Using a seven-point Likert scale, participants were asked to indicate how often they noticed particular symptoms, such as yawning and nodding, occurring during the previous driving session. The items ranged from 1 = not at all, to 7 = most of the time. Possible scores ranged from 11-77, with high scores representing low subjective alertness. This questionnaire was developed at the Sleep Disorders Unit at Austin Health, for use in research utilising the AusED Sampler Driving Simulator. Internal consistency has been demonstrated with a Cronbach's alpha of .95 (Radford, 2001). (See Appendix F)

Subjective estimates of when drivers would stop driving and of their driving performance. This was a two-part questionnaire that asked participants to rate how alert they were at that moment, with regards to 1) how they felt about driving for a short period in suburban traffic, and 2) how they felt about driving for a continuous long distance. For each part, possible scores ranged from 1 = I would continue driving, to 4 = I would have stopped driving some time ago. This questionnaire was also developed at the Sleep Disorders Unit at Austin Health, for use in research utilising the AusED Sampler Driving Simulator. (See Appendix G).

Psychomotor vigilance task (PVT) (Dinges et al., 1997). This is a computerised vigilance task, lasting 10 minutes, which evaluated sustained attention and was sensitive to performance variations as a result of sleepiness. The PVT is a vigilance reaction time (RT) task that required participants to respond to the appearance of numbers in a LED window by pressing a button on a hand-held device as quickly as possible. The numbers appeared randomly at intervals from 2 to 10 seconds. Lapses in attention were identified when reaction times equal to or greater than 500 milliseconds were obtained. The PVT provided a number of performance metrics for each trial. In this study, the following were used:

1. Median Reaction Time (RT): This was measured in milliseconds and high scores represented low levels of sustained attention. It reflected how long it took the participant to press the button following presentation of each number in the LED window.

2. Slowest 10%: this was calculated from the mean reaction time from the slowest 10 percent of reaction times, and showed increases in the duration of responses. High scores represented high levels of sustained attention.
3. Transformed lapses: Lapses were measured in milliseconds and were transformed in order to decrease the effect of very long lapses. High scores represented low levels of sustained attention.

AusED sampler driving simulator. This simulator was developed at Woolcock Institute NSW and assessed reaction time and vigilance while driving. It consisted of a 21-inch screen displaying a road, as well as a speedometer in the upper left hand corner. The area between 60 kilometres per hour (km/h) and 80 km/h was highlighted on the speedometer and participants were required to maintain speed between these two values. Attached to the table in front of the screen was a steering wheel, and on the floor was a pad with the brake and accelerator pedals attached. During the half-hour drive on the simulator, trucks randomly appeared in the left hand lane on ten occasions. Participants were required to brake as soon as the trucks were visible in front of them. In this study the following performance indicators were used:

1. Average steering deviation from the centre of the left lane. High scores represented large deviation from the centre of the left lane as well as decreased vigilance.
2. Average velocity deviation from the optimum 60 km/h to 80 km/h speed. High scores represented large deviations from the prescribed speed and decreased vigilance.
3. The number of crashes that occurred during each driving session.

Logical memory (LM) is a subtest of the Wechsler Memory Scale – Third Edition (WMS-III), and was used to assess auditory immediate short-term memory, long-term memory, and recognition. It is shown to have a reliability coefficient of .77 (Wechsler, 1997). This test lasted for approximately 10 minutes and required participants to listen to two stories, recalling each story immediately after presentation, and again after a 30-minute delay. They were also asked to recognise parts of the story read out as questions.

Visual reproduction (VR) is a subtest of the Wechsler Memory Scale – Third Edition (WMS-III), and was used to assess visual immediate short-term memory, long-term memory, and recognition, and has been shown to have a reliability coefficient of .70 (Wechsler, 1997). This test lasted for approximately 15 minutes, and required participants to draw a series of designs immediately after viewing the drawing for 10 seconds. Participants were then asked to recall the designs following a 30-minute delay, and view a series of designs from which they were asked to recognise the original designs.

Trail making test -Trails A & B (TMT-A & TMT-B). The TMT is influenced by attention, concentration, resistance to distraction, and cognitive flexibility (or set-shifting). The test lasted for approximately 5 minutes, and required participants to connect (by making pencil lines), in numerical order, 25 encircled numbers randomly arranged on a page (Trail A), and 25 encircled numbers and letters in alternating order (Trail B).

Austin Maze (Milner, 1965). This is an electric push-button maze and is a measure of visual-spatial ability, and procedural and visual-spatial memory (Crowe et al., 1999). Participants were required to learn the path of the maze by pushing a series of buttons using a trial and error approach. Each time a correct button was pushed, a green light illuminated, whereas a red light illuminated and buzz sounded when a button press was incorrect. The participants were required to follow rules which restricted particular movements (i.e., no diagonal moves and when an error was made, and the participants must return to the last correct button position and continue from there), until reaching the criterion of two errorless trials. The performance indicator used in this study was number of errors and administration was limited to 10 trials. Previous research has demonstrated a high correlation between errors to criterion and errors over 10 trials. A correlation coefficient of .89 has been shown in normal controls, and a coefficient of .94 in clinical populations (Bowden et al., 1992).

Optalert™ Fatigue Management Technology. The Optalert™ technology has been developed by Sleep Diagnostics Pty Ltd, an Australian research and development company founded by sleep expert Dr Murray Johns. It measures eye and eyelid movements at over 500 times a second, based on the reflectance of infrared (IR) light directed at the eyes. IR transducers are housed in a light frame such as would be worn with prescription lenses or sunglasses. The system assesses the driver based on the Johns Drowsiness Scale (JDS), which is an objective scale of drowsiness from 0 to 10 with alert subjects below 4 and persons with scores above 5 being considered unfit to drive.

1.2.3. Procedure

Patients were referred from an Austin Health physician following a diagnosis of moderate to severe obstructive sleep apnoea after an overnight polysomnographic sleep study. Control participants were similar to patients by age and gender and were screened for significant sleep disorders or excessive sleepiness. Potential control participants who showed significant sleepiness were excluded. An initial consultation with the participants was arranged in order to obtain consent, screen for exclusion criteria, and complete sleepiness questionnaires.

On the morning of the study, participants were asked to wake at 7.00 am, and to have had their normal amount of sleep on that night. No caffeine or other stimulant medication was allowed on the day of testing until after the study was completed.

On the day of the study session, participants presented at 17.30 at the sleep laboratory at Austin Health. Upon presentation, the participants were informed of the proceedings of the study for the session, and any questions the participants had were answered. Testing throughout the study period was separated into three test sessions. They were as follows:

1.2.3.1. Session 1

The first session involved performance on the PVT and driving simulator. It was also an opportunity for the examiner to appropriately fit the Optalert™ frame to each individual. This was to ensure that the IR pulses were directed up in a 30-degree beam centered on the lower edge of the upper eyelid.

The participants were seated at a computer desk in a quiet room, where the PVT was placed, and were instructed on what was required for the task. They were then given a practice session on the PVT, which lasted for a few minutes. Once familiarized with the task, the participants then completed the 10-minute PVT session. Recording of drowsiness using the Optalert™ system was commenced as soon as the task began. The participants were then left alone in the room with the lights off in order to complete the task. At the end of the task, the participants were able to have a 5-minute break while the examiner assembled the equipment necessary for the driving simulator.

Participants were then called back into the room, and were seated once again at the computer desk, where a steering wheel was attached, and pedals were on the floor. They were asked to read instructions regarding how to complete the driving simulator, and any questions they had were answered. The participants were required to remove their shoes and watch, and were asked to sit comfortably in the chair so that they could adequately operate the pedals. They were given a 5 minute practice session to familiarise themselves with the task. Once the practice was completed, the Optalert™ glasses were again fitted, and recording was commenced at the same time that the 30-minute driving simulator task began. Again, the lights were turned off in order to simulate driving at night. At the end of the session, the participants were asked to complete the Karolinska Sleepiness Scale in order to assess subjective sleepiness at that point in time, as well as the alertness questionnaire and stop driving questionnaire. They were then given another break.

1.2.3.2. Session 2

After completing the PVT, driving task, and sleepiness questionnaires, a series of neuropsychological tests assessing memory, learning, and executive functioning were administered. Participants were seated across the table from the examiner in a quiet room. The Trail Making Test (Trails A & B) was the first test administered. Participants were given a sample of each trail before being asked to complete the appropriate trail. Logical Memory I was the next test administered, followed by Visual Reproduction I. The Austin Maze was then administered, taking approximately 20-30 minutes to complete, providing the delay required for the Logical Memory II and Visual Reproduction II subtests, which were administered next.

1.2.3.2. Session 3

The final period of the study took place after the battery of neuropsychological tests and involved the polysomnography. OSA participants had previously had a polysomnography prior to the study day, so they were able to leave following session 2. All control participants proceeded to their polysomnography in the sleep laboratory. They were woken at 6am the next morning and were then able to go home.

1.2.4. Statistics

The data were downloaded from the PVT and Driving Simulator computer and were entered into the Statistical Package for Social Sciences (SPSS 14.0). Optalert™ data were analysed by researchers at sleep diagnostics, and raw data was entered into SPSS. Raw data from all questionnaires and neuropsychological

tests were coded and scored according to the scoring procedure outlined in the Method section (section 2.2) for each of the variables. These variables were then also entered into the SPSS data file.

Descriptive statistics were computed using SPSS to ensure that all data were in the specified ranges, and that there were no missing values. The data were found to be within the specified range and analysis-by-analysis exclusion of missing data was used to manage missing values.

In order to test for multivariate outliers, mahalanobis distance was used. The results demonstrated that there were no outliers and all values were below the Chi-Square cut off value for all variables. An analysis of the residuals and normality probability (P-P) was performed to test the assumptions of normality, linearity and homoscedasticity.

All normally distributed measures were analysed using One-Way Analysis of Variance (ANOVA). In the analysis each measure was entered as a dependent variable and Participant group (OSA, control) entered as the fixed factor.

Levene's Test was used to test the assumption of homogeneity of variances. Where the assumption of equal variances was met, the F -test was used. If this assumption was violated, adjustment was made by reporting the Welch F -ratio as recommended by Field (2005).

The violation of the assumption of normal distribution by some variables required the use of non-parametric statistical analyses. Furthermore, there were an unequal number of participants in each group. Rather than the Mann-Whitney test, the Kolmogorov-Smirnov Z test (D) was used as recommended by Field (2005). This test is thought to have better power than the Mann-Whitney test when sample

sizes are less than 25 per group, as was the case in the present study. Pearson's r was used to calculate effect sizes for all analyses.

Kendall's tau was used to conduct correlational analyses between the groups.

1.3. Results

1.3.1. Demographics

Means and standard deviations for the demographic variables for OSA and controls are shown in Table 1. One-way ANOVA demonstrated that in comparison to control participants, OSA participants weighed significantly more and had a significantly higher body mass index. OSA participants also scored significantly higher on the MAPI.

Table 1

Means and Standard Deviations for Demographic Variables for OSA Patients and Control Participants

	OSA Patients (n=14)		Control Participants (n=11)		df	F	p	r
	M	SD	M	SD				
Age	56.64	10.95	54.73	12.37	1,24	.00	.99	.00
Height (cm)	170.36	9.04	173.27	7.74	1,24	.72	.40	.17
Weight (kg)	91.71	16.69	77.55	10.44	1,24	6.04	.02	.46
BMI	32.04	8.09	25.96	3.95	1,24	5.19	.03	.43
MAPI	.69	.16	.25	.11	1,24	58.77	.001	.85

Note. MAPI = Multivariable Apnoea Prediction Index, BMI = Body Mass Index

1.3.2. Polysomnography

Results of the one-way ANOVA and Kolmogorov-Smirnov Z tests indicated that the OSA patients experienced a significantly higher number of arousals when compared to the control participants (Table 2). Results also demonstrated that the OSA patients had a higher apnoea-hypopnoea index and they had a higher percentage of sleep time where oxygen saturation was below ninety percent.

Table 2

One-Way ANOVA and Kolmogorov-Smirnov Z Test Results for Differences between OSA patients and Control Participants on Polysomnography Variables

	OSA patients (n=14)		Control Participants (n=11)		df	F	D	p	r
	M	SD	M	SD					
Total Sleep Time (min)	286.39	108.85	248.50	56.87	1,24	1.09	-	.31	.21
Sleep Efficiency (%)	76.58	11.04	73.23	15.75	1,24	0.39	-	.54	.13
Arousals (/hr)	32.86	15.52	12.40	7.82	-	-	2.03	.001	.41
AHI (/hr)	45.76	23.54	12.71	9.62	1,18.05	22.76	-	.001	.67
% total sleep time <90% saturation	10.29	22.95	.05	.12	-	-	1.60	.01	.32

Note. AHI = Apnoea-Hypopnoea Index

1.3.3. Sleepiness Measures

Kolmogorov-Smirnov Z tests demonstrated a significant difference between the OSA patients and control participants on the Epworth Sleepiness Scale and Karolinska Sleepiness Scale (Table 3). There was no significant difference between the groups on the stop-driving questionnaire (suburban or long distance) or on the alertness questionnaire.

Table 3

Kolmogorov-Smirnov Z test results for Differences on Sleepiness Questionnaires for OSA Patients and Control Participants

	OSA Patients (n=14)		Control Participants (n=11)		D	p	r
	M	SD	M	SD			
ESS	11.86	5.78	4.64	2.62	1.95	.001	.39
KSS	6.14	1.46	4.18	1.94	1.50	.01	.30
Stop Driving Questionnaire (Suburban)	1.36	0.63	1.18	0.60	0.48	.34	.10
Stop Driving Questionnaire (continuous long distance)	2.21	0.98	1.45	0.93	1.27	.02	.25
AQ	20.43	6.46	20.36	5.55	0.66	.60	.13

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; AQ = Alertness Questionnaire

1.3.4. Performance Measures

Table 4 display results of the one-way ANOVA and Kolmogorov-Smirnov Z tests comparing OSA patients and control participants on the psychomotor vigilance task (PVT) and driving simulator. The OSA patients had a significantly higher number of lapses and an increase in duration of responses as measured by the slowest 10% on the PVT in comparison to the control participants. There were no significant differences demonstrated between the groups on the driving simulator.

Table 4

One-Way ANOVA and Kolmogorov-Smirnov Z Test Results for Differences between OSA patients and Control Participants on the PVT and Driving Simulator

	OSA Patients (n=14)		Control Participants (n=10)		df	F	D	p	r
	M	SD	M	SD					
PVT Median	231.85	26.53	222.30	13.41	-	-	.86	.36	.18
PVT transformed lapses	4.21	2.63	2.51	1.02	1,17.97	4.79	-	.04	.38
PVT slowest 10%	2.61	.45	2.98	.39	1,23	4.42	-	.05	.41
Median Position Average*	80.96	20.06	94.72	79.84	1,23	.36	-	.55	.13
Speed 60-80kms average*	8.93	3.67	7.68	3.20	1,23	.74	-	.40	.18
Number of crashes*	1.00	1.63	1.00	1.89	-	-	.24	.98	.05

Note. PVT = Psychomotor Vigilance Task

* = OSA n = 13

1.3.5. Optalert™ Fatigue Monitoring System

Table 5 demonstrates Kolmogorov-Smirnov Z test results for differences in objective sleepiness, as measured by the Optalert™ fatigue monitoring system, between OSA patients and control participants. There were no significant differences between the groups on this measure of objective sleepiness.

Table 5

Kolmogorov-Smirnov Z Test Results for Differences between OSA patients and Control Participants on the Optalert™ fatigue monitoring system

	OSA Patients		Control Participants		<i>D</i>	<i>p</i>	<i>r</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
JDS % time eyes closed (PVT)*	.15	.21	.08	.07	.71	.58	.15
JDS % long eye closure (PVT)*	.02	.03	.00	.00	.71	.32	.15
JDS mean (PVT)*	.86	1.20	.89	1.11	.47	.92	.10
JDS % time eyes closed (driving)**	.05	.08	.16	.34	.51	.88	.12
JDS % long eye closure (driving)**	.01	.02	.12	.28	.47	.74	.10
JDS mean (driving)**	.48	.71	.47	.64	.39	.97	.08

Note. JDS = John's Drowsiness Scale

* = OSA n = 13, controls n = 9, ** = OSA n = 12, controls n = 10

1.3.6. Neuropsychological Tasks

Table 6 presents the mean and standard deviation of the neuropsychological tasks, and the results of one-way ANOVA and Kolmogorov-Smirnov Z tests for each measure. Results demonstrated that the OSA patients performed significantly worse than control participants on Logical Memory I and Logical Memory II.

Table 6

One-Way ANOVA and Kolmogorov-Smirnov Z Test Results for Differences between OSA patients and Control Participants on Neuropsychological Tasks

	OSA Patients (n=14)		Control Participants (n=11)		df	F	D	p	r
	M	SD	M	SD					
TMT A (time)	31.79	8.15	25.73	10.86	1,24	2.54	-	.12	.32
TMT A (errors)	.14	.53	.09	.30	-	-	.18	1.0	.07
TMT B (time)	85.71	32.93	59.98	16.65	-	-	1.06	.13	.21
TMT B (errors)	.50	.76	.27	.47	-	-	.36	.66	.07
Austin Maze	87.86	43.61	84.91	30.95	-	-	.60	.74	.12
LM I	30.14	8.76	40.91	8.70	1,24	9.36	-	.01	.54
LM II	17.00	6.25	23.55	5.85	1,24	7.14	-	.01	.49
VR I	89.07	8.60	85.90	12.52	-	-	.69	.50	.14
VR II	69.57	15.80	73.55	20.40	1,24	.30	-	.59	.11

Note. TMT = Trail Making Test, LM = Logical Memory, VR = Visual Reproduction

1.4. Correlational Analyses

1.4.1. Subjective sleepiness and performance on the PVT and driving simulator

Table 7 shows correlations (Kendall's tau) between measures of subjective sleepiness and performance on the PVT and driving simulator for both OSA patients and control participants. Control participants showed a significant negative correlation between KSS scores and average position deviation on the driving simulator (median position average).

Table 7

Correlations (Kendall's tau) between Sleepiness Questionnaires and Performance on the PVT and Driving Simulator for OSA patients and Control Participants

	PVT and driving simulator variables					
	PVT median	PVT transformed lapses	PVT slowest 10%	Median position average [^]	Speed 60-80kms average	Number of crashes [^]
A: OSA patients (n=14)						
ESS	.22	-.03	-.27	.23	-.16	-.16
KSS	.00	-.13	-.01	.22	-.37	-.38
B: Control participants (n=10)						
ESS	-.29	.28	-.29	.29	.29	-.06
KSS	.22	-.30	.17	-.50*	-.31	-.21

Note. MAPI = Multivariable Apnoea Prediction Index ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale.

[^] = OSA n = 13

* = significant at .05 ** significant at .01

1.4.2. Subjective sleepiness and performance on the neuropsychological tasks

Table 8 shows correlations (Kendall's tau) between measures of subjective sleepiness and performance on neuropsychological tasks for both OSA patients and control participants. OSA patients showed a significant negative correlation between scores on the KSS and number of errors on Trails A. KSS scores were also significantly negatively correlated with number of errors on the Austin and scores on Visual Reproduction I for the OSA patients. Similarly, the ESS was also significantly negatively correlated with scores on Visual Reproduction I.

Table 8

Correlations (Kendall's tau) between Sleepiness Questionnaires and Performance on Neuropsychological Tasks for OSA patients and Control Participants

	Neuropsychological Tasks								
	TMT A (time)	TMT A (errors)	TMT B (time)	TMT B (errors)	Austin Maze	LM I	LM II	VR I	VR II
A: OSA patients (n=14)									
ESS	-.13	-.12	-.17	-.36	.11	-.28	-.33	.55**	.15
KSS	-.20	-.44*	-.12	-.31	-.43*	-.07	-.13	.55**	.18
B: Control participants (n=11)									
ESS	.14	-.38	.06	.06	.32	-.06	.04	-.28	-.12
KSS	.04	.05	.14	.36	-.28	-.42*	-.06	.26	-.08

Note. TMT – Trail Making Test, LM – Logical Memory, VR = Visual Reproduction

* = significant at .05 ** significant at .01

1.4.3. Polysomnography and performance on the PVT and driving simulator

Table 9 shows correlations (Kendall's tau) between polysomnography results and performance on the PVT and driving simulator for both OSA patients and control participants. OSA patients showed a significant positive correlation between the total percentage of sleep time where oxygen saturation was less than ninety percent and median reaction time on the PVT. Control participants showed a significant positive correlation between the apnoea-hypopnoea index and average position deviation on the driving simulator (median position average).

Table 9

Correlations (Kendall's tau) between Polysomnography and Performance on the PVT and Driving Simulator for OSA patients and Control Participants

	PVT and driving simulator variables					
	PVT median	PVT transformed lapses	PVT slowest 10%	Median position average [^]	Speed 60-80kms average [^]	Number of crashes [^]
A: OSA patients (n=14)						
Total Sleep (min)	.13	.14	.02	-.13	-.08	-.11
Sleep Efficiency (%)	.22	.18	-.07	-.18	.08	.05
Arousals (/hr)	.22	.07	.04	-.18	-.08	-.24
AHI (/hr)	.29	.27	-.20	-.18	.03	-.08
% total sleep time <90% saturation	.60**	.19	-.22	-.33	.08	-.02
B: Control participants (n=11)						
Total Sleep (min)	.29	-.15	.16	-.16	-.02	.08
Sleep Efficiency (%)	.38	-.26	.07	-.16	-.11	-.14
Arousals (/hr)	-.20	.21	-.07	.33	-.07	-.19
AHI (/hr)	-.24	.21	-.02	.47*	.07	-.08
% total sleep time <90% saturation	-.12	.29	-.04	-.04	.18	.18

Note. AHI = Apnoea-Hypopnoea Index, PVT = Psychomotor Vigilance Task

[^] = OSA n = 13

* = Significant at .05

1.4.4. Polysomnography and performance on neuropsychological tasks

Table 10 shows correlations (Kendall's tau) between polysomnography results and performance on neuropsychological tasks for both OSA patients and control participants. OSA patients showed a significant positive correlation between the number of arousals experienced across the night and the number of errors on Trails B. Control participants showed a significant negative correlation between sleep efficiency and scores on Logical Memory I. There was also a significant negative correlation between percentage of total sleep time where oxygen saturation was below ninety percent and scores on Visual Reproduction I and II.

Table 10

Correlations (Kendall's tau) between Polysomnography and Performance on Neuropsychological Tasks for OSA patients and Control Participants

	Neuropsychological Tasks								
	TMT A (time)	TMT A (errors)	TMT B (time)	TMT B (errors)	Austin Maze	LM I	LM II	VR I	VR II
A: OSA patients (n=14)									
Total Sleep (min)	.04	-.15	.14	.25	.11	-.14	-.12	-.10	.06
Sleep Efficiency (%)	.09	-.38	.14	.28	-.09	.14	.17	-.15	-.06
Arousals (/hr)	-.31	-.38	.21	.40*	-.31	-.17	-.10	-.08	.14
AHI (/hr)	-.16	-.26	.26	.37	-.20	-.08	.10	-.19	.12
% total sleep time <90% saturation	-.05	.09	.34	.20	.12	-.09	.08	-.25	-.19
B: Control participants (n=11)									
Total Sleep (min)	.02	-.17	-.26	.28	.02	-.18	-.15	.15	-.18
Sleep Efficiency (%)	.09	-.26	-.15	.44	.13	-.44*	-.11	.11	-.15
Arousals (/hr)	.09	.34	.11	-.22	-.16	.40*	.19	-.15	.04
AHI (/hr)	.17	.43	-.15	-.22	.20	.33	.22	-.15	.04
% total sleep time <90% saturation	.28	-.15	.19	.19	.40	-.09	-.10	-.47*	-.47*
<i>Note.</i> TMT – Trail Making Test, LM – Logical Memory, VR = Visual Reproduction									
* = significant at .05									

1.4.5. Polysomnography and Subjective Sleepiness

Table 11 shows correlations (Kendall's tau) between polysomnography results and scores on measures of subjective sleepiness for both OSA patients and control participants. There were no significant correlations demonstrated for OSA patients. Control participants showed a significant negative correlation between ESS scores and total sleep time. There were also significant positive correlations noted between total sleep time and KSS scores, and between sleep efficiency and KSS scores.

Table 11

Correlations (Kendall's tau) between Polysomnography and Measures of Subjective Sleepiness for OSA patients and Control Participants

		Total Sleep Time (min)	Sleep Efficiency (%)	Arousals (/hr)	AHI (/hr)	% total sleep time <90% saturation
A: OSA patients (n=14)						
	ESS	.06	-.10	-.06	-.19	.04
	KSS	-.23	.03	.05	-.05	-.01
B: Control participants (n=11)						
	ESS	-.48*	-.12	.16	.36	.24
	KSS	.48*	.44*	-.32	-.36	-.10

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale
* = Significant at .05

1.5. Discussion

The aim of this study was to investigate simulated driving performance and subjective and objective sleepiness in patients with OSA compared to healthy control participants. A further aim of this study was to assess neuropsychological functioning in these groups, by comparing memory (verbal, visual and procedural) performance, visual-spatial ability, sustained attention, reaction time, and vigilance. In an effort to better understand the nature, extent, and source of these impairments this study also aimed to explore polysomnography characteristics of the groups, including total sleep time, sleep efficiency, number of arousals per hour of sleep, apnoea-hypopnoea index, and percentage of total sleep time where oxygen levels were below 90% saturation, and their relationship to performance variables.

1.5.1. Demographic Characteristics

It was hypothesised (Hypothesis 1) that patients with OSA would weigh more and have higher BMI and MAPI when compared to control participants. This was supported, as there were significant differences between the groups on these characteristics. Research suggests that obesity is a major risk factor for the development of OSA (Dagan, Doljansky, Green, & Weiner, 2006; Strobel & Rosen, 1996). The OSA patients in the current study had a mean BMI of 32.04, falling within the obese range and supporting previous research. Similarly, the OSA patients demonstrated a significantly higher MAPI when compared to control participants. This study therefore supports the practical utility of the MAPI in predicting sleep apnoea risk as initially reported by Maislin et al., 1995.

1.5.2. Polysomnography

Hypothesis 2 was partially supported as OSA patients demonstrated a significantly higher number of arousals per hour of sleep as well as a higher AHI when compared to the control participants. However, they did not experience significantly decreased total sleep time or sleep efficiency in comparison to the control participants as was hypothesised. Combining apnoeas and hypopnoeas gives an overall severity of sleep apnoea including sleep disruptions and desaturation. Sleep apnoea is formally defined as an apnoea-hypopnoea index of at least 15 episodes/hour, with scores greater than 30 indicating severe disease. The OSA patients in this study had a mean index of 45.76, indicating severe OSA. The control participants had a mean index of 12.71, indicating some mild sleep-disordered breathing, which is consistent with community control groups in previous studies. There is a high rate of undiagnosed sleep apnoea in the general community; with Young et al. (1997) finding that over 80% of individuals with moderate to severe OSA had not been clinically diagnosed. Therefore it is not surprising that the control participants demonstrated some level of sleep disordered breathing, however this did not reach the criteria of at least 15 episodes per hour that is necessary for a diagnosis of OSA. Furthermore, researchers have failed to adequately interpret the implications of AHIs of between 10 and 20, and this has been described as a “grey zone” (Sullivan & Rapoport, 2002).

The OSA patients also demonstrated a significantly higher percentage of total sleep time where oxygen saturation was below 90%. This finding also partially supports hypothesis 2 and is consistent with previous research that has

demonstrated that a major hallmark of OSA is the occurrence of hypoxia during sleep as a result of apnoeic periods (Beebe & Gozal, 2002).

1.5.3. Subjective sleepiness

As hypothesised (hypothesis 3), OSA patients reported significantly higher levels of subjective sleepiness when compared to control participants, with medium effect sizes indicated. Specifically, OSA patients reported increased daytime sleepiness (as measured by the ESS) and lower alertness (as measured by the KSS). This finding is highly consistent with previous research (Akerstedt & Gillberg, 1990; Engleman et al., 1997; George et al., 1996; Horstmann et al., 2000).

As described by Johns (1993) individuals who score within the ‘normal’ range of the ESS achieve scores between two and ten. The control participants in the present study demonstrated a mean score of 4.64, whereas the OSA patients had a mean score of 11.86. This finding indicated that the OSA patients were more likely to doze off in eight situations, including ‘lying down to rest in the afternoon’ and ‘sitting and talking to someone’. This demonstrated that OSA patients were likely to fall asleep in situations that are both highly sleep inducing, as well as less sleep-inducing, and supports other studies that have demonstrated that OSA patients have difficulty staying awake during the day, not only at rest, but also while performing a task (Bedard et al., 1991).

In patients who experience moderate to severe OSA, the level of oxygen desaturation in the blood during sleep has been associated with daytime sleepiness (Bedard et al., 1991; Johns, 1991). In his study, Johns found that ESS scores were correlated with RDI, as well as the minimum arterial oxygen saturation, suggesting

that daytime sleepiness may be related to hypoxaemia as well as sleep disruption associated with the number of apnoea/hypopnoea events during sleep. Although for the control participants, it was demonstrated that ESS scores were negatively correlated with total sleep time, this was not shown for OSA patients and does not support hypothesis 11. This indicated that only in healthy controls was less total sleep time associated with increased subjective daytime sleepiness.

The present study failed to find a relationship between ESS scores and AHI or oxygen desaturation in the OSA patients or control participants and failed to support this hypothesis (hypothesis 11). This is inconsistent with previous research, where some authors have considered the AHI to be the best predictor of daytime sleepiness (Bedard et al., 1991; Guilleminealt et al., 1988; Tangugsorn et al., 2000). However, as Bennett, Langford, Stradling, Davies (1998) described, measures of sleep fragmentation and respiratory disturbance correlate poorly with measures of daytime sleepiness. They explored EEG and non-EEG sleep fragmentation indices and found that a body movement index was the best predictor of subjective and objective sleepiness in OSA patients suggesting that such indices may be better than traditional EEG measures in quantifying sleep disruption resulting in daytime sleepiness. It would be useful for future research to continue to explore such indices in order to improve the assessment of sleep fragmentation.

In the present study, there was a significant difference in levels of alertness, as measured by the KSS, between OSA patients and control participants. This finding was in support of hypothesis 3. The KSS was administered at the beginning of the testing session, and as hypothesised, OSA patients reported feeling sleepier at this time when compared to control participants. Previous

studies have suggested that high scores on the KSS are linked to sleep deprivation. Gillberg et al. (1994) found higher scores on the KSS for subjects who were kept awake during a night. Similarly, Dinges et al. (1997) found that participant's who had their sleep restricted to 4-5 hours per night reported elevated ratings of subjective sleepiness. This suggests that the high scores indicated on the KSS by the OSA patients in the present study may be related to the degree of sleep disruption experienced by these individuals due to multiple arousals throughout the night. However, in the present study, KSS scores were not related to the number of arousals experienced across the night in OSA patients. For control participants, KSS scores were positively correlated with total sleep time as well as sleep efficiency, indicating that increased total sleep time and sleep efficiency in the laboratory were associated with increased levels of subjective alertness. These associations lend support to previous research that suggests that hypoxaemia alone is not responsible for excessive daytime sleepiness (Colt, Haas & Rich, 1991; Poceta et al., 1990).

OSA patients' self-reported ability to drive in suburban traffic was equal to that reported by the control participants. However, there was a significant difference between the groups for self-reported ability to continue driving for long distances. Following completion of the driving simulator test OSA patient were asked to rate how they felt about driving in suburban traffic and for a continuous long distance. These patients indicated that they would be significantly more likely to stop driving for long distances when compared to the control participants. This again highlighted the higher levels of subjective sleepiness experienced by the OSA patients, and indicated that they were feeling significantly less alert when compared to the control participants following completion of the driving simulator

test. Despite this finding, OSA patients did not appear to experience any of the more severe symptoms of sleepiness during the driving simulator test (e.g., Struggling to keep eyes open, nodding off to sleep, fidgeting.) as measured by the AQ, when compared to the control participants.

1.5.4. Psychomotor Vigilance Task

The impact of sleep deprivation on reaction time and sustained attention (as measured by the PVT) is likely to be a major factor contributing to road accidents. The present study found that whilst there were no significant differences between the OSA patients and control participants on median reaction time, there was a significant difference between the numbers of transformed lapses recorded between the groups. The difference between the groups on the slowest 10% of reaction times approached significance, and medium effect sizes were noted. This indicates that the OSA patients experienced lower levels of sustained attention during this task, and partially supports hypothesis 4.

The results of the present study are consistent with findings from previous research that have found poor performances on the PVT following sleep deprivation (Dinges et al., 1997). Dinges et al. found that after 7 days of sleep restricted to 4-5 hours per night, transformed lapses and duration of responses on the PVT increased significantly. These results suggest that individuals experiencing decreased sleep times, for example, patients with OSA may demonstrate neurobehavioral deficits during their waking hours. Dinges et al. also found that PVT performance was sensitive to the time-of-day that the task was administered, with performance being worse in the morning and better during the late evening.

Given that the participants in the present study completed the PVT in the evening, this may explain the lack of significant differences in median reaction time. The time-of-day may have resulted in improved performance, masking more significant impairment in performance. Testing at different times throughout the day, may have been revealed that OSA patients had dips and peaks in their alertness at different phases of the circadian rhythm, (Rosekind et al., 1994). Disruption to the 24-hour circadian rhythm, as a result of sleep disturbances, can upset physiological factors such as motor activity (e.g. slower reaction time), body temperature, sleep/wakefulness, hormonal secretions, blood pressure, and work performance (Rosekind et al.). In turn, this may have produced further significant differences between the two groups. This has important implications for safe driving and highlights the importance of being aware of fluctuations in performance across the day. Despite this, previous research has found that omissions and false responses on the PVT do provide a more sensitive assessment of impairment during waking hours when compared to reaction time (Sforza et al., 2004).

In this study there was a significant moderate correlation for OSA patients between median reaction time on the PVT and the percentage of total sleep time where oxygen saturation was less than 90 percent. This finding partially supports hypothesis 9 and is highly consistent with results reported by Bedard et al. (1991) who found that daytime alertness, as measured by a psychomotor task, was significantly correlated with percentage of total sleep time where oxygen saturation was less than 90 percent. Additionally, Bedard et al. also found that measures of reaction time could also be partially explained by nocturnal sleep disturbance, particularly by the number of awakenings. However, the present study

failed to find a relationship between sleep disruption and performance on the PVT and this does not support hypothesis 9. This may suggest that performance on the PVT is dependent on multiple factors that may be interrelated to impair performance. For example, adverse mood states (e.g., anxiety) have been found to negatively alter reaction times (Bolmont, Thullier & Abraini, 2000).

1.5.5. Driving Performance

This study did not support that hypothesis that OSA patients would demonstrate impaired simulated driving performance when compared to control participants (hypothesis 4). There was no significant difference found for average steering deviation from the centre of the left lane, average velocity deviation, or number of crashes as measured by the AusEd Driving Simulator. This finding does not support those of previous research. Findley et al. (1989) found that OSA patients had a higher number of errors on steering and speed than did the control group. In addition, higher errors were found for signalling, braking, and accelerating in this group. Similarly, George et al. (1996) found that patients with OSA performed much worse than control subjects on a driving simulator task that incorporated two features considered essential for driving; tracking and visual search. Similarly, Turkington et al. (2001) identified poor tracking error, an increased number of off-road events per hour, and poorer reaction time in patients with OSA.

In their study, Turkington et al. (2001) discovered that there were other factors not related to OSA that influenced performance on a driving simulator. This included patient characteristics such as older age, female sex, and self-reported alcohol consumption. In the present study, other factors that may

influence vigilance and simulated driving performance were not thoroughly examined. For example, such factors may include alcohol consumption, previous driving experience, and accident history. Furthermore, given the nature of the driving simulator used in this study, previous experience or proficiency with video games may have influenced the results obtained.

The non-significant results in this study may also indicate that patients with OSA may have had fatigue-management strategies, allowing them to perform on the driving task similarly to the control group, and that the task of 30-minutes duration was not long enough for an effect to be demonstrated. Indeed, as indicated by results of the alertness questionnaire, OSA patients did not indicate that they experienced more symptoms of sleepiness while performing the driving simulation when compared to control participants. Similarly, with regard to the stop-driving questionnaire, OSA participants were similar to the control participants in indicating that they would continue driving in suburban traffic following completion of the driving simulation. This may indicate that they were not experiencing significant fatigue during the simulation; hence their performance was comparable to that of the control participants.

Many factors affect vigilance, and consequently, driving performance. Ballard (1996) suggested that task parameters, environmental or situational factors, and participant characteristics all form complex interactions to affect performance. These interactions may be useful in explaining the lack of significant results obtained in the present study. Furthermore, the impact of circadian rhythms and time-of-day effects cannot be underestimated. Indeed, Contardi et al. (2004) demonstrated that driving performances on a simulator deteriorated or improved according to the variation in alertness induced by circadian rhythms.

A moderate negative relationship was demonstrated for the control participants between levels of alertness, as measured by the KSS, and the average steering deviation from the centre of the left lane on the driving simulator. The results partially support hypothesis 7 and showed that when participants indicated feeling more alert, they deviated less from the centre of the left lane. Risser et al. (2000) similarly found a positive correlation between lapses in attention (defined on EEG) and variability in lane position. Furthermore, for the control participants, average steering deviation from the left lane was positively correlated with the AHI. This demonstrated that a greater AHI resulted in greater deviation from the left lane. This finding again highlights the relationship between impaired alertness and increased accident risk affecting not only patients with sleep disorders, but also healthy individuals who may have a degree of disturbed sleep or increased sleepiness. Vehicle control abilities while sleepy contribute to high fatality rates in accidents caused by drowsiness (Liang et al., 2005), therefore the implications of being able to estimate these abilities is important. The current study has indicated that both subjective sleepiness measures (KSS) and polysomnography indicators are important in estimating driving performance.

1.5.6. Objective Sleepiness

It was expected that the OSA patients would demonstrate significant sleepiness as measured by the Optalert™ drowsiness monitoring system (hypothesis 5). However, this hypothesis was not supported. This is the first study to utilise the Optalert™ drowsiness monitoring system in OSA patients. The results of the present study do not support results found for healthy participants who experience sleep deprivation. Furthermore, it is possible that the non-

significant difference between the OSA patients and control participants on the driving simulator test may reflect the lack of differences obtained on the Optalert™ system.

Johns, Tucker, and Chapman (2005) found that in alert drivers the JDS ranged from 0.5 to 4.0. The mean JDS for both the OSA patients and control participants in the present study was 0.5. This indicates that they were in fact not displaying significant drowsiness as measured by this system. It is likely that the patients in this study did not display significant sleep deprivation in order to demonstrate an effect. When validating the Optalert™ system, Johns et al. (2006) induced sleepiness by sleep depriving participants for 20-40 hours, and when in this state, the means JDS was 7.6. The OSA patients were clearly not experiencing a level of sleep deprivation that would be equivalent to 20-40 hours, so it is not surprising that their JDS scores were comparable to the control participants. Furthermore, sleepiness is also affected by task duration. Shorter tasks are less likely to result in significant sleepiness and it is possible that measurement of sleepiness using Optalert™ during longer tasks might have identified differences between the groups.

1.5.7. Neuropsychological Performance

There were significant differences found between OSA patients and control participants on neuropsychological tests assessing verbal memory, supporting hypothesis 6. This finding is consistent with previous research and highlights specific impairments in the memory domain (Bedard et al., 1991; Decary et al., 2000; Findley et al., 1986; Naegele et al., 1998).

1.5.7.1. Trail Making Test

The Trail Making Test is believed to assess a combination of several cognitive functions, which are reflected differently by the two subtests, this includes motor speed, attention, sequencing, and mental flexibility (Strauss, et al. 2006). There was no significant difference between the amount of time it took OSA patients and control participants to complete Trail A of the test. This indicated a similar ability for visual attention and concentration between the groups. Similarly, OSA patients performed comparably to the control participants on the Trails B subtest. This indicated that they took a similar amount of time to alternate between numbers and letters on the page when compared to the control participants and made a similar amount of errors. Trails B is considered by many researchers to be a task of executive functioning that requires the ability to switch repeatedly between two mental sets, and is therefore sensitive to cognitive flexibility. The findings of this study suggest that the OSA patients did not have any more difficulty coping with the added cognitive demands of this task when compared to control participants.

This finding is not consistent with research by Bedard et al. (1991) who found that OSA patients required a significantly longer amount of time to complete the Trails B component of this task. However, other research has found results consistent with the current study, indicating no attentional or switching impairments as measured by the TMT (Verstraeten, Cluydts, Pevernagie, & Hoffman (2004). Verstraeten et al. indicate that such inconsistencies in the literature highlight the methodological and conceptual difficulties in demonstrating executive function difficulties. The authors suggest that factors including small

sample sizes, assessment of patient motivation, and choice of neuropsychological tests need careful consideration when making conclusions about executive deficits.

Despite inconsistencies regarding executive functioning in patients with OSA, it is known that the prefrontal cortex of the brain is important for these functions and has been found to be sensitive to the effects of hypoxaemia and sleep deprivation. (Drummond et al. 1999; Harrison & Horne, 2000). The present study supports the role of sleep disruption in effecting performance on Trails B, as there was a significant relationship between number of arousals across the night as measured by polysomnography and number of errors on Trails B in the OSA patients. This finding indicated that increased number of arousals across the night resulted in an increased number of errors on Trail B. Performance on Trails A also did not appear to be influenced by oxygen saturation, however there was a significant relationship between number of errors on Trails A and scores on the KSS. This indicates that OSA patients who reported feeling less alert, made more errors on Trails A. This finding may suggest that sleep disruption has an effect on visual attention and concentration, as well as on executive functioning.

Verstraeten et al. (2004) support this finding and concluded from their study that sleepiness explains attention deficits in patients with OSA. This is based on their finding that OSA patients did not indicate specific executive deficits such as disinhibition, distractibility, perseveration or attentional switching dysfunction. Rather, the OSA patients in their study appeared to demonstrate impairments in vigilance, attention capacity and slowed processing speed that are consistent with deficits consistently noted following sleep deprivation. Bedard et al. (1991) also supported these results and found that deficits in attentional functioning were

related to an increase in daytime sleepiness, and that patients who were more severely affected showed greater impairments.

1.5.7.2. Austin Maze

There was no significant difference between OSA patients and control participants with regard to the number of errors made on the Austin Maze. This task is a measure of visual-spatial ability and procedural and visual memory (Crowe et al., 1999). This finding is consistent with that found by Rouleau et al. (2002) where OSA patients did not have procedural skills learning impairments when completing the Mirror Tracing and Rotary Pursuit tasks. In their investigations of the cognitive determinants of the Austin Maze, Crowe et al. found that visuospatial ability and memory were critical skills required in order to perform the task. Results of the current study indicate that visuospatial ability and memory in the OSA patients were comparable to the healthy control participants thus enabling them to effectively learn the path.

The non-significant difference seen in the current study in relation to performance on the Austin Maze may be due to the choice of test used to assess the specific skills. The Austin Maze may not be sensitive enough to detect subtle differences in performance between the two groups.

1.5.7.3. Logical Memory and Visual Reproduction

When compared to the control group, OSA patients demonstrated poorer performance in the ability to remember verbal information both immediately (Logical Memory I) and following a delay (Logical Memory II), with medium effect size noted. However, their ability to remember visual information

immediately (Visual Reproduction I) and following a delay (Visual Reproduction II) was comparable to the control participants. These findings partially support hypothesis 6.

These findings indicate that patients with OSA demonstrated impairments in verbal but not visual short-term and long-term memory, compared to control participants. Studies have shown that OSA patients may show adaptive compensatory recruitment responses to compensate for reduced memory and learning (Drummond et al., 2000, 2005). Increased cerebral activation in OSA patients during learning tasks has been found to be associated with better cognitive performance and this has been interpreted as being a compensatory response (Cabeza, 2002; Reuter-Lorenz and Lustig, 2005; Drummond et al., 2000, 2005).

Ayalon et al. (2006) used functional MRI to investigate the mechanisms that allow OSA patients to perform adequately on some tasks, while showing impaired performance on other tasks. The OSA patients in their study demonstrated intact performance on a verbal learning task but showed increased activation while performing this task when compared with control participants. Furthermore, the increased activation in OSA patients was in areas not typically activated during verbal learning and involved the right hemisphere. The authors concluded that given that the OSA patients showed intact performance, the increased activation might represent recruitment of resources that are not typically utilized by healthy control participants. This may explain the lack of significant differences in results obtained for measures of visual memory in the current study. Brain imaging studies would be useful in this instance to determine whether additional brain regions are compensating for visual memory deficits.

The finding of reduced verbal memory in the OSA patient in the current study is consistent with previous research (Findley et al., 1986; Decary et al. 2000; Naegele et al., 1995; Bedard et al. 1991; Roehrs et al., 1995). Findley et al. reported impaired verbal and visuospatial short-term recall in their OSA patients. Furthermore, Bedard et al. demonstrated impaired delayed memory in severely apnoeic patients when compared with controls. Naegele et al. found similar results, but also described significantly decreased long-term memory efficiency in OSA patients. The pathogenesis of these deficits has been the focus of much research. Sleep fragmentation, sleepiness, respiratory disturbances, and nocturnal hypoxaemia have all been implicated however it remains difficult to find sound correlations. Consistent with this difficulty, the current study found no significant correlations for the OSA patients between verbal memory and measures of subjective sleepiness. However, for the control participants, a significant negative correlation was found between levels of alertness (as measured by the KSS) and immediate memory (Logical Memory I). This indicates that lower levels of alertness were related to a decreased number of details recalled following immediate presentation of the Logical Memory stories.

The findings of impaired verbal memory in the OSA patients in the current study provide support for possible damage to the hippocampus in these patients. This brain structure is important in the formation of episodic and declarative memory and is particularly sensitive to oxygen deprivation. Indeed, research has found decreased hippocampal volume in OSA patients, which is associated with deficits in memory performance (Barlett, 2004). However, in the present study there was no significant relationship between oxygen saturation and memory performance, suggesting that the verbal memory impairments demonstrated might

be a result of other interrelated factors. This also continues to highlight the difficulty in previous research of finding sound correlations.

Previous research has found that sleepiness during the awake state impairs memory formation and retrieval. Roehrs et al., 1995 found that the extent of sleep disturbance, which resulted in daytime sleepiness, was related to the degree of memory impairment noted. This suggests that dynamics of the sleep cycle have an effect on cognitive processes, including memory consolidation (Stickgold & Walker, 2007; Walker & Stickgold, 2006). Specifically, studies have found that memory consolidation is disrupted following either rapid eye movement (REM) or nonrapid eye movement (NREM) sleep deprivation (Walker and Stickgold, 2006). Also, structures such as the hippocampus, neocortex, and amygdala are highly activated during sleep, further implicating the role of sleep in memory processes (Capellini, McNamara, Preston, Nunn, and Barton, 2009). Research over the last decade has established that new neurons are generated in particular areas of the brain, specifically in the dentate gyrus of the hippocampal formation (Meerlo, Mistlberger, Jacobs, Heller & McGinty, 2009). Therefore the role of sleep restriction and disruption on the regulation of neurogenesis and how this may impact on learning and memory has begun to gain more attention. Preliminary findings in rats suggest that prolonged sleep deprivation or fragmentation reduces hippocampal cell proliferation and neurogenesis (Meerlo et al.). Such findings suggest that sleep loss may have an impact on the integrity of the hippocampus and this may in turn lead to cognitive dysfunction; memory impairment in particular.

Despite the insignificant results obtained for measures of visual memory in the current study, it was found that for the OSA patients, immediate visual

memory was significantly related to subjective sleepiness as measured by the ESS and KSS. That is, increased sleepiness and reduced alertness were associated with greater difficulty immediately recalling visual designs on the Visual Reproduction subtest. This is consistent with previous research that has demonstrated an association between excessive daytime sleepiness and deficits in visual memory performance (Bedard et al., 1991; Beebe & Gozal, 2002; Decary et al., 2000; Naegele et al., 1995). This finding may again highlight the effect that sleep loss has on memory processes and functioning of the hippocampus. Interestingly, for the control participants, both immediate and delayed visual memory performance were significantly negatively related to percentage of total sleep time where oxygen was below 90 percent saturation. That is, poorer immediate and delayed recall of information was associated with nocturnal hypoxaemia. The findings of the current study suggest that deficits in visual memory appear to be related to both sleepiness and to hypoxaemia.

1.6. Conclusion

Obstructive sleep apnoea is a disorder associated with brief arousals during sleep and intermittent hypoxaemia. This study was designed to investigate the effects of this disorder on subjective and objective sleepiness, simulated driving performance, vigilance and neuropsychological functioning.

The primary findings of this study were that OSA patients demonstrated significant subjective daytime sleepiness and decreased levels of alertness when compared to control participants. However, they did not demonstrate increased objective sleepiness. On a simulated driving task, there were no significant differences noted between OSA patients and control participants. However,

consistent with previous research OSA patients demonstrated vigilance impairment, and impaired performance on immediate and delayed verbal memory.

The deficits in performance on these tasks are often attributed to levels of daytime sleepiness and intermittent hypoxaemia. This study highlighted the difficulty experienced by other studies in drawing firm conclusions about the contribution of sleep fragmentation and hypoxaemia in producing such impairments. Measures of sleepiness were related to visual attention, immediate visual memory, procedural memory and cognitive flexibility. Hypoxaemia was related to immediate and delayed visual memory, and median reaction times. It is known that hypoxaemia results in damage to neural systems, including reduced functionality within brain regions and damage to the hippocampus. Furthermore, sleep fragmentation can interfere with memory consolidation and neurogenesis during sleep. Studies have indicated that in patients with OSA, alternative brain regions are recruited to compensate for deficits in particular functions. This finding may be useful in explaining the variable results between studies in areas of impairment.

It is also important to consider the difficulties in attentional functioning and concentration that are frequently identified in OSA patients, and the impact that these may have on other cognitive domains. Previous studies have suggested that these impairments may play a role in producing a range of neuropsychological deficits (Bedard, 1991). In order to assist in drawing firm conclusions about the pathogenesis of cognitive impairment in OSA patients, it will be important for future research to control for attentional deficits.

CHAPTER 2

2.1. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is now the fourth leading cause of death in Australia, with more than half a million Australians experiencing moderate to severe disease (Crockett, Cranston, & Moss, 2002; Tan, Seale, & Chaoenratanakul, 2001). It is the only leading cause of death that is increasing in prevalence. In 2002, COPD was the underlying cause of 5,599 deaths in Australia accounting for 4.2% of the total number of deaths. It represents a major burden of disease for Australia in terms of mortality, disability, impairment, and illness (Hurd, 2000). An annual health cost has been estimated at \$900 million, although this is likely to be an underestimate as hidden costs, such as misdiagnosis and carer burden are not accounted for (Crockett, Cranston, & Moss). More recently an Access Economics report suggested the true cost was substantially higher (Access Economics, 2008).

COPD is a collection of diseases including emphysema and chronic bronchitis, with cigarette smoking firmly established as a major cause. The disease is characterised by airflow limitation, producing oxygen desaturation, cell hypoxia, and hypercarbia (Stuss, Peterkin, Guzman, & Troyer, 1997). It is not fully reversible, but rather a progressive, disabling disease with serious consequences and complications (McKenzie, Frith, Burdon, & Town, 2003). Many patients experience a high level of discomfort and disability, including cough, shortness of breath, and excessive sputum (Croxtton, Weinmann, Senior, & Hoidal, 2002). Significantly reduced health-related quality of life, neuropsychological impairment, and emotional and psychological disturbances are also common sequelae of the disease (Ambrosino, Bruletti, Scala, Porta, &

Vitacca, 2002; Greenberg, Ryan, & Bourlier, 1985). Although available treatments have little effect on the long-term decline in lung function, which is a key feature of this disease, much can be done to optimise function, improve quality of life, and reduce morbidity in affected individuals. Smoking cessation and oxygen therapy for those who need it have also been demonstrated to improve mortality in COPD.

2.1.1. Prevalence of COPD

Historically, the prevalence and mortality of COPD has been significantly greater in men compared to women (Varkey, 2004). This trend most likely reflects the difference in exposure to risk factors, particularly cigarette smoking. However, COPD in women has gained more attention as gender differences in the susceptibility to and severity of COPD have emerged. Although an increase in tobacco use among women seems a likely explanation for an increase in COPD prevalence, recent research also suggests that women are more likely to develop COPD at an earlier age, may be more susceptible to developing impaired lung function, and may experience more severe symptoms of the disease (Han, et al., 2007; Prescott, Bjerg, Andersen, Lange, & Vestbo, 1997).

The specific reasons for these differences are largely unknown and understudied. However, it is likely that the interaction of sex differences, such as genetics and physiology, together with gender influences, such as culture and economics, plays a significant role (Greaves & Richardson, 2007). No matter the reason, the increase in hospitalisations and deaths from COPD in women suggests that further research, and policy development is of significant importance so that

the health system can better respond to the increasing problem of COPD in women.

2.1.2. Aetiology and Pathophysiology

Tobacco smoking is the most significant risk factor for COPD, and contributes approximately 85% of the risk (Crockett, et al., 2002). It is estimated that around half of all smokers develop some degree of airway limitation, with 15-20% developing significant disability (Fletcher & Peto, 1977). There are other less common causes of COPD, including air pollution, occupational dust and chemical exposure, passive smoking, and recurrent respiratory infections in childhood (McKenzie, Frith, Burdon, & Town, 2003). Genetic abnormalities can also be a predisposing factor, such as the α_1 -antitrypsin deficiency that results in emphysema (McKenzie et al.). Reduced exposure to these risk factors can slow the progression of the disease; however its underlying pathology is incurable and irreversible.

An accelerated decline in lung function is the hallmark of COPD, with airway and parenchymal inflammation being consistent findings (Croxtton, et al., 2002). Studies have shown that, compared with smokers without airway obstruction, COPD patients have a greater number of macrophages and neutrophils, as well as CD8-positive T lymphocytes in the airway wall (Pesci, Balbi, Majori, et al., 1998; Turato, Zuin, Miniati, et al., 2002). With increasing lung function deterioration, the number of these cells increases within the airways

and alveoli, and they play a role in the damage and remodelling of the airway walls that takes place in COPD (Hogg, 2003).

COPD includes chronic bronchitis and emphysema and many patients have features of both. Chronic bronchitis is clinically diagnosed and is defined as cough and sputum production for at least three months total duration within two consecutive years (McKenzie et al., 2003). When the bronchi are inflamed, airflow to and from the lungs decreases and excessive mucus accumulates, which obstructs the airways. Inflammation then causes scarring in the lungs. Ciliary function is reduced, where mucus is not effectively cleared and the lungs become an ideal breeding ground for bacterial infections (Solomon, Berg, & Martin, 1999). Fibrotic tissue then replaces granulation tissue, leading to a stenosis of the airways and airway obstruction. Symptoms of chronic bronchitis include chronic cough, increased mucus, frequent clearing of the throat, and shortness of breath.

Emphysema is diagnosed pathologically and refers to a destruction of lung alveoli (McKenzie et al., 2003). It results in a loss of the elastic recoil in the lungs, which increases the tendency for the lungs to collapse during expiration and causing flow limitation (Marieb, 1998). This is followed by hyperinflation and increased work of breathing (Ferguson, 2006). Exposure to components of cigarette smoke, pollutants, or genetic predisposition lead to destruction of the alveolar wall and other changes to pulmonary vessels that impair the surface area which means less surface area for oxygen (O₂) and carbon dioxide (CO₂) exchange (Solomon, et al., 1999). This poor exchange commonly leads to

hypoxaemia. Symptoms of emphysema include cough, shortness of breath (dyspnoea), and limited exercise tolerance.

Adequacy of gas exchange in the lung is determined by the ventilation/perfusion (V/Q) ratio. Ventilation refers to the movement of air in and out of the lungs, removing CO₂ from the blood and providing O₂ (Williams, 1998). When alveolar ventilation matches pulmonary blood flow, gas exchange is facilitated with oxygenation of blood and elimination of CO₂. However, in the damaged lung in emphysema, there is less surface area for O₂ to travel from the lungs into the blood, and for CO₂ to pass from blood into the lungs to be exhaled. This creates a diffusion impairment which then leads to hypoxemia (Fleetham, 2003). Furthermore, levels of CO₂ in the blood can also increase, leading to hypercarbia/hypercapnia (high levels of carbon dioxide in the blood).

Hypoxaemia is not a feature in all patients with COPD. The lungs have a large reserve capacity, which allows them to deal with high exertion, such as during exercise. As a result, COPD can often be 'silent' in the early stages, where symptoms may not be present. This would occur mostly under resting conditions, where demands on the respiratory system are low, resulting in adequate arterial oxygenation. However, during exercise, increased stress and metabolic demands are placed on the gas exchange system within the lungs, resulting in arterial haemoglobin oxygen desaturation (O'Donnell, Revill, & Webb, 2001). Therefore, exercise and activity limitation are common consequences of COPD pathophysiology.

Nevertheless, in more advanced COPD, disruption to normal gas exchange can become so severe, that arterial oxygen desaturation occurs not only during exercise, but also while at rest. The hypoxaemia can cause pulmonary artery

constriction, increased pulmonary artery pressure, and eventually episodes of cor pulmonale (change in structure and function of the right ventricle of the heart).

Acute exacerbations of COPD are another hallmark of the disease and represent an acute worsening of symptoms. These include worsened dyspnoea, increased sputum purulence and volume, acute hypoxaemia, hypercapnia, and also altered mental state (McCorry, Brown, Sarah, & Bach, 2001). Exacerbations are associated with an increased chance of mortality, deterioration in quality of life and functional status, and a likelihood of readmission to hospital (Connors, Dawson, Thomas, et al., 1994; McCorry, et al.). They are caused by tracheobronchial infections, environmental exposures, and may also be precipitated by other significant medical conditions (McCorry, et al.).

2.1.3. Diagnosis of COPD

The diagnosis of COPD is suggested by a history of persistent progressive symptoms, as well as physical examination, and is confirmed by laboratory tests (Calverley & Walker, 2003). A supportive risk factor such as cigarette smoking is also an important part of the diagnosis. The most common symptoms and signs include cough, dyspnoea on exertion, and increased phlegm production (Georgopoulos & Anthonisen, 1990; Thompson, et al., 1992). Additional signs and symptoms include wheezing, prolonged expiration with pursed lip breathing, barrel chest, use of accessory muscles of breathing and, in advanced cases, cyanosis, evidence of right heart failure, and peripheral oedema.

Ultimately, the diagnosis of COPD depends on the demonstration of expiratory flow limitation, which is not fully reversible (Pauwels, Buist, Calverley, Jenkins, & Hurd, 2001; O'Donnell, et al., 2001). This is achieved by

spirometry testing, which objectively confirms the presence of airflow obstruction. Spirometry measures the total amount of exhaled air (forced vital capacity, or FVC) and the amount of air exhaled during the initial one second (forced expiratory volume FEV₁) to establish the degree of airflow obstruction. These values are expressed as percentages of what is predicted for normal lung function, depending on the variables of height, age, race, and sex. A patient with COPD characteristically shows a decrease in FVC compared to a person with normal lung function, as well as reduced FEV₁, which is reduced to a greater degree than the entire FVC. Therefore, the ratio of air exhaled after 1 second is low compared to the total amount of air exhaled and falls below 70-75%, which is below that expected in healthy individuals (Siafakas, et al., 1995).

Since the degree of FEV₁ reduction has prognostic implications and correlated significantly with mortality and morbidity, many guidelines have developed a staging system based on the degree of airflow obstruction. Although FEV₁ criteria vary among the systems, a general consensus to a 3-stage classification system has been achieved. One of the most widely used systems to summarise current opinion and evidence about COPD is the global initiative for chronic obstructive lung disease (GOLD) that was developed by WHO and the US National Heart, Lung, and Blood Institute. The identification of arterial hypoxaemia is also important, and oximetry or arterial blood gases can determine the level of oxygenation. Oximetry is non-invasive and determines oxygen saturation by measuring the amount of light transmitted through an area of skin. It is commonly used during exercise and sleep, but is not as accurate as arterial blood gas measurement. Arterial blood gases are measured using blood drawn from an artery, to determine PO₂, PCO₂, pH and haemoglobin oxygen saturation

(Williams, 1998). Arterial blood gases are generally measured if the FEV₁ is < 40% predicted. The severity of COPD can be graded using the indicators highlighted in Table 12.

Table 12

Severity of Chronic Obstructive Pulmonary Disease (COPD)

Factor	COPD Severity		
	Mild	Moderate	Severe
Spirometry - FEV ₁ % predicted	≥80% predicted	<80% predicted	<50% predicted
Functional Assessment	Few symptoms. May be with or without chronic symptoms such as cough, sputum production or dyspnoea.	Increasing limitation on activities of daily living. Increasing dyspnoea.	Dyspnoea on minimal exertion. Respiratory failure or clinical signs of right heart failure. Significant impairment to activities of daily living
PaO ₂	60-70mmHg	40-59mmHg	<40mmHg

Note. FEV₁ = forced expiratory volume in one second. PaO₂ = partial pressure of oxygen, arterial. mmHg = millimetres of mercury.

(GOLD, 2009)

2.1.4. Treatment of COPD

Once the diagnosis of COPD is established, attention turns to the goals of treatment, which tend to fall into three broad categories: preventing the

progression of the disease, management of stable disease, and management of disease exacerbations. Preventing disease progression involves patient education to modify and reduce risk factors, to maximise functional status, and to improve coping ability (Sutherland & Cherniack, 2004). Smoking cessation is an essential part of patient management and education (Pauwels et al., 2001). Although it may lead to minimal improvement in lung function, it is essential to slowing the rate of decline and onset of disability.

Treatment is aimed to ameliorate the symptoms of the disease, such as dyspnoea, exercise tolerance, impaired sleep quality, exacerbations, and general quality of life. Pharmacological and non-pharmacological treatments (which may be used alone or in combination) include bronchodilators, glucocorticoids, pulmonary rehabilitation, and surgery.

The physiological and functional deficits observed in patients with COPD are often caused by contraction of the smooth muscle in the airway (Pauwels et al., 2001). Inhaled bronchodilators target this and provide symptoms relief and increased exercise tolerance (Belman, Botnick, Shin, 1996). They may also produce significant increases in FEV₁. Inhaled corticosteroids are used for people with moderate or severe COPD who have frequent exacerbations. They reduce airway inflammation and have been found, especially in combination with long acting beta agonists, to reduce the frequency of exacerbations in this patient group, as well as improving healthy related quality of life.

Supplementary oxygen therapy is prescribed for patients with COPD who have a decreased PaO₂ (McDonald, Crockett, & Young, 2005). In Australia oxygen treatment is generally delivered via oxygen concentrators or oxygen gas cylinders (Weg & Haas, 1998).

The intermittent breathlessness experienced in COPD is likely to increase on exertion or while performing everyday activities, such as dressing or cleaning (Royal College of Physicians, 1999). Such patients may benefit from short periods on oxygen during these exertions in order to reduce their breathlessness and increase their exercise capacity and quality of life (Rees & Dudley, 1998). For patients who experience more chronic and stable hypoxaemia, Long Term Oxygen Therapy (LTOT) for more than 15 hours per day is well established as the standard of care (Weg & Haas, 1998).

In early studies of LTOT, patients were found to experience reduced pulmonary hypertension, and increased exercise tolerance (Levine et al., 1967). Following these results, the Nocturnal Oxygen Therapy Trial Group (1980), and The Medical Research Council Working Party (1981) demonstrated the scientific foundation of LTOT that has since been the only treatment (apart from smoking cessation) proven to improve prognosis and alter the course of the disease (Petty, 2006). Specifically, LTOT reduces mortality, and impacts positively on haemodynamics, cardiac function, neuropsychological functioning, and psychological wellbeing when used for at least fifteen hours per day (Barnes, 2000; Pauwels et al., 2001). It is appropriate for individuals who have a PaO₂ that is consistently less than or equal to 55 mmHg and arterial oxygen saturation that is less than or equal to 88% (Pauwels et al. 2001) or in those patients whose PaO₂ is between 55 and 60 mmHg where there is evidence of long-term sequelae such as pulmonary hypertension or polycythaemia.

Nocturnal desaturation occurs in 25% to 45% of patients with severe COPD who do not experience hypoxaemia while awake (Levi-Valensi, Aubry, Rida, 1990). There is a natural slight decrease in ventilation during sleep, which

results in a drop in PaO_2 and rise in PaCO_2 , as well as changes in lung volumes. This results in further periods of desaturation that occur particularly during REM sleep, also resulting in increased pulmonary artery pressure. For those on LTOT, oxygen flow at night can be increased to minimise the decline seen during REM sleep. McDonald Crockett and Young, (2005) also highlight the importance of distinguishing hypoxaemia during sleep in COPD from hypoxaemia due to co-existent OSA, where alternative forms of therapy are required.

2.1.5. COPD and Sleep

Nocturnal oxygen desaturation in patients with COPD results from a combination of hypoventilation, and altered ventilation/perfusion ratios, as well as a relationship between nocturnal oxygen saturation and the level of daytime hypoxaemia; where the more pronounced the daytime hypoxaemia, the more severe the nocturnal hypoxaemia (Weitzenblum & Chaouat, 2004). The most severe episodes of nocturnal desaturation generally occur during rapid-eye-movement (REM) sleep and may contribute to cor pulmonale and nocturnal death (McNicholas, 2000; Weitzenblum & Chaouat). Although there are significant relationships between nocturnal desaturation and daytime hypoxaemia, hypercarbia, and exercise desaturation, these associations are not strong enough to allow prediction for nocturnal desaturation (Fletcher et al., 1992; Stradling & Lane, 1983). Therefore, overnight pulse oximetry allows direct assessment of nocturnal desaturation.

There is a lack of a universally accepted definition of nocturnal desaturation and the reported prevalence of 'significant nocturnal desaturation' in patients with COPD has varied between 25% and 70% depending on which

criteria are used (Chaouat et al., 1995; Fletcher et al., 1992). For example, Braghiroli (2002) used the definition of episodes that last at least five minutes and reach SaO₂ levels that are less than or equal to 85%. Other definitions include a drop in SpO₂ greater than 4% in relation to baseline (Little et al., 1999) and SpO₂ below 90% for more than 30% of total sleep time (Levi-Valensi et al., 1992). Despite this, in the UK and Europe, desaturation below 90% for greater than 30% of the night has been widely accepted as defining significant nocturnal desaturation (Chaouat et al.).

Sleep-related hypoxaemia may result in increased arousals, sleep disruption, and higher mortality (Gay, 2004). Indeed, patients with COPD report decreased sleep time and quality, delayed sleep onset, multiple awakenings, and a high number of arousals (Pauwels et al., 2001). The arousals result from a combination of hypoxia, hypercapnia, cough, and side effects of medication (Fleetham, 2003). Patients are observed to experience persistent snoring, episodes of choking, apnoeas, more changes in sleep stage and less REM sleep (Fleetham, 2003; GOLD, 2001). However, studies have found that symptoms of sleepiness are more common in moderate to severe COPD rather than in mild COPD (Klink, Dodge, & Quan, 1994). In an adult community setting, Sanders et al. (2003) found that patients with mild COPD demonstrated only mildly affected sleep quality and architecture, and that they did not report excessive daytime sleepiness. COPD patients complain of more daytime sleepiness than those without respiratory disease, although the effects of this on daytime functioning and quality of life have not been studied.

2.1.6. Neuropsychological Deficits in COPD

Hypoxia is known to damage multiple organ systems especially those with a high consumption of oxygen such as the central nervous system (Gale & Hopkins, 2004). It is implicated in the production of free radicals, neuronal damage, inflammatory responses, and increased glial activation (De La Torre, 1999). Furthermore, hypoxia results in cognitive impairment (Berry, et al. 1986; Grant et al., 1982; Prigatano, Parsons, Wright, Levin, & Hawryluk, 1983; Stuss et al., 1997). Cognitive impairment is one of the most common sequelae of COPD, particularly with the worsening of hypoxaemia and hypercapnia (Incalzi, et al., 2006). It can therefore be a marker of disease severity with important clinical and prognostic implications. Research has indicated that COPD is related to impairment in a number of cognitive functions, such as reaction time, memory, abstract reasoning skills, and complex visual-motor processes, relative to normal adults (Grant et al.; Stuss, Shallice, Alexander, & Picton, 1995). These impairments have been found to correlate with poor compliance with treatment, limited personal independence, and reduced ability to cope with activities of daily living (Incalzi et al.).

In an early study investigating the effects of continuous oxygen therapy in COPD, Krop, Block, and Cohen (1973) were one of the first groups of researchers who demonstrated cognitive impairment in COPD. They investigated differences in cognitive function between ten hypoxaemic patients (mean PaO₂ of 51 mmHg) and 12 patients who had the same degree of COPD, but who were less severely hypoxaemic (mean PaO₂ of 67 mmHg). The hypoxaemic patients scored significantly lower on five out of ten neuropsychological tests in comparison to the less severely hypoxaemic group. A limitation of this particular study was that

there was no control group recruited, therefore it is difficult to establish whether the non-hypoxaemic group had cognitive impairment relating to their COPD.

Grant and co-workers (1980) further documented impaired cognitive function in patients with hypoxaemic COPD. These findings were presented as part of the Nocturnal Oxygen Therapy Trial (NOTT) that investigated continuous O₂ therapy in comparison to nocturnal O₂ therapy (NOTT, 1980). Of 121 patients with COPD with arterial oxygen levels less than 55mmhg, 77% demonstrated neuropsychological dysfunction, with 40% experiencing moderate impairment. Since the NOTT study did not specifically address the effect of hypoxaemia on cognitive functioning in COPD, limitations of the study included a lack of adequately matched control group, and no opportunity to explore other disease sequelae that may have impacted on cognition. Consequently, Grant et al., as well as other researchers began to investigate the effects more systematically.

In 1982, Grant et al. presented updated results from the NOTT sample of patients that also included a control group who were matched on age, sex and education. Their findings were similar to those of the previous study where COPD patients were found to perform significantly worse on neuropsychological assessment when compared to controls. The most severe impairments were found in higher-order cognitive functioning, such as attention, abstract reasoning ability, and complex perceptual-motor integration. Stuss, et al. (1995) suggested that attentional deficits might be accounted for by diffuse damage secondary to hypoxia or as a result of specific damage to anterior frontal systems. Grant et al., also found impairments in simple motor tasks, where speed, strength, and co-ordination were poorly managed. In comparison to controls, COPD patients performed best on tests of verbal ability and verbal memory.

Despite this, further research has demonstrated that verbal memory is significantly impaired in patients with COPD (Incalzi et al., 1993; 1997; Stuss, et al. 1997). Incalzi and co-workers (1997) demonstrated that individuals with COPD showed verbal memory impairments for both immediate and delayed recall. Recognition and active recall of learned material were severely impaired in these patients, as demonstrated by low recognition accuracy and retrieval scores. These impairments in verbal memory were significantly correlated with a decline of overall cognitive functioning, and that together, this related to poor medication adherence.

Incalzi et al (2003) found that verbal memory retrieval deficits may be substantiated by the demonstration of impaired metabolism in frontal and/or subcortical regions of the brain. They investigated the cerebral perfusion patterns of hypoxaemic (H) and non-hypoxaemic (NH) COPD patients. They found normal patterns of cerebral perfusion in NH patients; however in H patients they were mildly depressed. This occurred mainly in the anterior regions of the brain, and was more evident in cortical than subcortical structures. Furthermore, Shim et al. (2001) used proton magnetic resonance spectroscopy to detect metabolic changes of the brain in non-hypoxaemic COPD patients (mean PaO₂ 89mmHg). A general decrease in cerebral metabolites was noted in the parietal white matter of the COPD patients, with choline levels correlating with memory function. However, other cerebral metabolic changes did not correlate with parameters such as pulmonary function, and resting PaO₂ or PaCO₂ levels. This suggests that other factors aside from hypoxaemia and hypercapnia may influence brain metabolism in COPD. The authors suggested that the oxygen desaturation during sleep or exercise might play a role in altering cerebral metabolites.

Ortapamuk and Naldoken (2006) investigated cerebral perfusion patterns, using single photon emission computed tomography (SPECT), and cognitive function in eight patients with COPD who were hypoxaemic, ten COPD patients who were nonhypoxaemic, and ten age-matched healthy participants. Although both patient groups demonstrated impaired verbal memory, hypoxaemic COPD patients showed more significant deficits in delayed recall and attention. Additionally, nonhypoxaemic patients showed significantly decreased perfusion in left frontal regions, whereas hypoxaemic patients showed perfusion decline in both frontal and parietal regions. This supports the results of Shim et al., where metabolic changes were also noted in the parietal region. These results highlight the role different levels of hypoxia play in producing variable patterns of cognitive impairments and changes in cerebral blood flow.

In COPD patients with severe hypoxia, there are abnormal electroencephalogram patterns and evidence of cortical atrophy on CT scans (Stuss et al., 1997). Atrophy has been found to occur in specific areas such as the hippocampus and other limbic regions (Stuss et al.). Such damage to the limbic region may be the basis for the specificity of memory dysfunction found in this patient group (Stuss et al.). Attentional deficits may be related to diffuse brain impairment as a result of prolonged oxygen deprivation. In terms of the possible biochemical underpinning of neurobehavioral change in hypoxia, Grant et al, (1987) found that neurotransmitter biosynthetic pathways are significantly affected. This is important given the growing evidence that acetylcholine is critical to cognitive functions, memory in particular.

Many authors have attributed cognitive deficits in COPD to decreased oxygenation of cerebral tissue and neuropsychological impairments have

predominantly been demonstrated in COPD patients who display moderate to severe hypoxaemia. However Prigatano, et al. (1983) demonstrated modest deficits in patients who were mildly hypoxaemic (mean PaO₂ of 66.3 mmHg). This suggests that cognitive deficits may be progressive, with more severe hypoxaemia producing more significant deficits. Prigatano et al. found that mildly hypoxaemic COPD patients differed significantly from controls on neuropsychological measures. Consistent deficits were noted in abstract reasoning ability, speed of information processing, and immediate and delayed memory. An important strength of this study was that depression and motivation to perform were studied as confounding factors, and these did not account for deficits in the COPD participants.

A more recent study found significant impairments in patients with COPD, who were non-hypoxaemic (Liesker, et al., 2004). Thirty COPD patients with an average PaO₂ of 76mmHg, and healthy subjects matched for age IQ and level of education were recruited. Significant impairments were seen in cognitive performance, especially in speed of information processing. Of note, memory performance was largely unaffected in the COPD group. This is in contrast to findings from a separate group of researchers who found impairments in memory, attention, visuo-spatial functioning, and motor skills in patients with severe COPD, but with a mean PaO₂ of 89mmHg (Shim et al., 2001).

Although the research suggests a relationship between the degree of hypoxaemia and extent of cognitive impairment in COPD patients, results suggest that hypoxaemia may not be the only cause of cognitive impairment. COPD is linked to other comorbid conditions, such as hypertension, stroke, and heart disease, as well as psychiatric conditions (e.g., depression) (Hung, Wisnivesky,

Siu & Ross, 2009). It is plausible that impaired cognitive functioning might be due to subclinical cerebrovascular disease attributable to these conditions. Therefore, further research is required to further investigate cognitive abnormalities in non-hypoxaemic patients.

2.1.7. Quality of Life

COPD is also associated with emotional and psychological disturbances that impact on daily functioning and treatment outcomes. The available literature is consistent in highlighting depression and anxiety as significant symptoms in COPD patients that can be related to characteristics of the disease, such as, difficulty breathing, reduced energy, and fluctuating symptoms (Access Economics, 2008; Greenberg, Ryan & Bourlier, 1985).

Depressive symptoms have been reported in as many as 74% of COPD patients with a loss of independence and life role found to contribute significantly (Gift & McCrone, 1993). A UK national survey of 2500 patients with COPD found that 73% were unable to undertake activities that were important to them, such as gardening or going out for social functions, therefore quality of life is markedly affected (Morgan, Threlfall, Sanders, Walden & Britton, 2001). Anxiety disorders are also common in the COPD population and are very much related to fear of breathlessness (dyspnoea), which in turn leads to a fear of behaviour that could induce dyspnoea (Greenberg et al., 1985; Carrieri-Kohlman, Gormley, Douglas, Paul, & Stulberg, 1996).

These examples of psychological distress highlight that COPD encompasses psychological disturbances in addition to the pulmonary pathology

that can impact significantly on COPD patients' quality of life. Therefore, access to psychological interventions and services is important to address these issues with the aim of improving life quality, treatment outcomes, and overall healthcare burden.

2.1.8. Reversal of Neuropsychological Deficits

LTOT is important in the management of COPD, and two comprehensively performed randomised control trials (NOTT, 1980; MRC, 1981) have demonstrated its beneficial effects on survival in patients with COPD who have severe resting hypoxaemia. Although the benefits of LTOT are fundamentally based on mortality data, studies have also suggested improvement in functional, psychological, quality of life and cognitive measures (Borak, Sliwinski, Tobiasz, & Zielinski, 1996; Heaton, Grant, McSweeney, Adams, & Petty, 1983; Krop et al., 1973; Okubadejo, Paul, Jones, Wedzicha, 1996).

In an early study, Krop et al. (1973) found that the reduction in cognitive function in hypoxaemic COPD patients was improved by relieving the hypoxaemia via continuous ambulatory oxygen therapy. As discussed earlier, ten hypoxaemic patients with COPD performed significantly worse on a battery of ten neuropsychological tests than twelve patients who were less hypoxaemic. After treatment with oxygen therapy for four weeks, the hypoxaemic group demonstrated improvement in eight out of ten neuropsychological tests. The patients in the comparison group who were less hypoxaemic demonstrated no improvement, and furthermore, the differences in performance initially noted between the groups were no longer apparent. Although methodological flaws were

apparent in this study, for example, lack of disease stability in patients, and no blinding of experimental treatment, the findings were an important contribution to examining the effect of LTOT on cognition.

In a comprehensive study as part of the NOTT trial, Heaton, Grant and McSweeney (1990) followed up 150 COPD patients who had either received nocturnal oxygen therapy (NOT) or continuous oxygen therapy (COT). When examined after six months of treatment, the improvements in neuropsychological functioning were comparable for the NOT and COT groups. These improvements were noted in the areas of verbal and language skills, abstract reasoning and flexible thinking, and simple sensory and motor abilities. However, when tested after twelve months of treatment, only those receiving COT demonstrated continued improvement in neuropsychological functioning, suggesting some advantage for COT over NOT. A significant strength of this study is that the neuropsychological assessments were performed when participants had ceased supplemental oxygen. This means that the results obtained are not likely to reflect the acute effects of oxygen, with the authors attributing the improved performance to more adequate preservation of neurons, production of neurotransmitters, and enhancement of metabolism.

Borak, et al. (1996) investigated cognition, psychological status, and attitudes in ninety patients with COPD before they began LTOT and again after one year of treatment. Impaired performance was initially noted on tests of cognitive function, with improvements in memory noted after treatment. Despite this, deficits in visual and spatial memory did not improve. However, given the progressive decline that can be expected in severe COPD (Incalzi et al., 1998), an absence of improvement in cognition over a certain period can still indicate that

LTOT is providing some benefit. As part of their study, Borak et al. also demonstrated significantly improved psychological functioning and attitudes.

Hjalmarsen, Waterloo, Dahl, Jorde, and Viitanen, (1999) assessed the effects of LTOT on cognition, as well as other central and autonomic nervous system functions in ten COPD patients. Although their findings indicated improvements in neuropsychological function, velocity of cerebral blood flow, and autonomic function, the results were not statistically significant. Undoubtedly, their small sample size precluded the authors from demonstrating any real effect; however the results are encouraging in lending support to the hypothesis of improvement in cognitive functioning following LTOT.

2.1.9. COPD and Driving

The evidence for compromised cognitive abilities, such as attention and concentration, motor skills, and complex perceptual-motor integration raises significant concerns in relation to driving competency in patients with COPD. Given these cognitive difficulties, as well as the serious functional consequences of the disease (for example coughing, shortness of breath), it is reasonable to assume that those with the disorder can potentially demonstrate impaired driving ability (Austroads, 2006). In this context, the effect that chronic hypoxaemia has on driving ability is of great concern. However, there are no studies that have explicitly explored the relationship between COPD and motor vehicle crashes.

A search of the literature identified one study by Vernon, et al. (2002) who investigated crash rates (including at-fault crashes) and citation rates for 2,688 drivers with pulmonary conditions in comparison to controls. Participants were classified according to whether they had restrictions on their drivers licenses or

not, with most participants having no restrictions. Those drivers with pulmonary conditions who had no license restrictions had significantly higher crash rates and at-fault crashes in comparison to the general population of drivers. On the contrary, the crash rates and at-fault crashes for drivers with pulmonary conditions with restricted licenses were not significantly different to the general population. This study highlighted that unrestricted drivers with pulmonary conditions have a higher risk of crashing than the general population of drivers (Vernon et al.). A limitation of this study is that the pulmonary group consisted of drivers with a host of conditions including pulmonary disease, pulmonary symptoms, or severe respiratory difficulties making it difficult to isolate the crash risk associated with particular respiratory conditions.

Similarly, there is only one publication outlining the effects of hypoxaemia on driving performance. Ramsey (1970) investigated reaction time in a group of thirty healthy male students compared to a group of thirty older patients with a range of respiratory illnesses. Although it was presumed that the patients were hypoxic, no information was provided with regard to their oxygen status. Ramsey exposed the participants to traffic conditions, assuming that a reduction in blood oxygen levels would occur as a result of an increase in carboxyhaemoglobin (COHb) concentration. However, neither of these parameters were measured or reported. Although a significant reduction in reaction time was found in those exposed to the traffic conditions, the findings of this study were within the context of poor methodology, data collection, and lack information made available, and are therefore questionable.

Patel (2003) assessed seven patients with hypoxic COPD on a steering simulator whilst breathing supplemental oxygen. When oxygen was increased

from 85% to 96%, response times were improved, and steering errors and off-road incidents reduced. The authors also exposed 6 normoxic COPD patients to oxygen levels that were reduced from 95% to 88% and found deteriorating driving performance. A valuable conclusion of this study is that supplemental oxygen improves steering ability. Pretto and McDonald (2008) further investigated whether acute oxygen therapy improves cognitive and driving performance in hypoxaemic COPD. Thirty hypoxaemic COPD patients performed a driving simulator task and a psychomotor vigilance task. There were no significant results found while breathing oxygen compared to air. The data did not support the use of oxygen while driving and it was concluded that acute oxygen therapy does not improve cognitive function and driving performance.

The paucity of well-controlled studies investigating the effects of hypoxaemia on driving performance means that decisions regarding driving competency for individuals with COPD are not based on risk data, rather, they are evaluated on consequences of the disease that impact on driving competency (Dobbs, 2005). Currently, the licensing guidelines for individuals who hold private licenses in Australia specify that only in cases of severe asthma are drivers to abstain from driving (Austroads, 2006). Similarly, in people with unstable COPD and require oxygen therapy, the criteria for an unconditional license are not met. If the COPD is stabilized and the person can control the vehicle, then they may be granted a conditional license, that includes the opinion of the treating doctor, and that is subject to periodic review. A study also indicated that people with moderate to severe respiratory disorders, had limited or ceased their driving due to an inability to walk to the car, difficulty parking or using seat belts (Briggs, Patel, Butterfield and Honeybourne 1990).

Further consideration needs to be made to the additional safety issues that occur when patients are required to transport oxygen in cylinders. The Australian Standard for the transportation of gas cylinders (2002) describes the conditions under which cylinders should be transported given their combustion properties. Whether improving blood oxygen levels has a positive impact on enhancing driving performance is yet to be firmly determined. Due to the difficulties and dangers associated with carrying oxygen cylinders in the car, further research is needed to address whether there is a major difference to driving performance when oxygen is used, and whether it is to be recommended.

EXPERIMENT 2

The aim of this study was to compare simulated driving performance and subjective and objective sleepiness in patients with chronic obstructive pulmonary disease with healthy control participants. A further aim of this study was to assess neuropsychological functioning in these groups, by comparing memory performance, sustained attention, reaction time, and vigilance. In an effort to explore the nature, extent, and source of these impairments this study also aimed to compare polysomnography characteristics of the groups and investigate the relationship between sleepiness, hypoxaemia and performance.

Hypotheses

1. There would be no significant difference in weight, BMI, and MAPI between COPD patients and control participants.
2. Patients with COPD would experience a greater percent of total sleep time where oxygen saturation was below 90% compared to healthy controls and

there would be no difference between the groups in relation to total sleep time, sleep efficiency, arousals per hour of sleep, and AHI.

3. There would be no significant difference in levels of subjective sleepiness between COPD patients and healthy control participants.
4. Patients with COPD would perform worse on tests of simulated driving performance, sustained attention, vigilance, and reaction time, than control participants.
5. There would be no difference between COPD patients and healthy control participants on measures of objective sleepiness.
6. Patients with COPD would perform worse on tests of neuropsychological function than control participants.
7. There would be a significant association between subjective sleepiness, as measured by the ESS and KSS, and sleep disruption and nocturnal hypoxaemia as measured by polysomnography.
8. There would be a significant relationship between subjective sleepiness, as measured by the ESS and KSS, and oxygen saturation and lung function measurements.
9. Sleep disruption, as measured by polysomnography, would be associated with poorer performance on the PVT and driving simulator.
10. A greater percent of total sleep time where oxygen saturation was below 90%, and reduced lung function and arterial blood gases would be associated with slower reaction times, and poorer performance on the driving simulator.

11. A greater percent of total sleep time where oxygen saturation was below 90%, and reduced lung function and arterial blood gases would be associated with poorer performance on neuropsychological tasks.
12. Increased subjective sleepiness would be associated with poorer performance on neuropsychological tasks.
13. Sleep disruption, as measured by polysomnography would be associated with poorer performance on neuropsychological tasks.

2.2. Method

2.2.1. Participants

A sample of 14 mildly hypoxaemic (PaO₂ 55-75 mmHg) COPD patients who did not yet qualify for LTOT were also referred from Austin Health. This group included 12 males and 2 females between the ages of 46 and 85 years (M = 67.07, SD = 11.65), with a mean BMI of 26.04 (SD = 4.93). COPD patients were diagnosed by a physician using GOLD criteria of FEV₁/FVC <0.7. In the present study, it was not appropriate to use COPD patients with more severe hypoxaemia, as treatment with LTOT would need to have been withheld to avoid the effects of oxygen therapy on performance and cognition.

Particular control participants who formed part of the sample in Chapter 1 were also used in the present study, as they were also age and gender matched to particular COPD patients. Further control participants were recruited from the community via advertisements (See Appendix A) and completed the group of 11 participants that consisted of 9 males and 2 females between the ages of 52 and 76 (M = 63.55, SD = 9.54), with a mean BMI of 25.50 (SD = 3.49). The control participants were excluded from the study if they had evidence of respiratory

symptoms, reported past or current tobacco use, or exposure to occupational and environmental pollutants.

Medical records of all COPD patients were examined against the selection criteria and any participant experiencing chronic neurological illness, chronic liver disease, diabetes requiring insulin, renal impairment, pregnancy or breast-feeding, chronic psychiatric illness, visual acuity problems not correctable with glasses, or regular use of medication known to affect cognition were excluded. Participants unable to speak and read English were also excluded. Any COPD participants with co-existing OSA were excluded from the study.

2.2.2. Materials

The materials described in Chapter 1 were also used in the present study. Please refer to section 1.2.2. for full details.

2.2.3. Procedure

The procedure described in Chapter 1 was also employed in the current study. Please refer to section 1.2.3. for full details. In contrast to the procedure previously described for OSA patients, the COPD participants proceeded to complete a polysomnography study in the sleep laboratory following the assessment session, as did the control participants. They were woken at 6am the next morning and were then able to go home.

2.2.4. Statistics

Statistical procedures used in the present study were the same as those used in Chapter 1. Please refer to section 1.2.4. for full details.

2.3. Results

2.3.1. Diagnostic Characteristics

Patient demographics including resting arterial blood gases obtained from each of COPD patient's medical file are shown in Table 13.

Table 13

Diagnostic Characteristics of the COPD patients

	Mean (SD)	Range
FEV ₁ , L	1.49(.65)	.59 - 2.70
FEV ₁ , L (% predicted)	50.36(22.01)	23.00 – 102.00
TLCO	14.49(4.76)	6.30 – 19.40
TLCO (% predicted)	45.64(9.55)	33.00 – 63.00
PO ₂	64.83(5.19)	57.00 – 74.00
PCO ₂	39.00(8.48)	29.00 – 64.00
PH	7.44(.02)	7.39 – 7.49

Note. TLCO = Transfer Factor of the Lung for Carbon Monoxide

n = 14

2.3.2. Demographics

Means and standard deviations for the demographic variables for COPD patients and control participants are shown in Table 14. One-way ANOVA demonstrated there were no significant differences between the groups on any demographic variables.

Table 14

Means and Standard Deviations for Demographic Variables for COPD Patients and Control Participants

	COPD Patients (n=14)		Control Participants (n=11)		df	F	p	r
	M	SD	M	SD				
Age	67.07	11.65	63.55	9.54	1,24	.66	.43	.17
Height (cm)	172.86	9.75	174.18	8.22	1,24	.13	.72	.07
Weight (kg)	78.64	19.30	76.91	8.43	1,18.65	.09	.77	.06
BMI	26.04	4.93	25.50	3.48	1,24	.09	.76	.06
MAPI	.41	.27	.32	.12	1,19.03	1.41	.25	.22

Note. MAPI = Multivariable Apnoea Prediction Index, BMI = Body Mass Index

2.3.3. Polysomnography

Results of the one-way ANOVA and Kolmogorov-Smirnov tests indicated that the COPD patients experienced a significantly higher percentage of sleep time where oxygen saturation was below ninety percent (Table 15).

Table 15

One-Way ANOVA and Kolmogorov-Smirnov Test Results for Differences between COPD patients and Control Participants on Polysomnography Variables

	COPD Patients (n=9)		Control Participants (n=11)		df	F	D	p	r
	M	SD	M	SD					
Total Sleep Time (min)	265.39	73.35	232.50	54.44	1,19	1.33	-	.27	.26
Sleep Efficiency (%)	67.50	18.65	65.97	15.24	1,19	.04	-	.84	.13
Arousals (/hr)	20.12	13.35	18.16	9.29	1,19	.15	-	.71	.09
AHI (/hr)	16.71	16.43	16.64	12.66	1,19	.00	-	.99	.00
% total sleep time <90% saturation*	33.48	39.66	.06	0.13	-	-	1.99	.001	.42

Note. AHI = Apnoea-Hypopnoea Index

* = COPD n = 12, Controls Participants n = 11

2.3.4. Sleepiness Measures

One-Way ANOVA and Kolmogorov-Smirnov Z tests demonstrated that there were no significant differences between the COPD patients and control participants on any of the subjective sleepiness variables (Table 16).

Table 16

One-Way ANOVA and Kolmogorov-Smirnov Z test results for Differences on Sleepiness Questionnaires for COPD Patients and Control Participants

	COPD Patients (n=13)		Control Participants (n=10)		df	F	D	p	r
	M	SD	M	SD					
ESS*	7.29	5.82	5.82	3.40	1,24	0.51	-	.48	.15
KSS*	4.36	1.60	3.36	1.02	1,24	3.20	-	.09	.35
Stop Driving Questionnaire (Suburban)	1.15	0.38	1.00	.00	-	-	.37	.49	.08
Stop Driving Questionnaire (continuous long distance)	1.46	.66	1.10	.32	-	-	.68	.18	.14
AQ**	19.92	5.71	19.33	2.35	1,24	.09	-	.77	.07

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; AQ = Alertness Questionnaire,

* = COPD patients n = 14, control participants n = 11

** = control participants n = 9

2.3.5. Performance Measures

Table 17 display results of the one-way ANOVA and Kolmogorov-Smirnov tests comparing COPD patients and control participants on the psychomotor vigilance task (PVT) and driving simulator. The COPD patients had a significantly higher median reaction time, higher number of lapses and an increase in duration of responses as measured by the slowest 10% on the PVT in comparison to the control participants. On the driving simulator, the COPD patients had a significantly higher average median position deviation from the centre of the left lane when compared with control participants.

Table 17

One-Way ANOVA and Kolmogorov-Smirnov Test Results for Differences between COPD patients and Control Participants on the PVT and Driving Simulator

	COPD Patients		Control Participants		df	F	D	p	r
	M	SD	M	SD					
PVT Median*	240.92	20.41	217.57	11.65	-	-	1.75	.001	.40
PVT transformed lapses*	6.03	1.79	2.76	1.06	1,23	19.13	-	.001	.72
PVT slowest 10%*	2.36	.55	2.89	.43	1,23	4.80	-	.04	.47
Median Position Average**	100.36	27.03	75.48	8.00	1,23	6.97	-	.02	.58
Speed 60-80kms average**	18.44	15.40	9.07	2.03	1,6.16	2.56	-	.16	.37
Number of crashes**	3.71	2.81	2.22	2.64	-	-	.69	.41	.17

Note. PVT = Psychomotor Vigilance Task

* = COPD patients n = 12, control participants n = 7

** = COPD patients n = 7, control participants = 9

2.3.6. Optalert™ Fatigue Monitoring Technology

Table 18 demonstrates Kolmogorov-Smirnov test results for differences in objective sleepiness, as measured by the Optalert™ fatigue monitoring system, between COPD patients and control participants. There were no significant differences between the groups on this measure of objective sleepiness.

Table 18

Kolmogorov-Smirnov Test Results for Differences between COPD patients and Control Participants on the Optalert™ fatigue monitoring system

	COPD Patients		Control Participants		<i>D</i>	<i>p</i>	<i>r</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
JDS % time eyes closed (PVT)*	.45	.85	.16	.28	.49	.92	.11
JDS % long eye closure (PVT)*	.22	.50	.09	.26	.51	.59	.12
JDS mean (PVT)*	2.07	2.21	1.10	1.25	.81	.42	.19
JDS % time eyes closed (driving)**	.58	.93	.20	.36	1.03	.17	.23
JDS % long eye closure (driving)**	.07	.12	.13	.29	.34	.91	.08
JDS mean (driving)**	1.23	1.01	.59	.64	.92	.28	.21

Note. JDS = John's Drowsiness Scale

* = COPD patients *n* = 11, control participants *n* = 8

** = COPD patients *n* = 11, control participants *n* = 9

2.3.7. Neuropsychological Tasks

Table 19 presents the mean and standard deviation of the neuropsychological tasks, and the results of one-way ANOVA and Kolmogorov-Smirnov tests for each measure. Results demonstrated that the COPD patients performed significantly worse than control participants on time to complete the Trail Making Test (A and B), Logical Memory I and Logical Memory II.

Table 19

One-Way ANOVA and Kolmogorov-Smirnov Test Results for Differences between COPD patients and Control Participants on Neuropsychological Tasks

	COPD Patients (n=14)		Control Participants (n=11)		df	F	D	p	r
	M	SD	M	SD					
TMT A (time)	35.07	8.66	24.44	9.19	1,24	8.80	-	.01	.50
TMT A (errors)	.29	.47	.09	.30	-	-	.48	.34	.09
TMT B (time)	94.50	21.83	64.98	30.49	-	-	1.58	.01	.32
TMT B (errors)	.36	.50	.09	.30	-	-	.66	.18	.13
Austin Maze*	80.82	12.96	78.20	31.70	1,11.70	.06	-	.81	.00
LM I	32.43	7.29	42.73	8.55	1,24	10.57	-	.01	.56
LM II	18.64	5.67	23.91	6.17	1,24	4.92	-	.04	.42
VR I	79.71	10.83	87.45	8.14	1,24	3.88	-	.06	.38
VR II	58.07	21.57	73.72	18.34	1,24	3.69	-	.07	.37

Note. TMT = Trail Making Test, LM = Logical Memory, VR = Visual Reproduction

* = COPD = 11, Control = 10

2.4. Correlational Analyses

2.4.1. Subjective sleepiness and performance on the PVT and driving simulator

Table 20 shows correlations (Kendall's tau) between measures of subjective sleepiness and performance on the PVT and driving simulator for both COPD patients and control participants. COPD patients showed a significant positive correlation between scores on the KSS and number of crashes on the driving simulator. There were no significant correlations between the measures for the control participants.

Table 20

Correlations (Kendall's tau) between Sleepiness Questionnaires and Performance on the PVT and Driving Simulator for COPD patients and Control Participants

	PVT and driving simulator variables					
	PVT median	PVT transformed lapses	PVT slowest 10%	Median position average ^	Speed 60-80kms average	Number of crashes^
A: COPD patients (n = 11)						
ESS	-.05	-.11	.13	.10	-.39	-.35
KSS	-.02	-.20	.19	.51	-.06	.69*
B: Control participants (n = 9)						
ESS	.05	.11	-.16	.45	-.21	-.06
KSS	-.05	-.06	.05	-.30	-.03	.00

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale;

* = Significant at .05

2.4.2. Sleepiness questionnaires and neuropsychological tasks

Table 21 shows correlations (Kendall's tau) between measures of subjective sleepiness and performance on neuropsychological tasks for both COPD patients and control participants. There were no significant correlations between the variable for COPD patients. Control participants showed a significant negative correlation between ESS scores and score on Logical Memory I.

Table 21

Correlations (Kendall's tau) between Sleepiness Questionnaires and Performance on Neuropsychological Tasks for COPD patients and Control Participants

	Neuropsychological Tasks									
	TMT A (time)	TMT A (errors)	TMT B (time)	TMT B (errors)	Austin Maze	LM I	LM II	VR I	VR II	
A: COPD patients (n=14)										
ESS	-.21	-.25	-.25	.19	.08	.09	.09	.19	.27	
KSS	.13	-.63*	.01	-.23	.30	-.01	.06	.07	.25	
B: Control participants (n=11)										
ESS	.38	-.37	.39	.27	.24	-.56*	.28	-.14	.28	
KSS	-.37	.25	-.37	-.20	-.49	.22	.39	.39	.28	

Note. TMT = Trail Making Test, LM = Logical Memory, VR = Visual Reproduction

* = significant at .05 ** significant at .01

2.4.3. Polysomnography and performance on the PVT and driving simulator

Table 22 shows correlations (Kendall's tau) between polysomnography results and performance on the PVT and driving simulator for both COPD patients and control participants. COPD patients showed a significant correlation between total sleep time and PVT median reaction time, PVT transformed lapses, PVT slowest 10% and number of crashes on the driving simulator all. COPD patients also demonstrated significant correlations between sleep efficiency and PVT median reaction time, PVT slowest 10% and number of crashes on the driving simulator. There was also a significant correlation between number of arousals and average speed deviation on the driving simulator. There were no significant correlations between performance variables and the percentage of total sleep time where oxygen saturation was below ninety percent.

Table 22

Correlations (Kendall's tau) between Polysomnography and Performance on the PVT and Driving Simulator for COPD patients and Control Participants

	PVT and driving simulator variables					
	PVT median [^]	PVT transformed lapses [^]	PVT slowest 10% [^]	Median position average	Speed 60-80kms average	Number of crashes
A: COPD patients (n=11)						
Total Sleep (min)	-.47*	-.43*	.40*	-.47	-.33	-.73*
Sleep Efficiency (%)	-.40*	-.35	.40*	-.33	-.20	-.60*
Arousals (/hr)	-.08	-.04	.06	-.20	-.80*	-.20
AHI (/hr)	.06	.08	-.08	.33	.33	-.10
% total sleep time <90% saturation	.05	-.09	-.05	-.20	-.20	.40
B: Control participants (n=9)						
Total Sleep (min)	-.05	.21	-.24	-.22	.56*	.35
Sleep Efficiency (%)	.14	.10	-.05	-.06	.28	.00
Arousals (/hr)	-.33	.10	.05	-.06	-.28	.06
AHI (/hr)	-.33	.21	-.14	.28	-.17	.12
% total sleep time <90% saturation	.00	.39	-.18	.04	.30	.23

Note. AHI = Apnoea-Hypopnoea Index, PVT = Psychomotor Vigilance Task

[^] = control n = 7

* = Significant at .05

2.4.4. Polysomnography and performance on neuropsychological tasks

Table 23 shows correlations (Kendall's tau) between polysomnography results and performance on neuropsychological tasks for both COPD patients and control participants. There were a number of correlations between sleep study variables and neuropsychological tasks for both COPD and control participants.

Table 23

Correlations (Kendall's tau) between Polysomnography and Performance on Neuropsychological Tasks for COPD patients and Control Participants

	Neuropsychological Tasks								
	TMT A (time)	TMT A (errors)	TMT B (time)	TMT B (errors)	Austin Maze	LM I	LM II	VR I	VR II
A: COPD patients (n=9)									
Total Sleep (min)	-.35*	.46*	-.26	.45*	-.32	.12	-.04	.56**	.18
Sleep Efficiency (%)	-.35*	.34	-.21	.45*	-.32	.06	-.04	.56**	.23
Arousals (/hr)	.19	.39	-.17	-.33	.09	.03	.02	-.13	-.26
AHI (/hr)	-.05	.45	-.39	.00	-.12	.00	.14	-.11	-.30
% total sleep time <90% saturation	.23	.00	.06	-.42	.25	-.02	.26	-.09	-.03
B: Control participants (n=11)									
Total Sleep (min)	-.28	-.09	-.42*	.09	.20	.09	-.07	.15	.04
Sleep Efficiency (%)	-.43*	-.09	-.53*	.17	.07	.06	.11	.18	.22
Arousals (/hr)	.57*	.09	.53*	-.08	-.11	.06	-.18	-.18	-.29
AHI (/hr)	.50*	.34	-.16	.08	-.16	.02	.15	.11	-.07
% total sleep time <90% saturation	.24	-.18	.13	-.18	-.04	.16	-.29	-.58*	-.50*

Note. TMT – Trail Making Test, LM – Logical Memory, VR = Visual Reproduction;

* = significant at .05 ** significant at .01

2.4.5. Polysomnography and Subjective Sleepiness

Table 24 shows correlations (Kendall's tau) between polysomnography results and scores on measures of subjective sleepiness for both COPD patients and control participants.

Table 24

Correlations (Kendall's tau) between Polysomnography and Measures of Subjective Sleepiness for COPD patients and Control Participants

	Total Sleep Time (min)	Sleep Efficiency (%)	Arousals (/hr)	AHI (/hr)	% total sleep time <90% saturation
A: COPD patients (n=14)					
ESS	.05	.10	-.22	-.02	-.39*
KSS	-.18	-.12	-.14	-.55*	.00
B: Control participants (n=11)					
ESS	-.31	-.23	.23	.35	-.14
KSS	.06	.12	-.24	-.07	-.37

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale

* = Significant at .05

2.4.6. Lung Function Tests and Arterial Blood Gases, and Subjective Sleepiness

Table 25 shows correlations (Kendall's tau) between lung function tests and arterial blood gas measurement and scores on measures of subjective sleepiness for both COPD patients and control participants.

Table 25

Correlations (Kendall's tau) between Arterial Blood Gases and Measures of Subjective Sleepiness for COPD patients

	FEV ₁ litres	FEV ₁ % predicted normal	PO ₂	PCO ₂
A: COPD patients (n=14)				
ESS	-.09	-.11	.47*	.01
KSS	-.19	-.06	.57**	.26

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale

* = Significant at .05

2.4.7. Lung Function Tests and Arterial Blood Gases, and Performance on the PVT and Driving Simulator

Table 26 shows correlations (Kendall's tau) between lung function tests and arterial blood gas measurement and performance on the PVT and driving simulator for both COPD patients and control participants.

Table 26

Correlations (Kendall's tau) between Arterial Blood Gases and performance on the PVT and Driving Simulator for COPD Patients and Control Participants

	FEV ₁ litres	FEV ₁ % predicted normal	PO ₂	PCO ₂
A: COPD patients (n=14)				
PVT Median	.55*	.52*	-.16	-.05
PVT transformed lapses	.65**	.61*	.02	.00
PVT slowest 10%	-.66*	-.63*	.06	.05
Median Position Average	.39	.52*	.20	.29
Speed 60-80kms average	.68*	.62*	-.30	.10
Number of crashes	.25	.59*	.35	-.36

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale

* = Significant at .05

2.4.8. Polysomnography and Optalert™ Fatigue Monitoring Technology

Table 27 shows correlations (Kendall's tau) between polysomnography results and sleepiness as measured by the Optalert™ fatigue monitoring technology for both COPD patients and control participants.

Table 27

Correlations (Kendall's tau) between Polysomnography and Measures of Objective Sleepiness for COPD patients and Control Participants

	Total Sleep Time (min)	Sleep Efficiency (%)	Arousals (/hr)	AHI (/hr)	% total sleep time <90% saturation
A: COPD patients (n=10)					
JDS % time eyes closed (PVT)	.21	.21	-.50*	.14	-.36
JDS % long eye closure (PVT)	.27	.27	-.54*	-.18	-.18
JDS mean (PVT)	.07	.07	-.50*	.00	-.21
JDS % time eyes closed (driving)	-.14	-.14	.29	-.21	.29
JDS % long eye closure (driving)	.00	.00	.00	-.32	.08
JDS mean (driving)	-.57*	-.57*	.43	.07	.43
B: Control participants (n=11)					
JDS % time eyes closed (PVT)	.18	.18	-.11	-.18	-.21
JDS % long eye closure (PVT)	-.05	-.05	.05	-.05	-.31
JDS mean (PVT)	-.04	-.04	.11	.11	.37
JDS % time eyes closed (driving)	.20	-.03	-.03	-.15	.40
JDS % long eye closure (driving)	.26	-.10	-.04	-.18	.34
JDS mean (driving)	-.20	-.38	.43	.09	.24

Note. JDS = John's Drowsiness Scale, PVT = Psychomotor Vigilance Task, AHI = Apnoea-Hypopnoea Index;

* = Significant at .05

2.5. Discussion

The aim of this study was to investigate simulated driving performance and subjective and objective sleepiness in patients with COPD compared to control participants. A further aim of this study was to assess neuropsychological functioning in these groups, by comparing memory (verbal and procedural) performance, visual-spatial ability, sustained attention, reaction time, and vigilance. In an effort to better understand the nature, extent, and causes of these impairments this study also aimed to explore polysomnography characteristics of the groups, including total sleep time, sleep efficiency, number of arousals per hour of sleep, apnoea-hypopnoea index, and percentage of total sleep time where oxygen levels were below 90% saturation, and their relationship to performance variables.

2.5.1. Demographic Characteristics

The diagnostic characteristics of the COPD patients indicated that, as a group, the mean forced expiratory volume on one second (FEV₁) was 50.36 when expressed as percent predicted. According to guidelines developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2009), this indicates moderate COPD. The COPD participants in the current study also had a PO₂ of 64.83 indicating mild hypoxaemia. As a group, the COPD patients were not experiencing acidosis, with a pH level of 7.44. They were also not noted to be hypercapnic (PCO₂ = 39). The value of transfer factor of the carbon monoxide (CO) transfer factor (TLCO) uptake was measured and found to be 45.64% of predicted normal. This indicates a moderate reduction in the diffusing capacity of

CO and demonstrates reduced integrity of the overall gas exchange functioning in the lungs.

It was hypothesised (Hypothesis 1) that there would be no significant difference in weight, BMI, and MAPI between the COPD patients and control participants. This hypothesis was supported, as there were no significant differences between the groups on these characteristics.

2.5.2. Polysomnography

As expected, the COPD patients demonstrated a significantly higher percentage of total sleep time where oxygen levels fell below 90% saturation. This indicates that the COPD patients experienced a significant degree of hypoxaemia compared to control participants and supports hypothesis 2. Consistent with previous research the COPD patients demonstrated nocturnal desaturation below 90% for 33.48% of the night. This meets criteria for significant nocturnal desaturation as defined by previous research (Chaouat et al., 1997). There was no significant difference between the COPD patients and control participants on other polysomnography variables, indicating no significant sleep disturbance or arousals over the night. Of note was that both groups showed low sleep efficiency (67.50 for COPD and 65.97 for control participants). Some authors describe an alteration of sleep structure (including sleep efficiency), termed 'first night effect', due to the unfamiliarity of a sleep laboratory (Vadim et al. 1998). This phenomenon may help to explain this result in the current study.

2.5.3. Subjective Sleepiness

Sleep disturbances are common in moderate to severe COPD and are usually related to severity of nocturnal hypoxaemia. Additionally, coughing, wheezing, and shortness of breath due to worse pulmonary mechanics and gas exchange that occurs over night can cause sleep disturbance (Klink, Dodge & Quan, 1994). Given that the COPD patients in this study were considered to be mildly hypoxaemic, it was expected that they would not have significant sleep disturbance and would not report excessive daytime sleepiness. This hypothesis (hypothesis 3) was supported as there was no significant difference between the COPD patients and control participants on any of the subjective sleep variables.

This finding is consistent with previous research, where in an adult community setting, Sanders et al. (2003) found that patients with mild COPD demonstrated only mildly affected sleep quality and architecture, and that they did not report excessive daytime sleepiness. Orr et al. (1990) also found similar results in their study. Clinically, none of their COPD participants complained of excessive daytime sleepiness. Although hypoxaemia has been shown to provoke an arousal response, this varies widely and patients may continue to sleep even though they have significantly impaired oxygen levels. This finding supports results of the present study that showed that although the COPD patients demonstrated significant oxygen desaturation when compared to control participants; their quality of sleep and subjective feelings of sleepiness were comparable.

COPD patients are a population of interest when studying the effects of hypoxaemia as a cause of excessive daytime sleepiness, in comparison to sleep deprivation. Indeed, studies have shown that treatment with oxygen during sleep in patients with COPD improves their sleep patterns (Calverley et al., 1982). In their study, Orr et al. (1990) concluded that there appeared to be no relationship between chronic daytime hypoxaemia and objective measures of daytime sleepiness. They suggested that severe hypoxaemia could exist without resulting in objective or subjective daytime sleepiness. However, their conclusions regarding subjective sleepiness were not based on formal assessment of daytime sleepiness using questionnaires, but rather on clinical interview.

In the present study, there was a significant moderate correlation between levels of subjective alertness, as measured by the KSS, and AHI for the COPD patients. This finding partially supports hypothesis 7. Specifically, the greater number of respiratory events experienced per hour of sleep was associated with decreased levels of alertness. Furthermore, there was a significant moderate correlation between PO_2 and levels of alertness as measured by the KSS. That is, decreased levels of oxygen were associated with decreased subjective alertness, providing partial support for hypothesis 8. These findings do not support those of Orr et al. (1990) and indicate that on a formal measure of subjective sleepiness, COPD patients do indeed demonstrate a relationship between hypoxaemia and subjective sleepiness.

The present study found no significant correlation between subjective sleepiness, as measured by the ESS, and nocturnal hypoxaemia and does not support hypothesis 7. In fact, the relationship noted in the current study was in the opposite direction expected. That is, a lesser percentage of time where oxygen

saturation was below 90 percent saturation over the night was associated with increased excessive daytime sleepiness as measured by scores on the ESS. Furthermore, increased levels of oxygen in the blood (PO_2) were associated with higher levels of subjective sleepiness on the ESS. This appears to be an anomaly in the data presented and cannot be adequately explained. However, the lack of appropriate significant correlation between hypoxaemia and ESS scores is consistent with previous research that suggests that apnoeas and hypopnoeas bear a closer relationship to ESS scores than measures of hypoxaemia (Johns, 1993). This finding does not provide support for hypothesis 8. There were no significant correlations demonstrated for control participants.

2.5.4. Psychomotor Vigilance Task

It has been documented that COPD patients demonstrate cognitive impairment related to poor attention and vigilance, and decreased reaction times (Orth et al., 2006; Prigatano et al., 1983). This study strongly supported the hypothesis that COPD patients would demonstrate significant impairment on a vigilance task as measured by the PVT (hypothesis 4). Although the PVT has been used in research on sleep and fatigue, it has not previously been used to investigate the effects of hypoxaemia on sustained attention and vigilance. The current study specifically demonstrated that the COPD patients had increased median reaction times, a significantly higher number of attentional lapses, and a higher mean reaction time taken from the slowest 10% of reaction times when compared to control participants. These results partially support those by Orth et al in their study of 32 patients with COPD. Although COPD patients and control participants

in their study demonstrated comparable divided attention and vigilance, the COPD patients showed significantly worse simple, selective, and sustained attention.

In patients with a high degree of oxygen desaturation, nocturnal hypoxaemia has been identified as a pathogenetic factor in contributing to attentional and vigilance impairment (Bedard et al., 1991). Stuss, et al. (1995) suggested that attentional deficits might be accounted for by diffuse damage secondary to hypoxia or as a result of specific damage to anterior frontal systems. However, no correlation existed in this study between nocturnal hypoxaemia, as measured by polysomnography, and attentional impairment. This does not support hypothesis 10 and suggests that there may be other factors that contribute to poor performance on the PVT in COPD patients that may interrelate to impair performance. Factors such as age, sex, mood, and environmental pollutants were not controlled for in the present study and may contribute to impaired performance.

Furthermore, sleep disruption is typically associated with vigilance impairment, and it is known that patients with COPD have decreased sleep quality and architecture. This is in the form of decreased sleep time and quality, delayed sleep onset, multiple awakenings, and a high number of arousals (GOLD, 2009). In the present study, it was found that for the COPD patients total sleep time was significantly correlated with all performance measures on the PVT. Increased total sleep time was associated with reduced reaction times, fewer lapses in attention, and reduced mean reaction time from the slowest 10 percent of reaction times. Also, sleep efficiency was significantly correlated with PVT measures, where increased sleep efficiency was associated with decreased median reaction times

and mean reaction time from the slowest 10 percent of reaction times. These findings provide support for hypothesis 9.

Pulmonary function has been shown to influence cognitive skills (Min et al., 2007). For example, decreased lung function is found to be associated with poorer cognitive function and increased subcortical atrophy (Sachdev et al., 2006). However, in the present study reduced FEV₁ and FEV₁% predicted were associated with better performance on the PVT. This finding is inconsistent with the presumed relationship between tests of lung function and neuropsychological performance and does not support hypothesis 10. Research suggests that impaired lung function results in changes in the central nervous system via a variety of processes including vascular disease, oxidative stress, and changes in neurotransmitter metabolism as a result of hypoxaemia (Richards, Strachan, Hardy, Kuh, & Wadsworth, 2005).

The findings of the present study support previous research that has suggested that slowed reaction time, lapses in performance and impaired attention can be impaired following sleep deprivation (Dinges et al., 1988; Johns, 1991). However, the findings provide inconsistent support for impaired central nervous system functioning as a result of impaired lung function. Nevertheless, this study provides excellent support for the use of the PVT in identifying attentional and vigilance impairment in COPD patients who demonstrate moderate hypoxaemia and further highlights the sensitivity of performance on the PVT to sleepiness, even in COPD patients. Future research is warranted to further explore the mechanisms that may explain the basis of this impairment in this patient group.

2.5.5. *Driving Performance*

The evidence already discussed that relates to compromised attention and vigilance, as well as functional consequences of COPD, raises significant concerns about driving ability. Unfortunately, there is a paucity of studies that have explored the relationship between COPD and driving performance. In the current study, it was expected that COPD patients would demonstrate impaired driving performance as measured by the AusEd driving simulator when compared to control participants (hypothesis 4). This hypothesis was partially supported, with COPD patients demonstrating significantly greater difficulty maintaining the vehicle in the centre of the left lane. There were no significant differences found for speed variability or number of crashes.

Results of the present study support those of previous research, although the results of previous studies are questionable due to significant methodological flaws. Such studies have tended to observe normal participants who are acutely subjected to hypoxic conditions so that the cognitive effects of hypoxaemia can be determined (Ramsey, 1970). This makes it difficult to generalise such results to individuals who are chronically hypoxaemic. The present study therefore provides valuable insight into the driving performance of individuals who experience recurrent nocturnal hypoxaemia as a result of COPD.

In the present study, there was a significant negative correlation for COPD patients between total sleep time and number of crashes, and between sleep efficiency and number of crashes, supporting hypothesis 9. These findings indicate that increased total sleep time and sleep efficiency were associated with fewer crashes on the driving simulator. This finding highlights that hypoxaemia may not be the sole cause of driving and vigilance impairment in patients with

COPD. This is consistent with research by Pretto and McDonald (2008) that identified no significant improvement in driving performance on the AusEd in a group of patient with significant daytime hypoxaemia tested with and without treatment with supplemental oxygen. This may also explain the lack of significant differences observed for number of crashes and speed variability between the COPD patients and control participants.

Correlations between measures of lung function and performance on the driving simulator demonstrated relationships that were in the opposite direction expected. That is, better lung function was associated with poorer performance on the driving simulator and does not support hypothesis 10. This indicates that hypoxaemia may play a less important role in impairing driving performance when compared to sleepiness, and it may be more important to consider sleep disruption and subjective sleepiness, rather than hypoxaemia when making decisions regarding the ability of COPD patients to drive safely and engage in high-risk activities.

As described earlier, Turkington et al. (2001) reported other factors that may influence performance on a driving simulator. Patient characteristics such as older age, alcohol consumption, and previous driving experience may all contribute to reduced vigilance and driving decrements. Furthermore, the COPD patients in the present study were classified as moderately hypoxaemic. Results from Grant et al. (1987) suggest that categorizing COPD patients in terms of disease severity is important in terms of determining the presence or absence of cognitive impairment. This may also be true for driving impairment; however the lack of studies explicitly examining the relationship between COPD and motor vehicle crashes prevents any firm conclusions from being made.

This study provides valuable preliminary insight into the possible driving impairment in patients with COPD. Further research is needed to examine the relationship between disease severity and driving performance, as well as specific neuropsychological functions and their relationship to driving impairment. It would be important to validate such measures against fitness to drive objectives.

2.5.6. Objective Sleepiness

This is the first study to examine levels of objective sleepiness in COPD patients by using the Optalert™ system. It was hypothesised that the COPD patients would not demonstrate increased sleepiness as measured by Optalert™ when compared to the control participants (hypothesis 5). This hypothesis was supported as there was no significant difference between the two groups on measures of objective sleepiness. This is not surprising, given that the COPD patients did not demonstrate altered sleep architecture on polysomnography compared to control participants. Furthermore, they did not report feelings of sleepiness or excessive daytime sleepiness as measured by subjective questionnaires.

As discussed earlier, hypoxaemia has been studied as a mechanism underlying excessive daytime sleepiness. The present study found no significant correlation between measures of objective sleepiness and hypoxaemia in the COPD patients. Again, this is consistent with research by Orr et al. (1990) who found no significant correlation between hypoxaemia and objective measures of sleepiness in their COPD patients. Interestingly, the current study found that the mean JDS score recorded during performance on the driving simulator was significantly related to total sleep time and sleep efficiency for the COPD patients.

This finding indicates that more total sleep time and sleep efficiency was related to reduced drowsiness and lends further support to the results of previous research that have linked excessive daytime sleepiness to sleep disruption rather than hypoxaemia (Colt, Haas, & Rich, 1991). Other significant correlations indicating that more arousals were related to lower objective levels of drowsiness could not be adequately explained by the data obtained.

2.5.7. Neuropsychological Performance

It is well documented in previous research that COPD patients experience impairments in a range of cognitive functions, including reaction time, memory, abstract reasoning, and visual motor skills (Grant et al., 1980; Incalzi et al., 1993, 2003; Prigatano et al., 1983). It was therefore hypothesised that the COPD patients in the present study would demonstrate impairments in neuropsychological functioning when compared to control participants (hypothesis 6). This hypothesis was supported, with COPD patients demonstrating impairments relating to attention, mental flexibility, and verbal memory.

2.5.7.1. Trail Making Test

As previously described, part A of the Trail Making test is thought to assess visual attention, sequencing, and visual-motor functioning. The COPD patients in this study took a significantly greater amount of time to complete this part of the test compared to control participants, indicating impairments in these cognitive domains. Performance on Trails A did not appear to be influenced by oxygen saturation and did not support hypothesis 11; however there was a significant relationship between number of errors on Trails A and scores on the

KSS, supporting hypothesis 12. This indicates that COPD patients who reported feeling less alert, made more errors on Trails A. Furthermore, the number of arousals per hour of sleep was also related to performance on Trails A, providing support for hypothesis 13. There were no significant correlations between performance on Trails A and measures of lung function, this result did not support hypothesis 11. These findings again lend support to the notion that sleep disruption has an effect on visual attention, and that Trails A is effective at demonstrating this impairment.

The COPD patients also demonstrated impairment on Trails B, taking a significantly longer time to complete the task when compared to control participants. This finding is consistent with previous research (Liesker et al., 2004; Shim et al., 2001) and highlights difficulty with cognitive flexibility, which is an important aspect of executive functioning. Deficits in executive function are often attributed to hypoxaemia, given that the frontal lobes are highly sensitive to oxygen deprivation (Borson et al., 2008). The prefrontal cortex (PFC) is innervated by the monoamines, dopamine (DA), noradrenaline (NA), and serotonin, as well as acetylcholine (Robbins & Roberts, 2007).

Cholinergic systems are particularly implicated in learning, working memory, and attention. Elevations in cholines are observed in systemic diseases that result in cognitive impairment (Friedman et al., 1998). Specifically, Borson et al. (2008) found that elevated brain choline is a direct result of frequent oxygen desaturation during day-to-day activity in patients with COPD. Grant et al, (1987) also found that neurotransmitter biosynthetic pathways are significantly affected in the brains of those with COPD. Borson and co-workers believed that increases in choline reflect membrane breakdown in the brain and damage to the myelin

sheath, and that this eventually manifests as white matter hyperintensities on structural imaging. Van Dijk et al. (2004) reported more severe periventricular white matter lesions in patients with COPD. They concluded that hypoxaemia, together with hypoperfusion, contributes to the aetiology of periventricular white matter lesions. White matter lesions are associated with cognitive impairment, particularly in the areas of attention and executive function (Boone et al., 1992). Although brain imaging was not conducted in the present study, it can be speculated that the impairment to attention and executive function observed in the COPD patients, may be related to white matter lesions as a result of chronic hypoxaemia.

In the present study, there was no relationship between performance on TMT B and measures of subjective sleepiness, and this does not support hypothesis 12. Furthermore, the relationship between nocturnal hypoxaemia and FEV variables and performance on TMT B was in the opposite direction expected. These findings do not support hypothesis 11 and suggest that other disease sequelae may be contributing to poor executive functioning and that changes to neural systems secondary to hypoxaemia may contribute to these impairments.

2.5.7.2. Austin Maze

There was no significant difference between COPD patients and control participants with regard to the number of errors made on the Austin Maze. As previously discussed, this task is a measure of visual-spatial ability and procedural and visual memory (Crowe et al., 1999). Although investigations of cognitive functioning in COPD patients include measures of memory, little is known about the impact of hypoxaemia in COPD on procedural memory. Given that these skills

are found to be important in being able to successfully complete the maze, and that patients with COPD present with impaired constructional and visuo-spatial skills (Incalzi et al., 2009) it was hypothesised that COPD patients would demonstrate poorer performance by having a higher number of errors when compared to control participants (hypothesis 6).

This hypothesis was not supported as the present study failed to find a significant difference between COPD patients and healthy control participants on performance on the Austin Maze. Furthermore, there were no significant associations between performance on the Austin Maze and measures of hypoxaemia, lung function, or sleepiness. Prior to this study, procedural learning had not been investigated in patients with COPD. The lack of significant findings may not necessarily reflect a true absence of impairment, but may be related to test choice. Given that the basal ganglia are vulnerable to hypoxaemia and that these brain structures are closely linked to the frontal lobes (Decary et al., 2000), it is possible that procedural learning may be impaired in these patients. Further research is warranted to investigate this particular memory function given its importance in the acquisition of new skills and execution of motor procedures.

2.5.7.3. Logical Memory and Visual Reproduction

When compared to the control group, COPD patients demonstrated impairment in the ability to remember verbal information both immediately (Logical Memory I) and following a delay (Logical Memory II). However, their ability to remember visual information immediately (Visual Reproduction I) and following a delay (Visual Reproduction II) was comparable to the control participants. This supports the hypothesis that COPD patients would demonstrate

poorer performance on neuropsychological tasks when compared to control participants (hypothesis 6).

Research has been variable when reporting on the effect of COPD on verbal memory. Grant et al. (1982) found that COPD patients performed best on tests of verbal memory when compared with other cognitive skills. However, other studies have demonstrated significant verbal memory impairments in COPD patients, which support the results of the present study (Incalzi et al., 1993; 1997; Stuss, et al., 1997). Incalzi and co-workers (1997) demonstrated that individuals with COPD showed verbal memory impairments for both immediate and delayed recall and that this likely reflects impaired metabolism in frontal and/or subcortical regions of the brain. Similarly, Shim et al. (2001) attributed cognitive impairment to altered cerebral metabolism in COPD patients. Stuss et al. suggested that atrophy in specific brain regions such as the hippocampus and other limbic regions may be the basis for memory dysfunction in this patient group.

It has been suggested that changes in cognitive function in patients with COPD may be secondary to chronic hypoxaemia and hypercapnia (Heaton et al., 1983; Ortapamuk & Naldoken, 2006). In their study, Grant et al. (1982) found that 77% of their sample of hypoxaemic COPD patients had neuropsychological impairment. Although a direct cause for this impairment was not identified, significant correlations between neuropsychological impairment and hypoxaemia suggested a relationship between the two.

However, other studies have shown that COPD patients who are non-hypoxaemic also demonstrate impaired performance on cognitive tasks (Liesker et al., 2004). Orapamuk and Naldoken (2006) compared non-hypoxaemic COPD patients to hypoxaemic COPD patients and found that verbal memory was

impaired in both groups. However, delayed recall scores were significantly worse in the hypoxaemic group, and these patients also demonstrated significantly altered cerebral perfusion in frontal and parietal areas. Furthermore, although oxygen therapy has been shown to have protective effects against cognitive decline (Heaton et al., 1983), even patients who receive oxygen treatment demonstrate impairments in verbal memory (Incalzi et al., 1983).

The present study supports the notion that there may be other factors other than hypoxaemia that impact on memory performance. This is because there was no significant relationship between nocturnal hypoxaemia or lung function tests and memory performance. This does not support hypothesis 11 and as previous research suggests, much of the variance in cognitive changes in patients with COPD remains unexplained (Borson et al., 2008). Low mood, systemic inflammation, and brain structural and neurochemical abnormalities are all factors that require research to determine their impact on producing cognitive impairment in COPD patients. For example, depressive symptoms have been found to be as high as 74% in people with COPD (Gift & McCrone, 1993), therefore the impact of low mood on cognition cannot be excluded.

Performance on the verbal memory task did not appear to be significantly related to measures of sleep disruption and does not support hypothesis 13. However, this was not the case for the visual memory task. Specifically, increased total sleep time and sleep efficiency was associated with better performance on both immediate and delayed visual memory as measured by the visual reproduction subtest.

This study highlights that impairments of cognitive performance in patients with COPD cannot be predicted on the basis of hypoxaemia, and that

sleep disruption can have a significant effect on visual memory performance. Therefore neuropsychological testing is recommended, especially to assist with quantifying impairment to day-to-day functioning and driving performance. Furthermore, COPD is associated with comorbid conditions, such as cardiovascular disease, stroke, hypertension and psychiatric disturbance. These factors require further investigation in to how they may contribute to altered cognitive performance.

2.6. Conclusion

Chronic obstructive pulmonary disease is a disorder characterised by an obstruction of airflow in the lungs, producing oxygen desaturation, cell hypoxia, and hypercarbia. This study was designed to investigate the effects of this disorder on subjective and objective sleepiness, simulated driving performance, vigilance and neuropsychological functioning.

The main findings of this study were that COPD patients demonstrated poor attention and vigilance, and decreased reaction times on the PVT, as well as significantly greater difficulty maintaining the vehicle in the centre of the left lane on the driving simulation task, when compared to control participants. There were no significant differences noted between COPD patients and control participants on measures of subjective or objective sleepiness. On tasks of neuropsychological functioning, COPD patients demonstrated impaired attention, mental flexibility, and verbal memory when compared to control participants.

Subjective sleepiness was found to be related to visual attention, and increased total sleep time and sleep efficiency were associated with better performance on the PVT and driving simulator. The deficits in performance on

neuropsychological tasks are often attributed to chronic hypoxaemia. However, in the present study there were no firm conclusions drawn about the contribution of hypoxaemia in producing neuropsychological impairments in COPD patients. These findings support previous research indicating much of the variance in cognitive changes in COPD patients remains unexplained. This highlights the importance in considering other factors such as mood, motivation, systemic inflammation, and cerebral structural and chemical abnormalities in contributing to impaired functioning. A further consideration needs to be made regarding the reversal of cognitive deficits with LTOT. Given the paucity of research assessing the cognitive effects of short term administration of oxygen therapy, this should be a focus of future research. This will also help to advise whether portable oxygen should be used by patients while driving and performing other high risk activities.

Chapter 3

3.1. Obstructive Sleep Apnoea vs. Chronic Obstructive Pulmonary Disease

The results of the studies described in Chapters 1 and 2 provide support for the finding that obstructive sleep apnoea and chronic obstructive pulmonary disease are both medical conditions that present with neuropsychological impairment, and poor performances on tests of vigilance and simulated driving. Whereas the impairment in COPD patients has been traditionally attributed to hypoxaemia, the evidence for OSA patients indicates that sleep disruption, as well as intermittent hypoxia can be contributing factors in impaired performance.

In an attempt to further investigate these relationships and determine the nature of cognitive deficits in these groups. Roehrs et al. (1995) evaluated 25 OSA patients and 24 COPD patients on polysomnography, sleepiness, and neuropsychological measures. They found that, overall the neuropsychological impairments in the OSA and COPD patients were non-specific to hypoxemia or sleepiness. However, the OSA patients performed worse on a task of sustained attention, whereas the COPD patients performed more poorly on a test of motor skill. Significant limitations of the Roehrs et al. Study were that the COPD patients were treated with LTOT at the time of testing, therefore any impairments in cognitive may have been underestimated. Furthermore, the study did not include any comparisons with a control group; therefore comparisons with a healthy population could not be made.

The current study was the first to examine cognitive functioning in *untreated* OSA and COPD patients, after having compared these groups to healthy control participants. The results observed in Chapter 1 of the current study further

highlight the difficulty in forming clear conclusions regarding the basis of poor performance in OSA patients. Furthermore, Chapter 2 highlighted that although COPD patients presented with hypoxaemia, there were no firm associations made between hypoxaemia and performance.

EXPERIMENT 3

In an effort to better understand the nature, extent, and source of the impairments noted in OSA and COPD patients, this study aimed to compare simulated driving performance and subjective and objective sleepiness in patients with OSA compared to patients with COPD. A further aim of this study was to assess neuropsychological functioning in these groups, by comparing memory performance, sustained attention, reaction time, and vigilance. In an effort to better understand the source of these impairments this study also aimed to compare polysomnography characteristics of the groups.

Hypotheses

1. Patients with OSA would weigh more and have a higher BMI and MAPI when compared to COPD patients.
2. OSA patients would demonstrate decreased total sleep time and sleep efficiency, and increased arousals per hour of sleep and AHI compared to COPD patients.
3. Patients with COPD would experience a greater percent of total sleep time where oxygen saturation was below 90% compared to patients with OSA.
4. Patients with OSA would report higher levels of subjective sleepiness in comparison to COPD patients.
5. There would be no significant difference between the OSA and COPD patients on tests of simulated driving performance, sustained attention, vigilance, and reaction time.

6. Patients with OSA would demonstrate increased objective sleepiness in comparison to COPD patients.
7. There would be no significant difference between the OSA and COPD patients on tests of neuropsychological function.

3.1. Method

3.1.1. Participants

The sample of OSA and COPD patients described in Chapters 1 (section 1.2.1.) and 2 (section 2.2.1.) formed the participants used in the present study.

3.1.2. Materials

The materials described in Chapter 1 (section 1.2.2) were also used in the present study. Please refer to this section for full details.

3.1.3. Procedure

The procedure described in Chapter 1 (section 1.2.3.) was also employed in the current study.

3.1.4. Statistics

Statistical procedures used in the present study were the same as those used in Chapter 1. Please refer to section 1.2.4. for full details. However, given that the COPD patients were significantly older than the OSA patients, Multivariate Analysis of Covariance was used to investigate the differences between the groups on neuropsychological tasks and on the PVT and driving simulator. This was to control for the effects of age on performance of these tasks.

3.2. Results

3.2.1. Demographics

Means and standard deviations for the demographic variables for OSA and COPD participants are shown in Table 28. One-way ANOVA demonstrated that the COPD participants were significantly older than the OSA patients. OSA participants also had a significantly higher BMI and scored significantly higher on the MAPI when compared to the COPD patients.

Table 28

Means and Standard Deviations for Demographic variables for OSA and COPD patients.

	OSA Patients (n=14)		COPD Patients (n=14)		df	F	p	r
	M	SD	M	SD				
Age	54.64	10.95	67.07	11.65	1,27	8.47	.01	.50
Height (cm)	170.36	9.04	172.86	9.75	1,27	.50	.49	.14
Weight (kg)	91.71	16.69	78.64	19.30	1,27	3.68	.07	.35
BMI	32.04	8.09	26.04	4.93	1,27	5.62	.03	.42
MAPI	.69	.16	.41	.27	1,20.96	10.98	.00	.54

Note. MAPI = Multivariable Apnoea Prediction Index, BMI = Body Mass Index

3.2.2. Sleepiness Measures

Table 29 presents the mean and standard deviation of the sleepiness measures and the results of one-way ANOVA and Kolmogorov –Smirnov tests for each measure. The results demonstrated that the OSA participants scored significantly higher on the KSS in comparison to the COPD patients, and that results approached significance for the ESS and stop-driving questionnaire (long distance).

Table 29

Means and Standard Deviations for Subjective Sleepiness Variables for OSA and COPD patients

	OSA Patients (n=14)		COPD Patients (n=13)		df	F	D	p	r
	M	SD	M	SD					
ESS*	11.86	5.78	7.29	5.82	1,27	4.35	-	.05	.38
KSS*	6.14	1.46	4.36	1.60	-	-	1.51	.01	.29
Stop Driving Questionnaire (Suburban)	1.36	0.63	1.15	0.38	-	-	.34	.65	.07
Stop Driving Questionnaire (continuous long distance)	2.21	0.98	1.46	.66	-	-	1.04	.05	.20
AQ	20.43	6.46	19.92	5.71			.53	.77	.10

Note. ESS = Epworth Sleepiness Scale; KSS = Karolinska Sleepiness Scale; AQ = Alertness Questionnaire

* = COPD patients n = 14

3.2.3. Neuropsychological Tasks

A one-way between groups multivariate analysis of covariance (MANCOVA) was performed to investigate differences in neuropsychological performance between the OSA and COPD participants, whilst controlling for the effect of age. Table 30 demonstrates that there was no significant difference between the groups on any of the neuropsychological tasks $F(13,10) = .10, p = .513$; Pillai's Trace = .564, partial eta squared = .564.

Table 30

Means and Standard Deviations for Neuropsychological Variables for OSA and COPD patients

	OSA Patients		COPD Patients		df	F	p	r
	(n=14)		(n=14)					
	M	SD	M	SD				
TMT A (time)	31.79	8.15	34.55	8.66	1,28	.70	.41	.03
TMT A (errors)	.14	.53	.27	.47	1,28	.05	.82	.00
TMT B (time)	85.71	32.93	93.18	21.83	1,28	.03	.86	.00
TMT B (errors)	.50	.76	.27	.50	1,28	.73	.40	.03
Austin Maze*	87.86	43.61	80.82	12.96	1,28	1.52	.23	.07
LM I	30.14	8.76	33.82	7.29	1,28	.47	.50	.02
LM II	17.00	6.25	19.55	5.67	1,28	.20	.66	.01
VR I	89.07	8.60	77.55	10.83	1,28	2.13	.16	.09
VR II	69.57	15.79	54.00	22.27	1,28	.79	.39	.04

Note. TMT = Trail Making Test, LM = Logical Memory, VR = Visual Reproduction

* = COPD patients = 11

3.2.4. Performance Measures

Table 31 displays results of a one-way between groups MANCOVA comparing OSA and COPD participant's performance on the PVT and driving simulator, whilst controlling for the effect of age. Results demonstrated that there was no significant difference between the groups on any of the performance measures $F(3,21) = .30, p = .824$; Pillai's Trace = .041, partial eta squared = .041.

Table 31

Means and Standard Deviations for PVT and AusEd driving simulator performance for OSA and COPD patients

	OSA Patients		COPD Patients		df	F	p	r
	M	SD	M	SD				
PVT Median*	231.86	26.53	240.92	20.41	1,26	.79	.38	.56
PVT transformed lapses*	4.21	2.63	6.03	1.79	1,26	.47	.50	.72
PVT slowest 10%*	2.61	.45	2.36	.55	1,26	.19	.67	.47
Median Position Average**	80.96	20.07	100.36	27.03	1,23	1.11	.31	.58
Speed 60-80kms average**	8.94	3.67	18.44	15.40	1,6.16	2.46	.14	.37
Number of crashes**	1.00	1.63	3.71	2.81	1,23	3.45	.08	.28

Note. PVT = Psychomotor Vigilance Task

* = OSA patients n = 14, COPD patients n = 12

** = OSA patients n = 13, COPD patients n = 7

3.2.5. Optalert™ Fatigue Monitoring Technology

Table 32 demonstrates that there was a significant difference between the OSA and COPD participants on JDS scores during performance on the driving simulator, where the COPD patients had a higher mean JDS score and percentage of time that the eyes were closed while performing the driving simulator. There were no other significant differences observed on objective sleepiness as measured by the Optalert™ technology.

Table 32

Means and Standard Deviations for the Optalert™ Fatigue Monitoring System for OSA and COPD patients

	OSA Patients		COPD Patients		<i>D</i>	<i>p</i>	<i>r</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
JDS % time eyes closed (PVT)*	.15	.21	.45	.85	.46	.94	.20
JDS % long eye closure (PVT)*	.02	.03	.22	.50	.44	.79	.09
JDS mean (PVT)*	.86	1.20	2.07	2.21	1.25	.06	.26
JDS % time eyes closed (driving)**	.05	.08	.58	.93	1.34	.04	0.28
JDS % long eye closure (driving)**	.01	.02	.07	.12	.65	.47	.14
JDS mean (driving)**	.48	.71	1.23	1.01	1.38	.02	.29

Note. JDS = John's Drowsiness Scale, PVT – Psychomotor Vigilance Task

* = OSA patients n = 13, COPD patients n = 11

** = OSA patients n = 12, COPD patients n = 11

3.2.6. Polysomnography

Table 33 indicates that the OSA participants had a significantly higher AHI and number of arousals compared to COPD participants. COPD patients demonstrated a significantly higher percentage of total sleep time where oxygen saturation was below ninety percent.

Table 33

Means and Standard Deviations for polysomnography variables for OSA and COPD patients

	OSA Patients (n=14)		COPD Patients (n=9)		df	F	D	p	r
	M	SD	M	SD					
Total Sleep Time (min)	286.39	108.85	265.39	73.35	1,19	.258	-	.62	.01
Sleep Efficiency (%)	76.58	11.03	67.50	18.65	1,19	2.17	-	.16	.09
Arousals (/hr)*	32.86	15.52	20.12	13.53	-	-	1.30	.04	.25
AHI (/hr)	45.78	23.54	16.71	16.43	1,19	10.36	-	.01	.33
% total sleep time <90% saturation*	10.29	22.95	33.48	39.66	-	-	1.33	.04	.26

Note. AHI = Apnoea-Hypopnoea Index

* = COPD patients n = 12

3.3. Discussion

The aim of this study was to compare simulated driving performance and subjective and objective sleepiness in patients with obstructive sleep apnoea with patients with COPD. A further aim of this study was to assess neuroneuropsychological functioning in these groups, by comparing memory performance, sustained attention, reaction time, and vigilance. In an effort to better understand the nature, extent, and source of these impairments this study also aimed to explore polysomnography characteristics of the groups, including total sleep time, sleep efficiency, number of arousals per hour, apnoea-hypopnoea index, and percentage of total sleep time where oxygen levels were below 90% saturation, and their relationship to performance variables.

3.3.1. Demographics

The results demonstrated that COPD patients were significantly older (mean age 67 years) than OSA patients (mean age 54 years). As hypothesised (hypothesis 1), the OSA patients had a significantly higher body mass index and multivariable apnoea prediction index when compared to the COPD patients. Whereas obesity is a risk factor for OSA, loss of body weight is common in COPD and is multifactorial in origin (Ting et al., 2009). Factors include elevated resting metabolic rate, systemic inflammation, and skeletal muscle wasting due to the use of corticosteroids (Agusti et al., 2003). A clear relationship between BMI and mortality is also shown in COPD patients (Ting et al.).

3.3.2. Polysomnography

As expected the OSA patients demonstrated a significantly higher AHI and number of arousals when compared to the COPD patients. This indicated that the OSA patients experienced a significantly higher number of apnoeas and hypopnoeas per hour of sleep and partially supports hypothesis 2. This is not unexpected as although sleep studies in COPD have shown poor sleep quality in terms of frequent arousals and decreased total sleep time, COPD patients do not tend to experience apnoeas and hypopnoeas to the same extent as OSA patients (Calvery, et al., 1982; Klink, Dodge, & Quan, 1994). There was no significant difference shown between the groups with regard to total sleep time and sleep efficiency.

It was expected that the COPD patients would demonstrate a significantly higher percentage of total sleep time where oxygen was less than 90% saturation. This hypothesis (hypothesis 3) was supported. Results indicated that the COPD

participants demonstrated 33.48% of total sleep time where their oxygen saturation fell below 90%. This was statistically significant when compared to the OSA participants, who demonstrated 10.29% of total sleep time where oxygen fell below 90%. This finding is expected since the nocturnal hypoxaemia in COPD patients is chronic, whereas the occurrence of hypoxaemia during sleep for OSA patients is intermittent.

3.3.3. Subjective Sleepiness

As expected, the OSA patients did report a significantly higher level of subjective sleepiness in comparison to the COPD patients (hypothesis 4). This is supported by previous research that shows that although patients at the more severe end of the COPD spectrum experience chronic hypoxaemia, clinically, they do not tend to demonstrate the degree of daytime sleepiness shown by patients with OSA (Orr et al., 1990). There was a significant difference between the groups on the KSS, indicating that the OSA patients reported feeling less alert at the time of testing. While not significantly different, trends indicated that OSA patients were also more likely to experience excessive daytime sleepiness as measured by the ESS, and to also report that they would discontinue driving long distances when compared to the COPD group. Although no significant difference was demonstrated on the ESS, the mean score for COPD patients was 7.29. As defined by Johns (1993), this score fell within the 'normal' range on this test, indicating minimal excessive daytime sleepiness. In contrast, the OSA patients scored 11.86 and demonstrated a higher level of daytime sleepiness. There was no significant difference noted between the groups on the AQ and self-reported ability to continue driving in suburbia.

This study supports the notion that COPD patients do report a degree of daytime sleepiness, however it does not appear to be as significant as that reported by OSA patients. Nevertheless, it is important to recognise that daytime sleepiness and reduced alertness are reported by COPD patients and that the impact on their ability to drive safely and perform high-risk activities needs to be adequately investigated.

3.3.4. Psychomotor Vigilance Task

There was no significant difference between the OSA patients and COPD patients on any of the PVT performance measures, providing support for hypothesis 5. This was expected, as although the impact of sleep deprivation on PVT performance is well established; hypoxaemia has been found to be a factor in contributing to attentional and vigilance impairment in both COPD and OSA patients. It was therefore hypothesised that the OSA and COPD patients would demonstrate comparable performance on the PVT and this was supported by the current results. It was demonstrated that compared to control participants, the OSA and COPD patients were both impaired on the PVT in relation to the number of attentional lapses and slowest 10 percent of reaction times experienced. Furthermore, COPD patients demonstrated significantly slower reaction times when compared to control participants.

Interestingly, in the present study PVT performance was correlated with nocturnal hypoxaemia for the OSA patients, but was correlated with sleep disruption for the COPD patients. This is consistent with previous research that has found impaired performance on the PVT following nocturnal sleep disruption, as well as a result of hypoxaemia (Bedard et al., 1991; Dinges et al., 1997). Sforza

et al. (2004) concluded that nocturnal hypoxaemia, sleep fragmentation, apnoea-hypopnoea index and subjective sleepiness can all influence performance on the PVT. The current results support this conclusion and further highlight that sleepiness or hypoxaemia alone are not the sole cause of attentional impairment in OSA and COPD patients.

3.3.5. Driving Performance

It was hypothesised that the OSA and COPD patients would be equally impaired on the driving simulator (hypothesis 5) and this hypothesis was supported. Although not significant, the COPD patients demonstrated more lane and speed variability compared to the OSA patients, as well as a higher number of crashes. Given the consistent research that demonstrates neuropsychological impairment in COPD patients, it is not unreasonable to suspect that their driving performance may also be negatively affected. However, there is a lack of research investigating this, and the present study is the first study to demonstrate impaired driving performance in patients with COPD. Furthermore, it is the first study to demonstrate that COPD patients may be more impaired than OSA patients in particular aspects of driving ability.

Particular results in the present study indicate that levels of alertness and sleep disruption were linked to driving performance. There was no relationship between hypoxaemia and driving performance, suggesting that there are other factors that may impact on this ability for both patient groups. Consequently, it is suggested that presently, decisions regarding fitness-to-drive should be made on an individual basis and that cognitive and/or on road driving assessments should be used to determine driving competence.

3.3.6. Objective Sleepiness

While there were no significant differences between the OSA and COPD patients on the Optalert™ performance measures while completing the PVT, results demonstrated significant differences between the groups while measuring objective sleepiness during the driving simulator. Specifically, COPD patients demonstrated a higher percentage of time where the eyes were closed while performing on the driving simulator, and also had a higher mean JDS (1.23) when compared to the OSA patients (0.48). Given that COPD patients do not typically demonstrate the level of sleepiness experienced by OSA patients, this finding is the opposite of that expected (hypothesis 6).

According to work by Johns et al. (2005), JDS scores between 0-4 are considered within the normal range for alert drivers, and drivers were noted to drive without incident when scores were within this range. This indicates that although the COPD patients in the current study had a significantly higher JDS when compared to the OSA patients, they were still considered to be within the normal range and safe to drive.

Nevertheless, the findings of the current study once again highlight the importance of considering sleepiness in COPD patients. Traditionally, these patients are thought to not experience the same degree of sleepiness as OSA patients; however the present study provides evidence to suggest that sleepiness is a significant problem for COPD patients. Furthermore, this study has shown that sleep measures are related to task performance.

3.3.7. Neuropsychological Performance

There was no significant difference noted on tasks of attention, executive functioning, procedural memory, verbal memory, and visual memory between the OSA and COPD patients. This supports the hypothesis that there would be no significant difference between neuropsychological functioning in OSA and COPD patients (hypothesis 7). Previous research has found that both OSA and COPD patients demonstrated impairments in a range of neuropsychological tasks, including attention, memory, abstract reasoning, perceptual motor skills, and executive functioning (Bedard et al., 1991; Decary et al., 2000; Findley et al., 1986; Grant et al., 1980; Incalzi et al., 1993, 2003; Naegele et al., 1998; Prigatano et al., 1983). Previous research has recognised that some neuropsychological tasks are sensitive to hypoxaemia, and others more sensitive to sleep deprivation (Grant et al. 1980; 1987).

Roehrs et al. (1995) compared OSA and COPD patients and found that impairments in memory were not specific to diagnosis. The present study supports this finding, as the OSA and COPD patients were equally impaired on measures of verbal memory in comparison to control participants.

Roehrs et al. (1995) also found that sustained attention was worse in the OSA group, reflecting its sensitivity to sleepiness. The present study did not support these results, as there was no significant difference between the OSA and COPD patients' performance on the PVT. Roehrs et al. also demonstrated that COPD patients performed worse than OSA patients on a task assessing motor skills, and concluded that this reflected sensitivity to hypoxaemia. The results of this study partially support this finding, as the COPD patients had significantly more difficulty maintaining the vehicle in the middle of the left lane on the driving

simulator. This may indicate some difficulty with motor skills, and would support the results of previous research (Roehrs et al.).

CHAPTER 4

4.1. General Discussion

Obstructive sleep apnoea and chronic obstructive pulmonary disease are both medical conditions associated with impaired sensory, motor and cognitive impairment. This in turn can have a significant impact on high risk activities, such as driving. However, there is a need to measure impaired performance on an individual basis, rather than rely on estimates of risk. The present study aimed to make unique contributions to the literature via three separate studies using neuropsychological testing, a reaction time task, simulated driving performance, and measures of sleepiness and hypoxaemia. In the first study, OSA patient were compared to healthy control participants, as were COPD patients in the second study. The third study aimed to compare OSA and COPD patients in an effort to better understand the source of impaired performance.

Previous studies have produced inconsistent results in determining the contribution that sleepiness and hypoxaemia make in reference to the deficits seen in OSA patients (Bedard et al., 1991; Beebe & Gozal, 2002; Decary et al., 2000). Experiment 1 demonstrated that measures of sleepiness were related to visual attention, immediate visual memory, procedural memory and cognitive flexibility. Hypoxaemia appeared to be related to immediate and delayed visual memory, and median reaction times. Discussion of these results highlighted that inconsistencies in the literature may be related to recruitment of neural resources that may compensate for various deficits. This study emphasised the importance of

detecting impairments so that physicians can alert patients to the potential dangers of driving while sleepy, as well as the possible cognitive deficits that may impact on social, occupational, and personal functioning. The current study also highlighted the use of cognitive testing and measures of subjective sleepiness to possibly identify those patients with OSA who may be more at risk of accidental injury due to poor attention, memory, or increased sleepiness.

Experiment 2 was unique in contributing to the literature in relation to cognitive, reaction time and driving impairments in patients with COPD. There is a paucity of research examining driving performance in these patients, and this is concerning given the complex medical and functional consequences of the condition. A significant finding of the current study was that although the psychomotor vigilance task (PVT) had been used in research on sleep and fatigue, it had not been used to investigate the impact of hypoxaemia on sustained attention and vigilance. COPD patients in the current study demonstrated significantly impaired performance on all measures of this task.

Furthermore, COPD patients had significant difficulty maintaining the vehicle in the appropriate lane while completing the driving simulation task. The present study did not form any firm conclusions regarding the impact of hypoxaemia on cognitive, vigilance, or driving performance tasks. This supported the notion that other factors may be interrelated that contributes to poor performance in COPD patients.

This was further investigated in Experiment 3, where performance in OSA patients was compared to patients with COPD. While this study indicated no significant difference between the groups in performance of cognitive tasks or performance on the driving simulator, trends indicated that COPD patients

demonstrated more lane and speed variability, as well as a higher number of crashes. Given the lack of formal investigation into the impact of hypoxaemia on driving performance, the results of the current study are important in raising awareness of this impairment. A major finding of Experiment 3 was that although COPD patients did not subjectively report the same level of sleepiness as OSA patients, more objective measures indicated a greater level of sleepiness while performing the driving simulation task. The fact that COPD patients may not be aware of their level of sleepiness has significant implications for the prevention of road traffic accidents.

Despite the conflicting results in the literature regarding impairments in driving performance and accident risk, neuropsychological performance, and objective sleepiness, studies do consistently show that deficits are present in various areas of functioning in patients with OSA and COPD and highlight the importance of detecting these impairments. The finding of equally impaired neuropsychological performance in OSA and COPD patients indicates that cognitive impairment should be considered as a primary component of the syndrome characteristic of each disease.

Cognitive impairment is important in contributing to personal independence in activities of daily living, including such tasks as managing money and self-administering medication. Poor compliance with treatment and medication may be partially attributable to cognitive impairment (Hung, et al., 2009; Incalzi et al., 2006). Indeed, executive dysfunction in particular has proved to be a determinant of personal independence, ability to give information consent, and functional autonomy in various populations. This indicates the importance of detecting such impairments so that rehabilitation goals and strategies can be

determined to increase quality of life and guide lifestyle decisions. Furthermore, identifying such impairments is necessary so that physicians can alert patients to the potential dangers of driving and engaging in high risk activities.

4.1.1. Limitations

This study may be criticised for its small sample size. It is difficult to assess how representative the sample is of OSA and COPD clinical patients. Furthermore, the small sample size of each of the groups in the current study limited the depth of statistical analysis that could be performed. In addition to assessing the relationship between variables, it would be beneficial to perform predictive analyses to determine the relative contribution of sleepiness and hypoxaemia in producing performance decrements.

Although cognitive changes in COPD were noted in the current study, much of the variance contributing to this remained unexplained. The literature is consistent in reporting emotional and psychological disturbances as significant sequelae of both OSA and COPD. Mood state, psychopathology, and depressive symptoms were not measured in the current study. It is difficult to know how these factors may have contributed to the poor performances observed. Furthermore, it would have been useful for this study to incorporate structural and functional neuroimaging to investigate brain integrity in patients with COPD.

4.1.2. Recommendations for Future Research

It will be necessary for future research to continue to improve the inconsistencies in reporting of specific neuropsychological task deficits. Brain imaging and the use of sound neuropsychological frameworks are necessary to

guide selection of neuropsychological test choice and interpretation. Furthermore, isolating the effects of general slowed processing speed and poor attention on other cognitive domains needs to be further investigated. It will be useful to assess how performance on neuropsychological tasks predicts driving performance in OSA and COPD patients, and how this relates to on-road driving.

Neuropsychological testing can then assist in guiding physicians in advising those patients who may need restrictions placed on driving and other high-risk activities.

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Appendix A: Recruitment Notice



Interested in having your memory, concentration and driving ability checked?

Austin Health is looking for healthy volunteers to participate in a project that will assess your concentration and memory, how well you drive and how well you sleep.

If you are interested in being involved in this exciting new project, please contact:

Daniela De Fazio or Dr Mark Howard on 9496 3871

Email: daniela.defazio@research.vu.edu.au

Appendix B: Epworth Sleepiness Scale

EPWORTH SLEEPINESS SCALE

The following questions refer to sleepiness or the tendency to doze off when relaxed.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you.

Choose the most appropriate box for each situation by putting an X in one box for each question.

<u>Situation</u>	Would never doze	Slight chance of dozing	Moderate chance of dozing	High chance of dozing
1. Sitting and reading	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Watching TV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Sitting, inactive in a public place (eg. theatre or a meeting)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. As a passenger in a car for an hour without a break	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Lying down to rest in the afternoon when circumstances permit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Sitting and talking to someone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Sitting quietly after a lunch without alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. In a car, while stopped for a few minutes in traffic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix C: Participant Information and Consent Form



An Exploratory Study of Neuropsychological Impairment, Driving Performance, and Sleepiness in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary Disease.

Principal Researcher: Dr Gerard Kennedy

Associate Researchers: Daniela DeFazio, Dr. Mark Howard, A/Prof Christine McDonald, Dr. Maree Barnes, Jeff Pretto

You are invited to take part in a research study looking at the way people with sleep apnoea or lung disease function during the evening. This Participant Information Form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from this project. You will not be paid for your participation in this project.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. You may withdraw from the project at any time without prejudice to your relationship with and treatment by this hospital.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of this Hospital.

PURPOSE OF THE STUDY

This project is designed to investigate the nature and extent of reduced learning, memory and concentration in patients with Obstructive Sleep Apnoea and patients with Chronic Obstructive Pulmonary Disease in comparison to people without these conditions. In this study a number of measures will be used to assess these functions, as well as performance on a computer-based driving task.

WHAT WILL THIS PROJECT INVOLVE?

Your participation in the study will involve a session at the Austin Hospital.

On the day of the session, you will be asked to wake yourself up at 7.00 am, and will be requested not to consume any caffeine or stimulant medication until the completion of the study in the evening. You will be asked to arrive after dinner at approximately 5.30pm and the session will finish at around 10.30pm. During this session your performance on a computer driving simulation task, and a reaction time task will be assessed. Following this, you will complete a series of questionnaires designed to assess sleepiness, as well as your driving and sleeping history. A series of tasks assessing learning, memory, and performance will then be administered. A supper break will be included in this evening.

ARE THERE LIKELY TO BE ANY SIDE-EFFECTS OR RISKS?

No significant physical or psychological risks are anticipated in the proposed study. The main inconvenience will be the time commitment involved.

BENEFITS

Your participation will help in improving our understanding of neuropsychological impairment in patients and will assist in advising them when it may be appropriate or inappropriate to drive a motor vehicle.

COSTS

There is no cost for being in this study.

WHAT WILL HAPPEN TO MY RESULTS?

At the end of the study you will receive a copy of your results and these will be explained to you by one of the researchers. At your request, we can also send copies to your local doctor and to other doctors you see. The results of the study will be published, but your identity will not be revealed, nor will your results be shared with anyone else for any other purpose. Members of the hospital Ethics Committee may ask to look at your results, but no other people will be authorised to access them. The records dealing with this study will be kept in safe storage for 7 years, then shredded.

CONFIDENTIALITY

Your confidentiality will be respected at all times. You are free to decline or withdraw from participation in this study at any time and this will not affect your present or future relationship with this hospital or doctor. If at any time you or your doctor feels it is in your best interest to discontinue, you will be withdrawn from the study. At all stages of the study, you will be encouraged to ask questions.

CONTACTS AND SUPPORT

For the duration of the study you will be under the supervision of Daniela De Fazio, Dr Mark Howard and Dr Gerard Kennedy. If you have any questions concerning the nature of the research or your rights as a participant, please contact:

Daniela De Fazio 0412 902 927 (Day and Evening)

Dr Mark Howard 9496 3688 After Hours: 9496 5000

Dr Gerard Kennedy 9365 2481 After Hours: 0418 312 160

If you wish to contact someone, independent of the study, about any complaints, ethical issues or your rights, you may contact Mr Andrew Crowden, Chairperson of the Austin Health Human Research Ethics Committee, phone 9496 2901.

An Exploratory Study of Neuropsychological Impairment, Driving Performance, and Sleepiness in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary Disease.

I,have been invited to participate in the above study which is being conducted under the direction of Daniela De Fazio and Dr. Gerard Kennedy. I understand that while the study will be under their supervision, other relevant and appropriate persons may assist or act on their behalf.

My consent is based on the understanding that the study involves attending a session at the Austin Hospital: During the session my performance on a driving simulation task, and a reaction time task will be assessed. Following this, I will complete a series of questionnaires designed to assess sleepiness. A series of tasks assessing learning, memory, and performance will then be administered. This will take approximately 5 hours.

- ◆ This is not a drug trial.
- ◆ The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

The main inconvenience is the time commitment involved.

- ◆ I have received and read the attached 'Participant Information Sheet' and understand the general purposes, methods and demands of the study. All of my questions have been answered to my satisfaction.
- ◆ I understand that the project may not be of direct benefit to me.
- ◆ I can withdraw or be withdrawn by the Principal Investigator from this study/project at any time, without prejudicing my further management.
- ◆ I consent to the publishing of results from this study provided my identity is not revealed.
- ◆ I hereby voluntarily consent and offer to take part in this study.

Signature (Participant) _____ Date: _____ Time: _____

Witness to signature _____ Date: _____ Time: _____

Signature (Investigator) _____ Date: _____ Time: _____



**PARTICIPANT INFORMATION AND
CONSENT FORM – Controls and COPD**

**An Exploratory Study of Neuropsychological Impairment, Driving
Performance, and Sleepiness in Obstructive Sleep Apnoea and
Chronic Obstructive Pulmonary Disease.**

Principal Researcher: Dr Gerard Kennedy

Associate Researchers: Daniela DeFazio, Dr. Mark Howard, A/Prof
Christine McDonald, Dr. Maree Barnes, Jeff
Pretto

You are invited to take part in a research study looking at the way people with sleep apnoea or lung disease function during the evening, compared to healthy individuals. This Participant Information Form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from this project. You will not be paid for your participation in this project.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. You may withdraw from the project at any time without prejudice to your relationship with and treatment by this hospital.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of this Hospital.

PURPOSE OF THE STUDY

This project is designed to investigate the nature and extent of reduced learning, memory and concentration in patients with Obstructive Sleep Apnoea and patients with Chronic Obstructive Pulmonary Disease in

comparison to people without these conditions. In this study a number of measures will be used to assess these functions, as well as performance on a computer-based driving task.

WHAT WILL THIS PROJECT INVOLVE?

Your participation in the study will involve a session at the Austin Hospital.

1. On the day of the session, you will be asked to wake yourself up at 7.00 am, and will be requested not to consume any caffeine or stimulant medication until the completion of the study in the evening. You will be asked to arrive after dinner at approximately 5.30pm and the session will finish at around 10.30pm. During this session your performance on a computer driving simulation task, and a reaction time task will be assessed. Following this, you will complete a series of questionnaires designed to assess sleepiness, as well as your driving and sleeping history. A series of tasks assessing learning, memory, and performance will then be administered. A supper break will be included in this evening.
2. You will then stay for an overnight sleep study.
3. At 6am the following morning you will go home.

WHAT DOES THE OVERNIGHT SLEEP STUDY INVOLVE?

The overnight sleep study takes place in the sleep laboratory.

When you arrive at 6pm, you will be shown to your private room. Bathroom facilities are shared. There is a small lounge/television room for your use, and microwave / fridge facilities are available. You should have your dinner before coming to the hospital, bring night attire, toiletries, something to read and are welcome to bring your own pillow. You should bring all your own medication and take any medication as you would normally. Since caffeine is a stimulant, you are asked to refrain from drinking coffee, tea or coke from 7am on the morning of the overnight study. If you wish, you may bring non-caffeinated drinks with you to the hospital. Alcohol should also be avoided all day on the day of this study.

The sleep technician is a trained scientist or nurse who is experienced in this area. After you complete the tests for the research study, he/she will explain the equipment and procedures to you, then will attach several electrodes to your head, face, chest and legs to monitor your heart and the activity of your brain, your eyes, and the muscles of your face and legs. You will also have 2 bands strapped around your chest and abdomen to monitor your breathing, an airflow detector attached to your nose and mouth and an oxygen sensor attached to a finger. This may sound very uncomfortable and restrictive, but you are able to walk around, read, watch television, eat and drink. You will be asked to go to bed at around 11pm, and the electrodes will be plugged in to a board at the head of your bed. There is an infra-red camera in your room which allows the technician to see you during the night.

ARE THERE LIKELY TO BE ANY SIDE-EFFECTS OR RISKS?

No significant physical or psychological risks are anticipated in the proposed study. The main inconvenience will be the time commitment involved.

BENEFITS

Your participation will help in improving our understanding of neuropsychological impairment in patients and will assist in advising them when it may be appropriate or inappropriate to drive a motor vehicle.

COSTS

There is no cost for being in this study.

WHAT WILL HAPPEN TO MY RESULTS?

At the end of the study you will receive a copy of your results and these will be explained to you by one of the researchers. At your request, we can also send copies to your local doctor and to other doctors you see. The results of the study will be published, but your identity will not be revealed, nor will your results be shared with anyone else for any other purpose. Members of the hospital Ethics Committee may ask to look at your results, but no other people will be authorised to access them. The records dealing with this study will be kept in safe storage for 7 years, then shredded.

CONFIDENTIALITY

Your confidentiality will be respected at all times. You are free to decline or withdraw from participation in this study at any time and this will not affect your present or future relationship with this hospital or doctor. If at any time you or your doctor feels it is in your best interest to discontinue, you will be withdrawn from the study. At all stages of the study, you will be encouraged to ask questions.

CONTACTS AND SUPPORT

For the duration of the study you will be under the supervision of Daniela De Fazio, Dr Mark Howard and Dr Gerard Kennedy. If you have any questions concerning the nature of the research or your rights as a participant, please contact:

Daniela De Fazio 0412 902 927 (Day and Evening)

Dr Mark Howard 9496 3688 After Hours: 9496 5000

Dr Gerard Kennedy 9365 2481 After Hours: 0418 312 160

If you wish to contact someone, independent of the study, about any complaints, ethical issues or your rights, you may contact Mr Andrew Crowden, Chairperson of the Austin Health Human Research Ethics Committee, phone 9496 2901.

 **Austin Health** **Consent Form to Participate in Research –
Controls and COPD**

An Exploratory Study of Neuropsychological Impairment, Driving Performance, and Sleepiness in Obstructive Sleep Apnoea and Chronic Obstructive Pulmonary Disease.

I,have been invited to participate in the above study which is being conducted under the direction of Daniela De Fazio and Dr. Gerard Kennedy. I understand that while the study will be under their supervision, other relevant and appropriate persons may assist or act on their behalf.

- ◆ My consent is based on the understanding that the study involves attending a session at the Austin Hospital: During the session my performance on a driving simulation task, and a reaction time task will be assessed. Following this, I will complete a series of questionnaires designed to assess sleepiness. A series of tasks assessing learning, memory, and performance will then be administered. This will take approximately 5 hours. I will then stay in the Sleep Laboratory for an overnight Sleep Study, and go home at 6am the next morning.
 - ◆ This is not a drug trial.
 - ◆ The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

The main inconvenience is the time commitment involved. Occasionally the cream used to attach the electrodes may cause minor irritation.

- ◆ I have received and read the attached 'Participant Information Sheet' and understand the general purposes, methods and demands of the study. All of my questions have been answered to my satisfaction.
- ◆ I understand that the project may not be of direct benefit to me.
- ◆ I can withdraw or be withdrawn by the Principal Investigator from this study/project at any time, without prejudicing my further management.
- ◆ I consent to the publishing of results from this study provided my identity is not revealed.
- ◆ I hereby voluntarily consent and offer to take part in this study.

Signature (Participant)	Date:	Time:
Witness to signature	Date:	Time:
Signature (Investigator)	Date:	Time:

Appendix D: Multivariate Apnoea Prediction Questionnaire

Appendix E: Karolinska Sleepiness Scale

KAROLINSKA SLEEPINESS SCALE

The following is a 9-point scale to describe sleepiness. Put a cross in the box next to the point that describes how SLEEPY you feel RIGHT NOW.

1. extremely alert
2.
3. alert
4.
5. neither alert nor sleepy
6.
7. sleepy – but no difficulty remaining awake
8.
9. extremely sleepy – fighting sleep

Appendix F: Alertness Questionnaire

Appendix G: Subjective estimates of when drivers would stop driving and of their driving performance

Stop Driving Questionnaire

PART 1. With regards to how alert you feel, which one of the following statements best describes how you feel about driving for a short period in suburban traffic right now.

(Circle one number)

1. I would continue driving
2. I would continue driving only if pressure to do so
3. I would stop driving now even if under pressure to continue
4. I would have stopped driving some time ago.

PART 2. With regards to how alert you feel, which one of the following statements best describes how you feel about driving for a continuous long distance right now.

(Circle one number)

1. I would continue driving
2. I would continue driving only if pressure to do so
3. I would stop driving now even if under pressure to continue
4. I would have stopped driving some time ago.