The effects of sleep deprivation on simulated driving, neurocognitive functioning and brain activity in professional drivers

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Abstract

Sleepiness contributes to between 20 and 30% of all heavy vehicle accidents throughout the world each year. Professional drivers are particularly susceptible to the effects of sleepiness, due to chronic or acute sleep deprivation, time-on-task effects, driving at circadian low points, and increased daytime sleepiness resulting from sleep disorders. Population surveys of heavy vehicle drivers indicates that a small proportion of drivers use pharmaceutical means in order to help maintain alertness during long-haul trips. Despite the known benefits of amphetamine-type stimulants on reducing fatigue and sleepiness, epidemiological evidence suggests that a large percentage of fatally injured professional drivers test positive to amphetamines. The primary objective of the current thesis was to determine the underlying causes of these sleep- and drug-related accidents.

Experimentally, driving performance can be broken down into specific components that can be examined independently. Measures of behavioural disposition provide an indication of the drivers’ mood, ability to determine a change in performance and sleepiness, and whether the driver can make appropriate decisions regarding their ability to drive safely when sleep-deprived. Simulated driving tasks are commonly used to detect driving-related performance in a controlled and safe environment. The task of driving involves a number of components, including attention and vigilance, processing speed and reaction time, visual processes, and executive functioning, which can be measured using neurocognitive tasks. Smaller, pre-conscious neural processes that are undetected by behavioural tasks may also be affected by sleep deprivation, and in turn, affect driving performance. Electrophysiological (event-related potentials; ERPs) and neuroimaging (functional magnetic resonance imaging; fMRI) measures can be used to determine the neural underpinnings of visual and auditory processes after sleep deprivation. The aim of this thesis was to determine the effects of one night of sleep deprivation on these driving-related processes in professional drivers.

In Experiment 1, nineteen professional drivers underwent two randomised sessions; one session following a normal night of sleep and one session following 24-hours of sleep deprivation. Behavioural disposition, simulated driving performance, neurocognitive measures related to driving, and visual and auditory ERPs were
examined in both sessions. Subjective ratings of sleepiness and sleepiness symptoms increased significantly following sleep deprivation. Simulated driving performance and neurocognitive measures of vigilance and reaction time were impaired after sleep deprivation, whereas tasks examining processing speed and executive functioning were less susceptible to sleep deprivation. Event-related potentials of visual and auditory processing indicated that early visual processes were unaffected by sleep deprivation, whereas the amplitude of later cognitive processing was attenuated after sleep deprivation.

Driving also involves the ability of the driver to divide his or her attention between different sensory modalities in the driving environment. Experiment 2 presents a functional neuroimaging experiment examining the effect of sleep deprivation on neural activations that occur in response to a cross-modal divided attention task. There was no significant effect of sleep deprivation on behavioural performance. Following sleep deprivation, increased activation was observed in the temporal gyrus, cerebellum and precuneus, compared to activations observed after normal sleep. As no behavioural changes were observed, the results suggest that additional activation may act as a compensatory mechanism.

The restorative effect of \( d \)-amphetamine on sleep deprivation related impairment was examined in Experiment 3. This pilot study examined eight professional drivers who were past or current users of amphetamine across four, randomised sessions; after normal sleep with oral placebo, after sleep deprivation with oral placebo, after normal sleep with 0.42mg/kg oral \( d \)-amphetamine, and after sleep deprivation and 0.42mg/kg oral \( d \)-amphetamine. Measures of behavioural disposition appeared to be more affected by \( d \)-amphetamine administration after sleep deprivation compared to simulated driving and neurocognitive performance, however these findings need further clarification in a larger sample.

The results of the present thesis highlight the detrimental influence of sleep deprivation on a range of driving-related processes. The experienced, professional drivers in this study were able to recognise signs and symptoms of sleepiness, and acted upon these indicators appropriately. Measures of driving-related performance on both simulated driving, and simple neurocognitive tasks were negatively affected by sleep loss, although there is likely to be a discrepancy between on-road and laboratory
behaviour. ERP and neuroimaging findings in the present thesis suggest that these sleep-related behavioural effects are caused by small changes in neural processing and neural recruitment. Sleep deprivation can have large implications for safe driving, and this study highlights the importance of promoting and educating the driving public about the dangers of driving when sleepy.
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This thesis is dedicated to the memory of Professor Rob Pierce, who perished in the Victorian Bushfires of 2009.
Declaration

I declare that the present thesis does not incorporate without written acknowledgement any material previously submitted for a degree in any University, College, or Advanced Education, or other educational institution; and to the best of my knowledge the present thesis does not contain any material previously published or written by another person except where due reference is made in the text.

I declare that the ethical principles and procedures specified in the Swinburne University of Technology Human Research Ethics document on human research and experimentation have been adhered to in the present thesis.

Name: Melinda Jackson

Signed: .................................
Publications Arising from this Thesis

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Publications Associated with this Thesis


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Figure 6.7 Grand Averaged attentional N100 ERPs at Fz in response to Foveal and Peripheral Visual Field Stimuli in each session.

Figure 6.8 Grand Averaged P300 ERPs to target stimuli presented in the Foveal and Peripheral Visual Field Stimuli in each session.

Figure 6.9 Grand Averaged ERPs for N1P2 complex of the TTI response at the Cz scalp site in the NSD + d-amphetamine (blue), NSD + placebo (green) SD + placebo (black), and SD + d-amphetamine (red) sessions.
Figure 6.10 Grand Averaged ERPs for P300 complex of the Auditory Oddball Task response at the Pz scalp site in the NSD + d-amphetamine (blue), NSD + placebo (green) SD + placebo (black), and SD + d-amphetamine (red) sessions.
CHAPTER 1
INTRODUCTION TO SLEEP RELATED MOTOR VEHICLE ACCIDENTS

Chapter overview

The current chapter provides an overview of the literature pertaining to sleep- and drug-related motor vehicle accidents, particularly in relation to professional drivers. It firstly outlines the significance of the Australian Transport Industry and provides a description of driving regulations in Australia, secondly discusses the literature relating to sleep-related motor vehicle accidents and the incidence of these crashes in heavy vehicles, thirdly discusses possible causes of and explanations for these accidents, including sleep disorders, circadian factors, time-on-task effects, sleep deprivation, and a novel explanation for sleep-related accidents and drug-use amongst professional drivers, and fourthly concludes with an overview of how these issues are examined in the current thesis.

1.1 The Australian road transport industry

The road transport industry is one of the largest industries in Australia, contributing significantly to the country’s economy. Road transport is particularly important in Australia because of the large land mass and relatively small population. As such, roads cover significantly more area in Australia compared to rail and ports. Australia maintains one of the most extensive road networks in the world, comprising approximately 800,000km of public roads (Austroads, 2005). Road transport carries most of the freight moved between all regions, and dominates the freight movements within the capital cities.

There are currently 2.5 million heavy vehicles on Australian roads (ABS, 2006), and the growth of the industry is increasing each year. The 2006 Australian Census found that the proportion of light commercial vehicles rose by 16.2%, while rigid trucks rose by 12.3%, and articulated trucks rose by 12.2% over the past 4 years (ABS, 2006). Of this, rigid trucks accounted for 2.7%, with articulated trucks accounting for 0.5% of all vehicles on register in Australia in 2006, and Victoria had the largest share (9,257) of these (Austroads, 2005). There has been a 34% increase in road freight transport in the past five years in Australia (Figure 1.1). These figures highlight the importance of
the road transport industry workforce in Australia, and the role that transport drivers play in the sustainability and management of a significant proportion of the Australian economy.

![Figure 1.1: Indicators of road use trends per 5 years in Australia, from 2000 to 2005. From Austroads, 2005 (http://www.austroads.com.au/pdf/RoadFacts2005)](image)

1.2 Driving regulations in Australia

All drivers of commercial buses and heavy trucks in Australia are required to comply with the National Driving Hours Regulation (VicRoads, 2007). This regulation stipulates that the maximum driving time is 12 hours per 24-hour period, and drivers are required to take a 30-minute rest break every 5.5 hours of driving. As in many other countries around the world, the regulation of these hours is enforced in Australia by the verification of drivers’ log books. These regulations have been put in place in order to control drivers’ working hours and ensure that drivers are obtaining sufficient rest stops and sleep periods, to improve the safety of professional drivers. Despite these regulations, however, there are still a large number of sleep-related accidents on Australian roads each year, which are discussed in Sections 1.3 and 1.4.
1.3 Road accidents

The Global Burden of Disease Study estimated traffic injury to be the ninth leading cause of death and disability in the world in 1990, and projected it would be the third leading cause of death by 2020 (Murray & Lopez, 1997). Conservative estimates indicate that there are up to 700 fatalities and over 10,000 serious injuries per year from motor vehicle accidents (MVA’s) in Victoria, Australia (TAC, 1994), with a cost estimate of AUS$3 billion per year (Fell & Black, 1997; TAC, 1994). In Australia, 1,605 road fatalities were reported in 2006, which is a reduction of 18.5% than accidents reported in compared to 1996 (BTRE, 2007). This rate has fallen with measures to reduce speed and alcohol related MVA’s. However, the incidence of fatalities involving heavy vehicles is on the increase; during the 12 months to the end of March 2008, 294 people died from 251 crashes involving heavy trucks or buses, with fatal crashes involving heavy rigid trucks increasing by 19.7 % compared with the previous 12-month period (ATSB, 2008). Two of the other primary causes of MVAs reported in Australia are fatigue and drugs other than alcohol. In particular, sleep loss and fatigue have been noted as one of the primary causes of heavy vehicle accidents (Swann, 1999). The next section describes the issue of sleepiness in the transport industry, and the incidence of sleep-related heavy vehicle accidents in Australia and throughout the world.

1.4 Sleep-related accidents in heavy vehicles

Driver sleepiness has been implicated in a number of studies as a cause of heavy vehicle crashes both in Australia (Lyznicki et al., 1998; Sweedler, 1990), and throughout the world (Maycock et al., 1997; Sabbagh-Ehrlich, 2005). Sleepiness is an on-going occupational hazard amongst transport drivers as a result of long work hours, sleep restriction, time of day or circadian influences, irregular shifts and sleep disorders, all of which are related to increased accident risk (Folkard, 1997; Howard et al., 2004). Additionally, drivers can be placed under considerable commercial pressure to reach scheduled destinations, regardless of how sleepy they are feeling. Therefore, transport drivers are particularly susceptible to sleep-related MVA’s than most other road users. Driver sleepiness contributes to MVA’s in two ways; firstly, the driver may actually fall asleep at the wheel, and/or lose attention and make judgment errors (Philip & Mitler, 2000).
Driver sleepiness problems appear to be not just a concern for long-haul drivers. Hakkanen and Summala (2000) found that although working conditions and individual characteristics differed between long- and short-haul drivers, there were few differences in self-reported sleepiness and sleep patterns. However, falling asleep at the wheel was more common amongst long-haul drivers, most likely because they drive more often at night (Hakkanen & Summala, 2000). To control for any possible differences between long- and short-haul drivers, only drivers who work permanent day-shift will be recruited in the current thesis.

1.4.1 Defining sleep-related crashes

It is difficult to determine the exact proportion of truck accidents that are a direct result of sleepiness, firstly due to a lack of standardisation in the definition and reporting of a “sleep-related accident”, and secondly due to differences in the determination of causation of these accidents between states and countries. The main problem is that, unlike alcohol-related accidents, there is little physical or other evidence in sleepiness-related accidents that a driver was drowsy or fell asleep at the wheel, and there is a lack of a clear definition of a sleep-related accident. Sleep related accidents are generally defined by the presence of a combination of the following criteria:

a) a single vehicle collision
b) the driver has a blood alcohol concentration below the legal limit
c) the car drives off road or into back of another vehicle
d) there are no signs of braking
e) there are no mechanical defect in vehicle
f) there was good weather, clear conditions
g) elimination of speeding or driving too close as causes
h) the police officer’s judgement
i) for several seconds immediately before the accident the driver could have seen clearly the point of run off or the vehicle hit.

The driver may or may not have admitted to having fallen asleep (Horne & Reyner, 1995). Therefore, it is believed that sleep-related accidents are underreported and that the extent of the problem is likely to be underestimated. Despite this, sleepiness
remains one of the most probable major causes of MVA’s (MacLean, Davies, & Thiele, 2003).

1.4.2 Incidence of sleep-related heavy vehicle accidents

Sleep-related heavy vehicle accidents have a higher fatality rate than other MVA’s. Truck accidents tend to occur at higher speeds than other vehicles, which, together with the larger vehicle mass, result in a greater impact force (Greibe, 2003). As such, heavy vehicle accidents have three times the fatality rate of other accidents, accounting for 20% of all road fatalities, mostly relating to occupants of other vehicles (Swann, 2002).

A number of studies have reported sleep-related truck accidents using police and government reports (Philip et al., 1999), or population surveys (Arnold et al., 1997; Fell & Black, 1997; Lyznicki et al., 1998; Maycock, 1997). In Australia, driver sleepiness is argued to contribute to between 20% and 60% of truck accidents (Fell & Black, 1997; MacLean et al., 2003; TAC, 1994). In Victoria, Australia, it is estimated that the proportion of truck crashes attributable to driver sleepiness is 25% (Naughton & Pierce, 1991). In terms of fatalities, it is estimated that between 20% and 31% of fatal-to-the-driver truck crashes are attributed to driver sleepiness (NTSB, 1990).

Similar proportions of sleep-related truck accidents are reported throughout the world. UK data suggests that 10% to 25% of truck crashes are related to driver sleepiness (Maycock, 1997). Data from the US indicates that 58% of truck drivers attributed their crash to fatigue (NTSB, 1995), and 67% of truck drivers in Israel self-reported that their crash was attributable to fatigue (Sabbagh-Ehrlich, Friedman, & Richter, 2005). Given the large contribution of sleep-related accidents to road fatalities, the causes of these accidents have been a major focus of research in recent times.

1.4.3 Incidence of professional drivers falling asleep at the wheel

It is important for drivers to be able to recognise when they are significantly sleepy and not safe to drive in order to take compensatory action (e.g. a nap). It is well established that sleep deprivation impairs cognitive abilities (as outlined in Chapter 3), but it can also impact on an individual’s ability to monitor and assess their own behaviour and fitness to drive (Brown, 1997). Self-reported falling asleep at the wheel
is common amongst transport workers. In a Swedish study of train drivers, 11% of the drivers reported that they fell asleep at work on most nights, and 59% had fallen asleep at least once during night shift (Torsvall & Akerstedt, 1987). Similarly, an Australian survey of truck drivers indicated that 14% of drivers admitted to having fallen asleep at the wheel at least once in the past nine months (Arnold et al., 1997), and 22% of long-haul truck drivers surveyed in Helsinki reported having dozed off at the wheel at least twice during the preceding three months (Hakkanen & Summala, 2000). These statistics suggest that drivers may be poor at perceiving that sleepiness is impairing their driving ability (for review see Brown, 1997). Due to the importance of this issue to drivers’ safety, the ability of drivers to recognise symptoms of sleepiness and performance impairment will be explored in the current thesis.

1.4.4 Causes of sleepiness and fatigue in heavy vehicle drivers

Commercial drivers’ risk of being involved in a sleep-related accident is far greater than that of non-commercial drivers (McCartt et al., 2000). McCartt et al. (2000) identified factors associated with why long-distance truck drivers reported falling asleep at the wheel. They found six underlying, independent factors; (1) greater daytime sleepiness, (2) more arduous schedules, with more hours of work and fewer hours off-duty, (3) older, more experienced drivers, (4) shorter, poorer sleep on the road, (5) symptoms of sleep disorder, and (6) greater tendency to night-time drowsy driving. Working for long hours, lack of sleep prior to driving, and fatigue related to loading trucks and delays in loading trucks are the most reported contributors to sleepiness in truck drivers (Arnold et al., 1997). The correspondence of accident peaks with the human peak propensity for sleep (Pack et al., 1995), reports from truck drivers concerning the timing of road incidents (Maycock, 1996), the incidence of single vehicle fatal crashes (Hamelin, 1987), and the occurrence of sleep-related brain activity (as measured by electroencephalography) in truck drivers (Kecklund & Akerstedt, 1993; Mitler et al., 1997) all indicate that sleepiness appears to be the primary causal factor in many heavy vehicle accidents. These factors are discussed in Sections 1.4.4.1 to 1.4.4.4.

1.4.4.1 Chronic, partial or total sleep deprivation

Professional drivers often experience short periods of total sleep deprivation (i.e. 24 hours) in order to meet deadlines. Further, due to their irregular work hours, many drivers are unable to obtain sufficient sleep before or after extended shifts, and
therefore may continue to drive with an accumulated sleep debt. A survey of 1,249 drivers found that 20% reported less than six hours sleep the night before, and a further 12% reported less than four hours sleep on one or more working days in the week preceding the survey (Arnold et al., 1997). Chronic partial sleep restriction and acute sleep deprivation contribute to deficits in simulated driving and neurocognitive performance (Banks & Dingess, 2007), which can lead to increased accident risk.

1.4.4.2 Time-on-task effects
Drivers who are travelling for long distances need to maintain a high level of alertness and attention for long periods of time. Driving long distances has been shown to be the most important risk factor for sleepiness-related accidents (Philip et al., 1999). Arnold et al. (1995) found that long-haul drivers had a crash risk 2.5 times greater after 14 hours of work, when compared to less than ten hours of work. This finding suggests that long-distance professional truck drivers are at particularly high risk of falling asleep at the wheel when driving. Additionally, driving is a boring, monotonous and repetitive task, and professional drivers generally drive alone on long, high-speed highways. Consistent with these factors, reduced driver vigilance and increased reaction time and sleepiness occur with increasing trip time and are associated with an increase in accident rates (Hakkanen & Summala, 2001).

1.4.4.3 Circadian factors
Work schedules and economic pressures that professional drivers face result in them working long, irregular hours, which often conflict with natural circadian rhythms. Reports clearly demonstrate a diurnal pattern of accident rates across the day, corresponding to the circadian nadir periods (Pack et al., 1995; Figure 1.2). Peaks in sleep-related accident rates and accidents in industrial operations typically occur during our natural time for maximum sleep propensity; either in the early hours of the morning (02:00h and 06:00h) or early afternoon (14:00h and 16:00h) (Folkard, 1997; Harma & Ilmarinen, 1999; Horne & Reyner, 1996; Pack et al., 1995). Pack et al. (1995) examined 4,333 crashes in the US between 1990 and 1992, in which the driver was judged to be asleep but not intoxicated. These crashes primarily occurred between midnight to 07:00h, and around 15:00h (Figure 1.2). Similarly, Horne & Reyner (1995) assessed 679 sleep-related accidents in the UK, and reported that these accidents more frequently occurred around the hours of 02:00h, 06:00h and 16:00h. When traffic density is taken into account, it is 20 times more likely that a sleep-
related accident will occur between the hours of 06:00h than at 10:00h (Smith & Kushida, 2000). Professional drivers commonly drive during their circadian low points. The influence of the sleep-wake regulatory system on performance will be further described in Chapter 2, Section 2.2.2.

![Figure 1.2: Frequency histogram of time course of crashes across the 24-hour period in which the driver was deemed to be asleep. Data for years 1990 to 1992 (Pack et al., 1995).](image)

1.4.4.4 Sleep disorders

Many drivers have difficulty maintaining a healthy lifestyle, including a nutritious diet and regular exercise, which can lead to obesity and increase the likelihood of a number of medical problems. In particular, professional drivers have a higher incidence of Obstructive Sleep Apnoea (OSA) when compared to the general population (Horne & Reyner, 1995; Howard et al., 2001). OSA is a respiratory impairment characterised by severely disturbed breathing during sleep due to the blockage of airflow in the upper airways (Bedard et al., 1991). Patients suffering OSA experience excessive daytime sleepiness and often report falling asleep briefly when stopped at traffic lights or while sitting quietly on the couch in the afternoon (Jewett et al., 1999; Johns, 1997; Johns, 1993; Simpson et al., 1984). Patients with OSA are statistically more likely to be involved in car crashes (George, Boudrea, & Smiley, 1997; Young et al., 1997). A study of 153 professional drivers who reported no sleep disorders, found that 77% were diagnosed with OSA by overnight polysomnography, with 47% found to have significant “sleepiness” as assessed by an objective sleep
latency measure, the Multiple Sleep Latency Test (Dagan et al., 2006). Truck drivers with a sleep disorder or who are obese have a two-fold higher crash rate than drivers without these negative health issues (Stoohs et al., 1994). An Australian study found that 16% of heavy vehicle drivers had both sleep-disordered breathing and symptoms of excessive daytime sleepiness and this was associated with a two-fold increased risk of having an accident (Howard et al., 2001; Howard et al., 2004). As an indication of the importance of this factor, a major programme was implemented in 2003 in Victoria, Australia, to screen 15,000 professional drivers for medical disorders (including sleep disorders), to improve the health and safety of the industry. Participants in the current thesis will be screened for and excluded if they have a sleep disorder.

1.4.5 Alternate explanations for sleep-related accidents

An alternative explanation for the increased fatigue-related accidents amongst heavy vehicle drivers may be illicit drug use. Amphetamine-type stimulants, such as d-amphetamine, are used by some truck drivers to combat the symptoms of fatigue and sleepiness during long-distance driving (Goldberg & Cone, 1994). There has been an increase in the proportion of drivers using drugs worldwide, with many reports detailing the incidence of drugs in both fatally injured drivers (Crouch et al., 1993; del Rio & Alvarez, 2001; Drummer et al., 2003; Logan, 1996), drivers apprehended for driving under the influence of drugs (Augsburger et al, 2005; Gustavsen, 2006; Jones & Holmgren, 2005; Silva et al., 2003), and transport company surveys (Arnold & Hartley, 2001). For instance, a survey of 84 transport company managers in Western Australia revealed that 6% of respondents reported that their drivers used drugs (Arnold & Hartley, 2001). One respondent indicated that all of his seven drivers used drugs to assist them in driving, and another estimated that half of his 250 drivers used stimulant drugs (Arnold & Hartley, 2001).

The involvement of psychotropic substances (medicinal or illicit) in road accidents has predominantly been examined by determining which drugs were present in the body tissues, blood, or urine of drivers killed or injured in road accidents, or involved in traffic violations. Drugs other than alcohol have been estimated to play a role in between 10% and 15% of all road deaths world-wide (Milner, 1972). In particular, there appears to be an over-representation of professional drivers who test positive to amphetamines compared to the general population. There are only three prevalence
studies to date. These studies indicate that there is a relatively high use of stimulants (between 18% and 23%), among transport workers in comparison to the general driving population in the US and Australia (Couper et al., 2002; Crouch et al., 1993; Drummer et al., 2003). In one large drug incidence study, 3,398 driver fatalities were investigated (Drummer et al., 2003). This report demonstrated that drivers tested positive for cannabis in 13.5% of road fatalities, 4.9% for opioids, 4.1% for stimulants and 4.1% for benzodiazepines (Drummer et al., 2003). More specifically, 23% of 139 truck drivers involved in fatal accidents tested positive to stimulants (including amphetamines, MDMA, cocaine and ephedrine) (Drummer et al., 2003). Almost half of these drivers had blood levels that are considered toxic.

This is in line with other reports of positive stimulant results among this group in studies around the world (Couper et al., 2002; Crouch et al., 1993; Kelly, Darke, & Ross, 2004; Mabbott & Hartley, 1998). The National Institute for Drug Abuse (NIDA) and National Transport Safety Bureau (NTSB) in the US conducted tests on 168 fatally injured truck drivers (Crouch et al., 1993). One or more drugs were detected in 67% of the truck drivers, with 7% containing amphetamine or methamphetamine, and 7% containing ephedrine or pseudoephedrine. In the majority of these cases (50 of 56) where psychoactive drugs or alcohol were detected, driving impairment due to substance use was judged to be the main contributing factor in the fatal accident (Crouch et al., 1993).

Culpability studies have shown that specific drug classes are associated with an increased fatal collision risk (Drummer et al., 2003). Drivers who tested positive to stimulants were 1.8 times more likely to be culpable than drug-free drivers, and in 90% of these cases, the stimulant use was considered to be at least partially responsible for the accident (Drummer et al., 2003). The odds ratio that has been calculated for drivers using stimulants was 2.3 (where 1.0 infers no increase, and 2.0 infers a doubling of risk), however, this increased to over eight-fold in heavy vehicle drivers who had stimulants in their system (Drummer et al., 2004; Swann, 2002). However, the increased odds ratio of crash risk compared to other road users is possibly due to increased time on road and fatigue experienced by truck drivers (Swann, 2002). These data suggests that, although amphetamines improve vigilance in drivers who are sleepy, they may have a detrimental effect on other functions that
are important for driving. The impact of \textit{d}-amphetamine on driving-related processes in sleep-deprived drivers will be examined in the current thesis.

\textbf{1.4.6 Reasons for driving whilst sleep deprived or under the influence of illicit drugs in the transport industry}

The competitive nature of the transport industry imposes unique pressures on professional drivers compared to other road users. Many drivers find it difficult to balance the need for rest and the consequences of failing to meet schedule demands, or the possibility of gaining financial rewards (Hanowski et al., 1998; McCartt et al., 2000). Non-compliance to driving (working) hours is not uncommon amongst transport drivers, as many of their delivery schedules are very tight. It is common for drivers to work a second shift after their regular day shift, and so avoid company driving-hours regulations. One study of 2,000 truck drivers found over half of the drivers were in violation of their company regulations by at least one hour (Hertz, 1988). An Australian study found that 51\% of long-haul drivers exceeded 14 hours of driving within 24-hours, well outside legal regulations (see Section 1.2 for regulations)(Arnold et al., 1997).

Arnold et al.’s (1997) survey of 1,249 Australian truck drivers found that 16\% reported using drugs to manage their fatigue. The high prevalence of amphetamine-type stimulant use in transport drivers compared to other road users is likely due to a number of factors. Drug use is accepted as part of the industry culture by a small percentage of drivers, and therefore there is little encouragement within some workplaces for drivers to stop taking drugs (see Neville et al., 2000 for review). Despite the evidence that stimulant use is related to an increased risk of road accidents, many drivers continue to use amphetamine-type stimulants to assist them in working for prolonged periods and believe that they are safer to drive with stimulants than without them (Neville et al., 2000). Because of the conflict between physiological needs and economic or work pressures faced by professional drivers, ad the prevalence of drug-use in this population, it is increasingly important to understand the impact of sleep deprivation and drug-use on driving to better inform accident prevention programmes and driver education.
1.4.7 Possible explanations for sleep- and drug-related MVA’s

Although amphetamine-type stimulants are consumed in an attempt to counteract the effects of sleepiness, drug use is actually associated with an increased risk of crashes (Drummer et al., 2003). Sleepiness can also exacerbate the effects of other factors, such as alcohol and drugs (Howard et al., 2007; Swann, 2002) resulting in impaired driving ability and increasing crash risk.

In amphetamine abuse, excessive sleepiness during drug abstinence has been consistently reported (Drummer, 2001). A rebound effect can be experienced when the blood drug concentrations become too low, during which a driver experiences excessive sleepiness (Drummer, 2001). This increased sleepiness can last up to five days, and is likely to be the result of reduced sleep time during drug administration, or a component of the withdrawal process. In addition, drug use has the capacity to disrupt nocturnal sleep patterns, thereby increasing daytime sleepiness. Long-term methamphetamine use is also known to be associated with reductions in grey-matter density (Thompson et al., 2004), which may also have deleterious effects on cognitive function and behaviours important for safe driving. All these factors can increase accident risk in drivers who use amphetamine-type-stimulants.

Given that amphetamine-type stimulants improve at least some of the detrimental effects of sleep loss (Caldwell, Caldwell, & Darlington, 2003; Caldwell & Caldwell, 1997; Weigmann et al., 1996), the above-described pattern of increased accident risk is unexpected, and the reasons behind it are in urgent need of clarification. The interactive effect of sleep deprivation and d-amphetamine on specific driving-related processes will be examined in the current thesis, to determine whether d-amphetamine is useful in reversing all aspects of sleep-related performance impairment.

1.5 Summary

This chapter has described the incidence and causes of sleep-related accidents amongst professional drivers. A clearer understanding of the effects of sleepiness on driving-related processes and introspective assessment of sleepiness in this population is essential in order to aid education and prevention programmes about sleep-related motor vehicle accidents. Experimentally, driving-related performance can be examined using a number of different methods. This thesis will examine and explore
the underlying causes of the increased accident risk in sleep deprived drivers, using a range of measures which reflect different aspects of the driving task; from a behavioural, neurocognitive and psychophysiological perspective. Chapter 2, Methods in Sleep Deprivation Research, provides an overview of the protocols and tools used in the current thesis in order to experimentally examine the effects of sleep deprivation on driving-related processes. Specifically, this chapter outlines the research procedures which have been used to examine this issue, including actual and laboratory-based driving, tests of behavioural disposition, neurocognitive tasks related to driving, and psychophysiological techniques, as well as the justification for using the particular techniques and tools. Chapter 3, Effect of Sleep Deprivation on Driving-related Performance provides a review of the literature pertaining to effects of acute sleep deprivation on on-road driving, simulated driving tasks, behavioural dispositions, driving-related neurocognitive domains, and event-related potential (ERP) and functional neuroimaging measures of visual and auditory neural processes that underlying driving performance. The overall aims of the thesis are outlined.

The first experiment of the thesis, described in Chapter 4, examines and determines the effects of sleep deprivation on driving-related processes. Specifically, this experiment examines a simulated driving task, measures of behavioural disposition, and measures of attentional processes by means of neurocognitive tasks and electrophysiological measures. The second experiment, Chapter 5, explores attentional processing using a more detailed approach; functional MRI. In this experiment, a cross-modal divided attention task is assessed under conditions of sleep loss in a sample of professional drivers. Finally, in order to determine whether the increased sleep-related accident rate is influenced by stimulant drug use in this population, Chapter 6 presents a pilot study that examines the effects of d-amphetamine and sleep deprivation, alone and in combination, on driving-related processes. Limitations of the current thesis and future directions of this research are discussed in Chapter 7, and Chapter 8 summarises the major findings of the thesis.
CHAPTER 2
METHODS IN SLEEP DEPRIVATION RESEARCH

Chapter overview

This chapter defines and discusses the experimental manipulations that have been used to examine driving-related functions in the current thesis. Firstly, a description of the types of participants recruited for the experiments is provided. Secondly, an overview of sleep deprivation is given, defining fatigue and sleepiness as concepts used in this thesis, the physiological processes involved in the sleep-wake drive, and different types of experimentally-induced sleep deprivation. Finally, the methods for measuring driving-related processes are discussed, including behavioural dispositional measures, simulated driving, driving-related cognitive domains, and psychophysiological techniques.

2.1 Participants

As outlined in Chapter 1, professional drivers represent a group who are particularly vulnerable to the effects of sleepiness on their driving, and are more likely to be involved in a sleep-related accident. For example, self-report surveys of male professional drivers have indicated that this population report significantly more daytime sleepiness compared to males in the general population (Carter et al., 2003). There is a paucity of literature specifically targeting this population of drivers. Therefore, the current thesis will use professional drivers in order to examine the specific effects of sleepiness on driving-related processes in this population.

For the purpose of this thesis, the definition of “professional drivers” includes all individuals whose primary job is to drive a vehicle. Primarily this includes heavy vehicle drivers, both long-and short-haul, interstate and local (city) drivers, and extends to commercial bus drivers (more than 12 passengers), couriers and taxi drivers.
2.2 An overview of sleep deprivation

This section will provide a working definition of fatigue and sleepiness, and describe the physiological aspects of sleep-wake regulation, including the homeostatic drive for sleep, and circadian rhythm effects. A definition of sleep deprivation is then given, with an explanation of the level and type of sleep deprivation used in the current thesis.

2.2.1 Defining fatigue and sleepiness

A number of definitions have been postulated for both fatigue and sleepiness, however it has been argued that there are distinct differences in their aetiology and outcome (Pigeon, Sateia & Ferguson, 2003). Fatigue is a complex phenomenon, involving a number of behavioural and psychosocial processes (Shen, Barbera & Shapiro, 2006). It is generally seen as a gradual and cumulative process caused by sustained activity, and is usually more of a physical state of exhaustion, which may or may not arise from sleep deprivation (Shen et al., 2006). The fatigued state is usually associated with a decline in performance efficiency (Grandjean, 1979), and has been described in driving scenarios which require sustained attention for long periods (Lal & Craig, 2001). Fatigue is reduced or abolished by a period of rest.

Sleepiness, on the other hand, is more often used to describe a subjective experience or subjective feeling of difficulty remaining awake, or objective measurement demonstrating increased sleep propensity (Johns, 1993). Sleepiness is often associated with a variety of cognitive abnormalities, including reaction time, vigilance and peripheral vision, and ultimately results in falling asleep (Akerstedt, 1988; Dinges et al., 1997; Russo et al., 1999; Williamson, Feyer, & Friswell, 1996). Sleepiness, therefore, is most often a result of lack of sleep, related to circadian and homeostatic influences. Sleepiness is generally resolved after sleep, but not rest. For the purpose of this thesis, the term sleepiness will be used to describe the psychological response to sleep deprivation, circadian nadir or extended wakefulness.

2.2.2 Sleep-wake regulation

Two primary factors contribute to the sleep-wake cycle; the homeostatic drive for sleep, and circadian influences. The sleep propensity at any particular time is a
function of the ratio of the total sleep drive to the total wake drive with which it competes. These systems are controlled by a central pacemaker, the suprachiasmatic nuclei (SCN), located in the anterior hypothalamus (Hobson, 1995). This region of the brain is responsible for the coordination and control of physiological, neurobiological and behavioural systems. This pacemaker is entrained to the 24-hour day/night cycle, and is prompted by external, environmental cues (i.e. light-dark cycle). Sleeping and waking, temperature fluctuations, hormonal secretions and neurocognitive functions are all controlled by this system, and synchronise with the external environment (Rogers, Dorrian, & Dinges, 2003). A two-process model of sleep-wake regulation has been posited to describe the temporal nature of sleep and wakefulness, consisting of a sleep homeostatic process and a circadian process (Borbély, 1982). This model has been used to predict and model neurobehavioural performance (Akerstedt & Folkard, 1997; Van Dongen & Dinges, 2003).

2.2.2.1 Homeostatic drive for sleep

One of the strongest influences on human physiological and behavioural activity is the homeostatic system (Rogers et al., 2003). One of the functions of this system is to influence the need or drive for sleep, which increases during wakefulness and decreases during slow wave sleep (Durmer & Dinges, 2005; Van Dongen & Dinges, 2000). During periods of deprivation of sleep, the homeostatic drive increases and when a threshold is reached, there is an increased likelihood of sleep onset. This sleep need is accompanied by a decrease in alertness and increased sleepiness, and is often associated with a gradual decline in neurocognitive performance (Dinges et al., 1997). Further, this physiological need for sleep can only be reversed or overcome by a period of sleep.

2.2.2.2 Circadian effects on performance

In addition to the homeostatic drive for sleep, humans also exhibit a natural 24-hour oscillating variation in the propensity for sleep, the circadian system. The circadian system involves a bi-circadian oscillatory modulation of the sleep nadir, which peaks during the night-time and during the early afternoon. This typically occurs between 13:00h and 16:00h (termed the “post-lunch dip”) with a second decline between 04:00h and 06:00h. Importantly, alertness levels, subjective sleepiness, and changes in performance are subject to this diurnal variation, and are also controlled by the circadian pacemaker (Figure 2.1; Jewett et al, 1999; Gillberg et al., 1996; Lenne,
For example, the circadian drive for wakefulness may enhance alertness in the early evening hours, despite a sleepless night the previous night. On the other hand, deprivation of sleep can heighten homeostatic pressure to a level where waking cognitive functioning will be impaired even during peak circadian times (Durmer & Dinges, 2005).

2.2.2.3 Separating homeostasis and circadian effects

It is the interaction between circadian effects and the homeostatic drive for sleep that determines the level of sleepiness, the likelihood of falling asleep, and neurocognitive functioning. During sleep deprivation paradigms, the homeostatic drive for sleep, and its effect on performance, is the primary outcome sought. If performance is assessed during the circadian nadir in a sleep-deprived individual, it cannot be determined whether the change in performance is due to circadian influences, homeostatic influences, or a combination of the two systems. It is therefore important in experimental research, that the circadian influences are taken into account and controlled for to some extent, by examining performance and behaviour outside the circadian nadir. The current thesis attempted to overcome this issue by testing participants who were sleep-deprived, during the mid-morning, prior to the afternoon.
propensity for sleep, and avoiding any early-morning circadian effects on performance.

2.3 Physiological indicators of sleepiness

The detection of sleepiness has important implications for driving. Sleepiness measures should be able to detect deterioration in performance, or periods of driver inattention, which may result in a driver failing to respond to hazards in the road environment and potentially having an accident. Therefore, a method that is sensitive to increased periods of sleepiness while an individual is driving would be useful for alerting a driver and potentially reducing sleep-related accidents. A number of potential measures have been proposed to objectively measure state-related sleepiness in active individuals. Two promising methods that have emerged are the detection of brief periods of sleep using EEG, and the measurement of brief periods of slow eyelid closure.

During wakefulness with eyes open, the EEG has predominant beta activity (>12 Hz). With progressive increasing sleepiness there is an increase in alpha activity and then theta activity prior to formal onset of stage one non-REM sleep (Santamaria & Chiappa, 1987). Microsleeps are described as brief periods of transient physiologic stage 1 slow wave sleep (Guilleminault et al., 1975). Sleep deprivation results in increased sleep propensity and microsleeps (Corsi-Cabrera et al., 1992; Howard et al., 2002; Torsvall & Akerstedt, 1988). These periods of falling asleep are initially very brief, lasting from 3 to 15 seconds (Priest et al., 2001) but as fatigue increases longer periods of sleep occur (Riemersma et al., 1977). Methods for measuring microsleeps include standard manual scoring of the EEG, spectral analysis of the EEG and video of the face to indicate sleep (Hakkanen et al., 1999; Torsvall & Akerstedt, 1987). These EEG changes can occur with or without behavioural signs of sleep (i.e. long eyelid closures, drooping eyelids, nodding of the head), can occur with eyes open or closed, and often occur without warning in sleep-deprived individuals. Importantly for driving, responsiveness to environmental stimuli is impaired or completely absent during a microsleep (Akerstedt, 1988). This may result in accidents due to failure to respond appropriately to hazards in the driving environment, such as avoiding obstacles, or adjusting steering and speed. An increase in brief sleep periods, measured by increased EEG alpha bursts, have been demonstrated in on-road driving
studies, after extended wakefulness of 21 hours (Summala & Mikkola, 1994), and during night driving (Kecklund & Akerstedt, 1993; Miller, 1997). Assessment for microsleeps has also been used to objectively measure sleepiness in sleep-deprived normal individuals on a driving simulator, and has been shown to correlate negatively with simulated driving performance (Wierwille & Ellsworth, 1994).

Manual analysis of EEG data for brief alpha and theta periods is often impractical, and difficult to perform in “real-time” on the road. Another promising method for detecting sleepiness during driving is the measurement of slow eyelid closure. Normal eye blinks usually lasts for less than 200ms. The neurological basis of eye closure is intimately connected with the sleep-wake functions. Wakefulness is maintained by tonic activity in the reticular activating system, reinforced by sensory input (McCarley, 1999). During sleep onset or when a person becomes drowsy, all conscious synaptic transmission through the thalamus is obliterated as the reticular nucleus inhibits the sensory nuclei of the thalamus. This causes a reduction in inputs to the thalamic motor projections to the face, including eyelids, leading to these muscles relaxing and eyelids closing. Levator palpebrae superioris maintains the eyelids in an open position during wakefulness and opens them after blinking (VanderWerf et al., 1997). There is a reduction in tonic activity of facial muscles during drowsiness, which occurs in association with descending inhibition of motor neurones and attenuation of blink and vestibulo-ocular reflexes in these states (Culebras, 2002). As a result, increased duration of eyelid closure occurs in sleepy subjects who are trying to remain awake with their eyes open (Cajochen et al., 1999). If a driver’s eyes are closed for an extended period of time, it is obvious that they would be at an increase risk of failing to respond to their environment and having an accident.

A number of methods have been used to determine the amount of slow eyelid closure in sleepy subjects’, including video recording of the face with manual or automated analysis, and vertical EOG measures. One measure that has been used previously is PERCLOS; video scoring of eye closure to assess the percentage of time that the eyes are more than 80 percent closed (Wierwille & Ellsworth, 1994). While each method has technical problems in obtaining adequate recordings and interpreting the data, PERCLOS has been shown to be the most reliable (Dinges et al., 1999; Hakkanen et al., 1999). Dinges et al. (1999) assessed the validity of six different methods for detecting drowsiness or microsleeps in terms of lapses on a psychomotor vigilance
task (Dinges et al., 1999). Two EEG algorithms, PERCLOS, a head tracker device and two eye blink monitors were compared to assess sleepiness in subjects who were sleep-deprived for 42 hours. Only PERCLOS produced a high correlation with PVT lapses for all subjects across all sessions. PERCLOS also correlated better with PVT lapses than individuals rating of sleepiness. These results are supported by studies that suggest that monitoring of eye closure is a promising way of detecting sleepiness and performance failure (Dinges et al., 1999; Wierwille & Ellsworth, 1994). The current thesis will examine a automated measure of PERCLOS, the Copilot, during the simulated driving task, to determine whether increases in slow eyelid closure are detectable in these drivers after one night of sleep deprivation.

2.4 The definition of sleep deprivation in the current thesis

One way of experimentally manipulating sleep homeostasis and increasing sleep propensity is to sleep deprive an individual. “Sleep deprivation” is a broad term used to describe a period where wakefulness occurs when sleep would naturally occur. As outlined in Section 2.22, during periods of deprivation from sleep, the influences of both circadian and sleep homeostatic systems come into play.

‘Total’ sleep deprivation is the term used to describe an extended period of sleep deprivation. The length of total sleep deprivation required to induce deterioration in cognitive performance is still under debate. It has been argued that sleep deprivation periods of more than 45 hours are required before any significant deterioration in performance can be detected (Naitoh, 1976), whereas others have reported performance deterioration after as little as 18 hours without sleep (Dawson & Reid, 1997; Morris, Yuen, & Becker, 1992). This difference is likely to be task-dependent. A period of 24-hours of total sleep deprivation was chosen in the current thesis to examine driving-related impairments in performance. Experimentally, this amount of sleep deprivation also allows for the assessment of performance outside the circadian nadir (i.e. so participants can wake at a regular time in the morning such as 06:00h to 07:00h, and then complete testing the following morning, around 10:00h, which would not be influenced by circadian effects). This is also a common period of sleep deprivation experienced by transport workers, and one in which performance has previously been shown to induce performance changes in neurocognitive tasks (Pitcher & Huffcutt, 1996; Kim et al., 2001).
2.5 Measurement of driving-related performance impairment

Driving is a complex task that requires a number of skills. The driver continuously receives information, analyses it, and reacts according to knowledge of traffic systems, driving regulations, conditions of the vehicle, applications of the road rules and their previous driving experiences. This section describes measures which have previously been used to assess and determine performance impairment in sleep deprived participants. Experimental methods that have the greatest relevance for real-world driving, from behavioural disposition measures, including mood and subjective sleepiness, to on-road driving and simulated driving tasks, through to measures with the greatest experimental control, including neurocognitive domains, and electrophysiological and neuroimaging measures of driving-related processes are then outlined. A summary of advantages and limitations of each area is provided. This section is not exhaustive, but defines the driving-related processes that are examined in the current thesis.

2.5.1 Behavioural disposition

The ability of drivers to make introspective assessments of their level of performance impairment when driving is essential for avoiding accidents. Two key aspects of behavioural disposition particularly relevant to safe driving are 1) the ability to recognise sleepiness and impairment in driving performance, and 2) deciding to act upon these judgements (e.g. stop driving).

Changes in mood are commonly observed in sleepy individuals, and often reflect changes in sleepiness levels (De Valck & Cluydts, 2001; Dinges et al., 1997). In a meta-analysis of the literature describing the effects of sleep deprivation on measures of mood, cognitive performance and motor performance, mood was most affected by sleep loss than performance measures (Pilcher & Huffcutt, 1996). Alterations in an individual’s mood state may in turn affect his or her decision-making ability or judgement, which may have implications for driving. A number of validated mood scales have been developed, including the Profile of Mood States, and Visual Analogue Mood Scales.

Some individuals have a chronic increased propensity to fall asleep, reflecting a trait-related sleepiness. This may arise from a number of factors that are present among
transport workers, such as chronic sleep disorder, or as a result of chronic inadequate sleep or disruption to sleep. Several tools have been developed for subjective measurement of chronic sleepiness and have been used for research as well as in clinical settings. The Epworth Sleepiness Scale (ESS) is one such measure, which asks subjects to record how likely they are to “doze off” or “fall asleep” in eight different daily situations (Johns, 1991).

Sleepiness is perceived by an individual well before he or she is overcome by sleep (Akerstedt, 1988). Acute or state-related sleepiness measures may also provide information of an individuals’ level of sleepiness and their ability to drive safely. There are a number of validated measures used experimentally to examine subjects’ state-sleepiness, including the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale (KSS). The KSS is used to subjectively assess state-related sleepiness by asking individuals to rate how sleepy they feel right now. The KSS requires the participant to integrate and translate a number of sensations to a continuum that is fairly abstract in spite of the verbal descriptions (Gillberg, Kecklund, & Akerstedt, 1994).

Rather than asking how sleepy an individual is feeling, asking them to detect specific physiological indicators of sleepiness may be a more effective way of helping a driver make an introspective assessment of their sleepiness. There is currently little research into drivers’ ability to judge specific symptoms of sleepiness, such as blurred vision or yawning. Specific symptoms of sleepiness are important as they are can be promoted as cues that drivers can use to help identify when they are too sleepy or impaired to drive. In the laboratory setting, asking participants’ whether they feel their performance has improved or worsened, and whether they would consequently continue to drive in their current state, allows the assessment of the level of sleepiness and performance change required for an individual to decide to pull over. These measures of behavioural disposition will be utilised in the current thesis.

Tests of behavioural disposition may provide a more holistic understanding of performance impairments of drivers compared with only using laboratory-based tasks. This is because behavioural information provides more evidence as to what factors lead to a driver’s decision to stop driving. One limitation of using subjective measurements is the potential for reporting bias. Participants may under-report
sleepiness because of the potential impact on employment or licensing or, because of its chronic nature, they may fail to perceive sleepiness as abnormal. It is difficult to generalise from laboratory-based studies to what drivers may notice on the road or how they would act in situ. For instance, drivers have less motivation to remain awake and be more or less aware of cues indicating sleepiness in the laboratory environment. Further, there is less motivation to maintain performance and avoid adverse events in the laboratory setting compared to on-road driving, and subjects may be more lenient with their responses because there is less risk in the laboratory. Additionally, although subjective measures of sleepiness have been successfully employed experimentally in the assessment of sleepiness, these measures correlate variably with motor vehicle accident risk (Connor et al., 2002; George et al., 1997; Sauter et al., 2000; Young et al., 1997). Combining subjective measures with more robust, objective performance measures appears to be a more valid way of assessing driving impairment.

2.5.2 On-road and simulated driving

On-road driving studies provide the most accurate assessment of driving performance in a realistic and controlled environment is realistic. These studies use instrumented, dual-control vehicles, and have a ‘co-pilot’ or driving instructor, who sits next to the participant and can intervene with the control of the car throughout the study should an emergency situation arise. These cars may also be equipped with sensors and cameras, which can capture and record different variables such as speed, lane crossing and braking. On-road studies can be conducted in two ways. Firstly, these studies can be performed in a naturalistic driving scenario, in which the participant drives on an actual road under normal traffic conditions (i.e. not closed off to the public). Secondly, on-road driving studies can be performed on an actual road which has been blocked off to other traffic, or on a closed circuit. These methods allow the evaluation of driver performance, safety and acceptability of the technology under typical driving situations.

Relative to actual driving, closed circuit driving studies allow the investigation of experimental manipulations with reduced risk to the participant (driver) and pedestrians. The primary advantage of closed course driving studies is that they provide the most accurate assessment of driving in a controlled environment, in which the environment is realistic (not computer generated graphics) and a driver’s
Peripheral vision is not compromised due to the use of computer projection or monitor.

On-road driving studies are often argued to be the “gold-standard” of determining driving impairment. However, they may not be able to assess the full extent of driver impairment, as only low-level behaviours are measured. Since participants have to stop driving if they feel significantly sleepy for safety reasons, on-road studies cannot measure high-level behaviours such as emergency responses and risk-taking. It is also very expensive to undertake on-road studies, as especially designed, instrumented cars need to be used, and a qualified driving instructor needs to be employed to be the co-pilot during the experimental session. Due to ethical restrictions imposed by ethics committees, it is often difficult to undertake such studies, particularly involving drug administration. Participants are also aware of the fact they are part of an experimental study, and therefore it is difficult to extrapolate motivational, risk-taking, and other factors when participants are examined in the experimental environment. In summary, whilst on-road driving studies provide an ecologically valid measure of driving performance it is difficult to evaluate extreme driving impairment (i.e. to the point of the participant having a crash) because of safety reasons.

As an alternative to on-road driving studies, driving simulators are designed to be reliable and valid in their assessment of driving-related skills. Simulated driving tasks overcome the limitations of on-road driving tasks by assessing driving-related functions in a controlled environment. Driving involves the processing of complex visual, tactile, and auditory information in order to produce a well-coordinated motor output (George, 2001). Driving performance simulators have been designed to include these multiple demands, and tap into the key processes that are involved in the task of driving (Gillberg, Kecklund, & Akerstedt, 1996). Generally, simulated driving tasks include a visual display of a road scene, either projected onto a large screen in front of the participant, or on a computer screen. A computerised steering wheel and pedals are also used. More complex simulators also include road sounds, indicators and gears. Most simulators provide real-world outcome measures, such as lane crossings, crashes and variations in speed. Currently, simulated driving tasks are most beneficial in terms of safety, efficiency and cost, and measure driving-related skills and quantify accident risk (George, Kab & Levy, 2003). As an alternative to on-road driving, simulators also allow for greater experimental manipulation and precise measurement.
of driving related skills without the interference of external factors that operate in a real-life driving setting. Therefore, in this thesis, a simulated driving task will be utilised to assess deficits in driving performance under conditions of sleep deprivation.

There are some limitations inherent to simulated driving tasks. The main difficulty of simulated driving is the lack of sensory feedback (visual, vestibular, proprioceptive). Some participants experience “simulator sickness” due to delays in the motion and visual subsystems, and are unable to complete experiments. The validity of laboratory studies is also reduced because of difficulties in simulating driving task demands adequately, and the absence of personal exposure to risk, therefore participants may not as motivated to perform well on simulated tasks as they are for real-world tasks (i.e. the consequences of crashing on the simulator are not as severe as crashing during actual on-road driving).

It is difficult to reproduce all of the situations and variables that arise in real-life driving in the laboratory setting. To date there has been little validation of driving simulators in relation to sleepiness and on-road driving, and so the effect and extent of sleepiness on real-life driving performance is not fully understood. Strong associations have been reported between on-road driving and simulated driving performance in non-sleepy participants indicating a high transferability of observations between simulated driving and actual driving situations (Lee et al., 2003). Conversely, weaker associations have been drawn between on-road and simulated driving performance under sleep restriction conditions (Philip et al., 2005). This study only used one performance criterion, whereas other skills related to driving (such as reaction time to emergency situations) may produce different findings. Further research is required to evaluate the validity of simulated driving in relation to in situ driving. Results of the present thesis are thus interpreted with these limitations in mind.

As an alternative to simulated driving, neurocognitive measures related to driving may provide more specific information about driving-related performance. Assessment of neurocognitive domains related to driving are more likely to detect subtle underlying impairments in an individuals’ driving performance, which may not be detected by real-world driving or simulator studies.
2.5.3 Specific neurocognitive domains related to driving

Driving is a complex task that involves attention, working and procedural memory, mental flexibility, processing speed and reaction time, visual processing and executive function (Anstey et al., 2005; Szlyk et al., 2002). According to a review by Anstey et al. (2005), studies which have examined the relationship between neurocognitive tasks and crash risk/on-road driving have used a range of tasks, which can be divided into groups according to the general cognitive ability they measure (Anstey et al., 2005). These broad categories are attention and vigilance, visual processes, processing speed and reaction time, working memory and executive function. In the current thesis, only those neurocognitive domains that have previously been shown to be affected by sleep deprivation, specifically those domains related to attention and vigilance, visual processing, processing speed and reaction time, and executive functioning will be examined and discussed.

2.5.3.1 Attention & Vigilance

Driver inattention has been identified as one of the two leading causes of motor vehicle accidents (Treat et al., 1977). Attention, vigilance, and sustained attention, are broad terms used to describe a number of functions, including divided, focused, and selective attention. Focused and divided attention are important aspects of driving since a small driving error, such as a failure or lapse of attention, has the potential to lead to a crash (Brookhuis et al., 2003). In a review of studies reporting associations between cognitive functions and crash risk, low scores on attention tasks were related to increases in crash-risk and on-road driving performance (Anstey et al., 2005). Measures of focused and divided attention and cognitive processing speed have been found to correlate most highly with lane position, driving speed and brake pedal pressure (Anstey et al., 2005). Specifically, visual attention has been demonstrated to be one of the two best predictors of real-world accident frequency (Owsley et al., 1991). Increases in visual tracking performance are associated with better driving, which may relate to drivers paying greater attention to the surrounding road scene (Szlyk et al., 2002). The current thesis examines aspects of visual attention and vigilance.

2.5.3.2 Visual processes

Vision is the primary modality utilised during the task of driving. A number of aspects of vision, including depth perception, visual search, acuity, visual processing,
and ability to attend to the whole visual field, are essential components of driving (Anstey et al., 2005). Tasks examining visual acuity are not associated with crash risk, possibly due to the fact that such tasks do not tap into the visual and cognitive complexities of the driving task (Anstey et al., 2005).

Other visual processes, such as the extent of the visual fields, are more promising predictors of driving outcomes (Roge et al., 2003). Drivers with visual field loss in both eyes have been shown to have a two-fold increase in accidents rates than those with visual field loss in one eye, or no visual problems (Johnson & Keltner, 1983). A restriction of the visual field can also occur in individuals with no physical problem with the eye. “Tunnel vision” refers to a restriction in the functional field of view (Mackworth, 1965). This results in a reduced capacity of the individual to gather information from the entire visual field efficiently. Improvements occur at the focus of attention, due to a perceptual restriction to the focal point, with corresponding functional decrements in the peripheral regions of focus (Easterbrook, 1959). This phenomenon has been described under conditions of increased sympathetic arousal, such as increased stress, and during high demand tasks, for instance it is often reported as the cause of accidents by police officers during high arousal car pursuits (Mills et al, 2001; Williams, 1988, 1995). Tunnel vision has also been reported to occur with inexperienced drivers, where dangerous driving scenarios have promoted perceptual narrowing, increases in fixation duration, and decreases in visual scanning (Chapman & Underwood, 1998). This phenomenon is generally measured experimentally as the differential visual detection of foveal versus peripheral stimuli (Roge et al., 2003). The extent of the functional visual field has been demonstrated as a potential predictor of accident risk (Anstey et al., 2005). Assessment of a driver’s visual field may be a good indicator of how well a driver can perform when sleep deprived.

2.5.3.3 Processing speed and reaction time

Driving is primarily automatised, although it does involve some shifts to controlled processing when routine reactions are insufficient to deal with novel or complex traffic situations (Lundqvist, 2001). Information processing speed, therefore, is important for driving. The driver needs to process multiple stimuli simultaneously, select and filter stimuli according to the road situation, and process the information in a short time frame in order to judge the traffic scene and act appropriately (Lundqvist,
The Digit Symbol Substitution Test (DSST) is one measure that assesses information processing and motor speed, and has been shown to be related to simulated driving performance in normal participants (Szlyk et al., 2002). Other aspects of motor speed, such as simple visual reaction time, are also important skills in adverse situations (i.e. being able to brake quickly if a pedestrian steps out on the road). Moderate correlations have been observed between simple reaction time tasks and on-road driving performance, with stronger correlations observed for complex reaction time (McKnight & McKnight, 1999). A number of simple and complex visual reaction time tasks, and measures of information processing speed, are examined in the current thesis.

2.5.3.4 Executive functioning

Executive, higher order function is required for integrating information and planning a response, and is therefore an essential element of driving (Anstey et al., 2005). Drivers are required to demonstrate flexible, innovative thinking and the ability to revise plans in light of new introspective, sensory and situational information, whilst suppressing distracting information by focusing attention on relevant stimuli (Anstey et al., 2005; Sagaspe et al., 2006). The frontal cortex is largely thought to control attention and executive function (Beebe & Gozal, 2002). Therefore, conditions which affect frontal lobes functioning, such as sleep deprivation, may negatively impact on driving performance. This can potentially lead to a driver taking inappropriate risks, having poor insight into performance deficits, perseverating on thoughts and actions, and having problems making behavioural modifications based on new information. A number of tasks that tap into executive functions have been found to correlate with driving skills and have been used to measure skills related to driving (Daigneault, Joly, & Frigon, 2002; Lundqvist, 2001; Szlyk et al., 2002; Ramaekers et al., 2006a; Ramaekers et al., 2006b). Overall, it appears that impairment in executive functioning may impact on an individual’s ability to drive safely.

2.5.4 Psychophysiological techniques

The behavioural responses measured by neurocognitive tasks are the summations of a number of neural processes. Thus it is possible that only some processes are affected by sleep deprivation, and neurocognitive tasks may not be sensitive enough to detect these effects. Further, some participants may be able to perform relatively well on certain neurocognitive tasks for a short period of time, despite the detrimental effects
of fatigue or sleepiness, by conscious effort and recruiting cognitive reserve (Raz, Deouell, & Bentin, 2001). As such, other techniques have been employed to assess the neural related to cognitive processes; for example, by examining the underlying electrical activity and blood flow activity in the brain. Advances in functional brain imaging techniques have allowed the investigation of the neurophysiological changes that occur before and after sleep deprivation that may underlie behavioural changes. Non-invasive neuroimaging techniques can be classified into two broad groups: electrophysiological techniques, such as event-related potentials (ERPs) and magnetoencephalography (MEG), and haemodynamic techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A description of EEG and ERPs, followed by an outline of fMRI and the advantages and limitations of these techniques will be discussed in Sections 2.4.5.1 – 2.4.5.5.

### 2.5.4.1 What is Electroencephalography (EEG)?

EEG is the neurophysiologic measurement of the electrical activity of the brain by recording from electrodes generally placed on the scalp (Stern et al., 1980). The recording is obtained non-invasively, by placing electrodes on the scalp, usually after preparing the scalp area by light abrasion and application of a conductive gel to reduce impedance between the neural activity and the scalp electrodes. Electrode placement is determined by measuring and marking the scalp using a system called the International 10-20 system (or with a scalp cap that employs the same placements). This system ensures a system of placement that is reliable and reproducible. Each electrode is connected to an input of a differential amplifier which amplifies the voltage between it and a reference electrode (typically 1,000 to 100,000 times, or 60 to 100 dB of voltage gain; Stern et al., 1980). The resultant amplitude is between 10 to 100 µV when measured on the scalp, and between 1 to 2 mV when measured on the surface of the brain. The resulting EEG traces represent the summed electrical signals from a large number of neurons. Electrical currents are not measured, but rather voltage differences between different parts of the brain are recorded.

### 2.5.4.2 What are Event-related Potentials (ERP)?

A common derivation of the EEG is the event-related potential (ERP). ERPs are a series of positive and negative voltage deflections in response to an external event, such as a visual or auditory stimulus. The ERP represents electrical brain activity to
the stimulus, time-locked to the event (Andreassi, 2000). ERPs may both precede and follow the event. The measurement of the components within the signal can be achieved by determining the amplitude and latency. Amplitudes can be measured in relation to another feature in the waveform (‘peak-to-peak’ measure) or in relation to baseline (Rugg & Coles, 1995). They are thought to reflect the intensity of neuronal activity. Latency is measured in terms of the temporal relationship between the component in the waveform and the stimulus or event. This measure provides an indication of the speed of cognitive processing. Examination of the amplitude and latency of the responses may help to determine where in the sequence of information processing sleep deprivation is influencing the behavioural response. Hord et al. (1894) suggested that ERPs may be used as an objective measure of fatigue that do not depend on subjective judgment or complex behavioural tests, while also excluding cases of drowsiness as opposed to fatigue (Hord & Tracy, 1984).

2.5.4.2.1 Visual Processing Components

There are a number of visual ERP components that can be used to examine the integrity of the visual system during a simple visual task. The typical early visual components consist of P100 (a positive component peaking around 100 ms post stimulus) and N100 (a negative component around 100 ms) elicited over occipital sites (Schechter et al., 2005). The P100 is believed to reflect early activation of the primary visual cortex and is related to spatial attentive processes (Mangun & Hillyard, 1991). The N100 early sensory component follows the P100 and is believed to represent activation of the ventral stream structure (e.g. the lateral occipital cortex (Schechter et al., 2005). These components have been shown to be modulated by visual attention an arousal levels, therefore reflecting processing changes in the prestriate visual cortex (Donchin & Coles, 1988; Hillyard & Munte, 1984; Mangun & Hillyard, 1988). This is manifest as progressive reductions in the early visual amplitudes, as attention is directed to locations further from the focal point, reflecting the filtering of early sensory visual information.

One method used to assess the integrity of the early visual system is to examine the magnocellular and the parvocellular visual pathways (Farrag, Khedr & Abel-Naser, 2002; Schechter, Butler & Zemon, 2005). Both of these pathways start in the retina, and project via the lateral geniculate nucleus (LGN), to the primary visual cortex (striate cortex, V1) (Livingstone et al., 1991). The magnocellular pathway has high
temporal resolution, is responsible for the processing of transient visual stimuli (Schechter et al., 2005); (Samar, Parasnis & Berent, 2002), and responds to achromatic patterns of low contrast and coarse detail (Schechter et al., 2005). In contrast, the parvocellular pathway is a sustained system with slower processing speed, with high spatial resolution and chromatic processing (Alexander et al., 2005), and is sensitive to pattern and fine-grained stimulus information (Farrag et al., 2002). Although some crossover does occur between the pathways, the two visual systems are largely independent (Livingstone et al., 1991). Although not an absolute measure, these pathways can be emphasised by assessing responses to different types of checkerboard patterns that evoke different visual ERPs (Mezer et al., 2004; Valberg & Rudvin, 1997). For example, luminance modulation biases the magnocellular pathway, whereas isoluminant chromatic modulation favours the parvocellular pathway (Alexander et al., 2005). The description of these pathways suggests that the magnocellular pathway may be preferentially implicated in driving, in which processing of fast, spatially specific information is required. As such, examination of these visual systems may provide some indication of driving-related visual functioning.

Middle latency components, such as the attentional N100, are more attention-related. The N100 attentional component is elicited primarily over frontal sites (Hillyard & Anllo-Vento, 1998) and is elicited with both visual and auditory stimuli. This component is not directly evoked by the stimulus, but depends on the conditions under which the stimulus is presented (Naatanen & Picton, 1987). For instance, this attentional component is believed to be a general characteristic of the spatial focusing of attention to stimuli, and is enhanced to attended-location stimuli (Hillyard & Anllo-Vento, 1998). Thus, impairments in this visual component may indicate problems with visual spatial attention which may lead to neglect of particular areas on the driving scene, which can have serious consequences.

The P300 (a positive component around 300 ms) is argued to reflect the allocation of attentional resources, updating of memory in response to changing environmental stimuli and the speed of processing (Donchin & Coles, 1988). Thus, the P300 ERP may reflect the driver’s ability to constantly update information coming from the driving scene. These aspects of the ERP are essential component of the driving task, as the driver must continually incorporate incoming information from the road scene
within a small time-frame, and allocate attention appropriately; both of these aspects of driving are related to an increased crash risk (Anstey et al., 2005).

2.5.4.2.2 Auditory Processing Components

There are a number of auditory components that can be used to examine neural processes related to driving. The Startle response involves rapid reflexive increase in muscle tension in the facial muscles surrounding the eye (orbicularis oculi) in response to a sudden loud sound (although it can be evoke with ‘startling’ stimuli from other modalities) (Samuels et al., 2007). This response occurs between 30 ms and 40 ms following stimulus onset, and is quantified in humans via the amplitude and latency of this eye-blink response to the startling stimulus (Lang, 1995). The startle response is believed to be a primitive defensive reflex that serves a protective function, avoiding injury and acting as a behavioural disruption that clears other processors to cope with a possible threat (Graham, 1975). The presentation of a brief, low intensity acoustic stimulus 30 ms to 500 ms prior to the startle stimulus, attenuates the amplitude of the startle response, a phenomenon referred to as the pre-pulse inhibition (PPI; Graham, 1975; Koch, 1999). This inhibitory mechanism is believed to represent a form of pre-attentive sensorimotor “gating”, reflecting mostly involuntary and automatic information processing, where the amount of gating is reflected by the degree to which the reflex response is suppressed by the weaker pre-pulse (Graham, 1975). PPI is believed to reflect an individual’s ability to regulate environmental inputs by ‘filtering out’ irrelevant or intrusive sensory stimuli, thus preventing an overload of information (Kisley, Olincy, & Freedman, 2001; Samuels et al., 2007; Swerdlow & Geyer, 1998). It is also believed to selectively allocate attentional resources to relevant stimuli, and ‘protect’ information contained in the weak stimulus so that it can be adequately processed, without interference from the subsequent startling stimulus (Blumenthal, 1996). In terms of driving, the driver is constantly experiencing substantial incoming sensory information that is competing for attentional resources, and that needs to be attended to in terms of relevance. It is important that the driver can filter out irrelevant information and avoid the overloading of attentional capacity in order to drive safely.

Mismatch Negativity (MMN) is another component of the auditory ERP that can provide information about driving. This is a large negative component, occurring between 100 ms and 250 ms after a deviant auditory stimulus, and is maximal over
fronto-central scalp sites (Näätänen, 1995). MMN is generally evoked using an auditory oddball paradigm following the presentation of an infrequent, deviant auditory stimulus during a series of rapidly presented, homogenous standard tones. The MMN can occur in the absence of attention, and thus believed to be a pre-attentive automatic process (Näätänen, 1990). Driving is a relatively automated task, which requires the constant, pre-conscious, shifting of attention. This aspect of the auditory ERP is an important indicator of how well a driver can automatically attend to different stimuli in the driving environment. If a driver cannot shift attention to a change, or potential hazard, in the road scene efficiently, this may increase their likelihood of having an accident.

The auditory P300 is a late auditory component elicited maximally over parietal regions. Description of this component is the same as for the visual P300 (refer to Section 2.4.5.2.1 for details).

### 2.5.4.3 Conclusions

There are a number of characteristics of ERP which make them advantageous over other techniques for exploring brain activity – ERPs have excellent temporal resolution, and are capable of detecting changes in electrical activity in the brain on a millisecond-level, are non-invasive, employ the only method that measures brain electrical activity directly, are intrinsically multidimensional measures of neural processing and can therefore measure the separate subcomponents of cognition (Luck, Woodman, & Vogel, 2000), and ERPs do not require overt responses in order to measure the underlying neural processes (Luck et al., 2000). The participant does not need to make a decision or behavioural action in order for a neural response to be recorded, and it can detect covert responses to stimuli, such as reading. Often it is important to assess and compare the processes of attended and unattended stimuli without the participants actually responding to unattended stimuli (Luck et al., 2000). This is particularly important in attention and sleep research, where the assessment of lapses in attention and the underlying neural processes that occur during these response omissions are imperative to understanding behaviour. Overall, ERPs provide an objective and quantifiable physiological marker of cognitive impairment, and are sensitive to fluctuations in alertness (Morris et al., 1992). ERP waveforms appear to add support to neurocognitive performance measures, as well as providing clues as to where in the sequence of information processing sleep deprivation is impacting.
One major limitation of ERP analysis is that it has poor spatial resolution in comparison to other functional brain imaging techniques such as functional magnetic resonance imaging (fMRI). Additionally, ERP has relatively imprecise localisation of the electromagnetic field patterns relating to neural current flow (Logothetis et al., 2001). These limitations will be overcome in the current thesis by utilising another neuroimaging technique, functional MRI.

2.5.4.4 Functional magnetic resonance imaging (fMRI)

Over 100 years ago, scientists discovered that changes in blood flow and blood oxygenation, or haemodynamics, in the brain are closely related to neural activity (Roy & Sherrington, 1890). Active nerve cells consume oxygen carried by haemoglobin, and the local response to this oxygen utilisation is an increase in blood flow to the particular region. This typically occurs after a delay of between two and three seconds, and the hemodynamic response rises to a peak of four to six seconds before falling back to baseline levels after a few seconds (Logothetis et al., 2001). This delay between neural activation and the peak haemodynamic response resulting from that activity is referred to as the haemodynamic lag. This leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and changes in local cerebral blood volume in addition to this change in local cerebral blood flow. MR techniques have been used to examine the functionality of the brain, using the natural phenomenon of paramagnetic substances in blood. The magnetic properties of haemoglobin change according to the state that it is in; it is magnetic when oxygenated but paramagnetic and weakly attracted by a magnetic field when deoxygenated. The magnetic resonance (MR) signal of blood is therefore slightly different depending on the level of oxygenation. The technique of fMRI is able to demonstrate cerebral activation arising from changes in intrinsic blood oxygenation level dependant (BOLD) contrast (Ogawa et al., 1990). Higher BOLD signal intensities arise from decreases in the concentration of deoxygenated haemoglobin since the blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility. Increased neuronal activity in an area of the brain is associated with a predictable rise in cerebral blood flow, which alters the local fMRI signal. Therefore, the BOLD response reflects brain areas of increased neuronal activity (Logothetis et al., 2001). Using appropriate scanning parameters, structural MRI can also be used to produce high resolution three-dimensional in vivo images of human brain structure.
The primary advantage of this technique over electrophysiological measures is the spatial resolution. The spatial resolution of MR images is in the order of three to six millimetres. Through the MR images, the rich detailed structure of the brain, deep structures and networks of arteries can be defined, in which specific active brain regions can be identified. Functional MRI is a relatively safe and non-invasive technique with the advantage of determining the neurobiological correlates of behaviour by identifying the brain regions that become “active” during the performance of specific tasks in vivo.

There are some criticisms of the fMRI technique, both as a research tool and in the way its results have been interpreted. The temporal response of the blood supply, which is the basis of fMRI, is poor relative to the electrical signals that define neuronal communication. This has been overcome by some groups by combining fMRI with data collection techniques such as electroencephalography (Foucher et al., 2004). The interpretation of the MR signal, and what information the signal is actually providing is unclear. There is an underlying assumption that the haemodynamic response reflects neuronal activity, that is, a specific region will “light up” when there is increased blood flow to the area while an individual performs a specific task. However, the magnitude and extent of the haemodynamic response may reflect more than just a single energy-requiring process. The haemodynamic response may also reflect the extent of the post-synaptic depolarisation, or neuronal firing. Studies of the relationship between the measured fMRI signal and the underlying neural activity, using intracortical recordings of the neural signals and fMRI responses, clearly demonstrated a direct relationship between spatially localised increases in BOLD contrast mechanism and increases in neural responses elicited by a stimulus (Logothetis et al., 2001). The firing of inhibitory neurons could also contribute a small amount to the overall increase in local energy requirement and the haemodynamic response, however, this would be less energy-consuming than neuronal firing. This implies that some of the regions that appear to be activated during task performance may actually be selectively inhibited (Logothetis et al., 2001). Finally, different brain areas may have different hemodynamic responses, which would not be accurately reflected by the general linear model often used to filter fMRI time signals. These limitations must be taken into account when interpreting fMRI findings.
2.6 Chapter Summary

This chapter has described a number of different techniques which can be used to experimentally examine the task of driving, and highlighted those techniques that will be used in the current thesis. Each technique has advantages and limitations, however, they all evaluate functions related to driving; from examining a drivers’ behavioural disposition, the actual act of driving a simulated vehicle, performing an overt behavioural response, or measuring the underlying neural processes related to driving. The following chapter outlines the experimental literature examining the effects of sleep deprivation on each of these driving-related domains.
CHAPTER 3
EFFECTS OF SLEEP DEPRIVATION ON DRIVING-RELATED PERFORMANCE

Chapter overview

Experimental studies investigating sleep deprivation have demonstrated that sleep loss leads to subjective changes, and a deterioration of a range of performance measures related to driving. The current chapter discusses these deficits in more detail, beginning with experimental methods that have the most relevance for real-world driving, including behavioural dispositional measures of the driver, on-road driving and simulated driving tasks, followed by a description of measures with the greatest experimental control, including neurocognitive tasks related to driving and psychophysiological measures.

3.1 The effects of sleep deprivation on behavioural disposition

Professional drivers often drive for very long periods alone, and introspection is the only feedback that they have available to assess their performance and sleepiness. Some individuals continue to drive despite being significantly sleepy or their performance being impaired. The decision to stop driving for professional drivers is not a simple one and may be based on a number of factors, including safety, social, the degree of subjective sleepiness, the cost of stopping in terms of money and time, and work schedules. These factors may make it difficult for drivers to stop driving even when they are extremely fatigued and therefore they do not take into account the risk involved in their decision to continue to drive (Akerstedt, 1988). This pressure often pushes professional drivers to travel for extended periods without rest, increasing their risk of an accident. This section outlines the laboratory-based and field studies which have examined different behavioural dispositions related to sleepiness and sleep deprivation.
3.1.1 Mood

Changes in mood during periods of sleep deprivation are the most sensitive and consistently reported finding, and are often detected before changes in performance (Pilcher & Huffcutt, 1996). In a meta analysis of literature describing the effects of sleep deprivation on all aspects of functioning, mood was found to be the most affected domain relative to cognitive and motor performance (Pilcher & Huffcutt, 1996). Mood is often assessed by self-report, and therefore may be overestimated. There is some evidence that people differ in their susceptibility to mood and sleepiness, and some may overestimate their mood, whereas others may underestimate it. Using subjective mood ratings in conjunction with objective measures of performance may provide a more robust assessment of an individual’s mood state during sleep-deprivation.

The Profile of Mood States questionnaire (POMS) has been used previously to examine the specific mood changes associated with sleepiness (Dinges et al., 1997; Szuba et al., 1991; de Valck et al., 2001). POMS subscale scores for fatigue, confusion, tension, and total mood disturbance were all found to increase during periods of partial sleep deprivation (Dinges et al., 1997). Similarly, de Valck et al. (2001) found increased rating on the depression subscale of the POMS after subjects were sleep restricted to 4.5 hours in bed the previous night. These POMS scores are also affected by total sleep deprivation and circadian rhythmicity (Wesensten et al., 2002), however, these changes have not been examined extensively. Therefore, the current thesis will examine changes in mood ratings following sleep deprivation to determine whether ratings on different mood domains exist after total sleep deprivation.

3.1.2 Trait-related sleepiness

Some individuals have a chronic increased propensity to fall asleep, reflecting an increase in trait-related sleepiness. As described in Chapter 2, Section 2.5.1, the Epworth Sleepiness Scale (ESS) is a commonly used and well-validated measure of trait-level sleepiness (Johns, 1991). The ESS is commonly used to assess chronic sleepiness in several populations, including transport drivers (Howard, Worsnop, Campbell, Swann, & Pierce, 2000; Maycock, 1997). For instance, Maycock et al. (1997) found a mean score of 5.7 in a group of 996 heavy vehicle drivers from the
United Kingdom. Five percent of the drivers assessed had a score of 12 or more, indicating excessive sleepiness. This is compared to a group of car drivers from the United Kingdom, of whom the mean ESS score varied between 5.7 and 6.6, depending on age (Maycock, 1997). Approximately 7% of these car drivers had a score over 11. The response rate was much lower for these car drivers (51% compared to 90% of the transport drivers), raising the possibility of response bias. Nevertheless, these studies suggested that heavy vehicle drivers in the United Kingdom reported similar sleepiness levels as drivers from the general population. Similarly Carter et al. (2003) directly measured sleepiness in 1,034 professional drivers and 2,608 Swedish residents (Carter et al., 2003). A small but significant difference was found in the mean ESS scores between the professional drivers (ESS = 7.1) compared to the reference group (ESS = 6.7). The transport drivers reported more sleep debt, and were heavier, and so potentially at greater risk of sleep disordered breathing. Australian statistics have also indicated that transport drivers may be sleepier than the general population, with 16% of professional drivers reporting significant sleepiness according to the ESS (Swann, 1999), compared to fewer than 11% in an Australian workers’ population (Johns & Hocking, 1997).

There is some evidence to suggest that high ESS scores may relate to an increased accident risk (Maycock, 1997; Powell et al., 2002). For example, higher ESS scores were reported in drivers who had four or more accidents in the past three years in a sample of car drivers (Powell et al., 2002), and accident liability increased with increasing scores on the ESS in a sample of heavy vehicle drivers (Maycock, 1997). An Australian study of transport workers found that the sleepiest 5% of drivers on the ESS had an increased risk of an accident (odds ratio [OR] 1.91, p = 0.02) and multiple accidents (OR 2.67, p < 0.01) (Howard et al., 2004). Trait sleepiness is therefore an important factor that should be assessed and controlled for in experimental studies of the effects of sleep deprivation. In order to avoid any effects of trait-related sleepiness on performance in the current thesis, drivers’ who report significant trait-level sleepiness, as measured by the ESS, will be excluded.

3.1.3 State-related sleepiness

If a sleep-deprived individual is able to accurately assess their own level of impairment or sleepiness, it may significantly reduce their willingness to engage in risk taking behaviour and subsequently reduce the risk of an accident (Dorrian,
Lamond, & Dawson, 2000). However, there is currently conflicting evidence with regards to whether an individual is able to predict when they are about to fall asleep. There is some evidence that sleepiness is perceived by an individual well before he or she is overcome by sleep (Akerstedt, 1988), with strong associations reported between increasing sleepiness and an increase in the number of incidence on a driving simulator (Reyner & Horne, 1998). However, some people fail to appreciate that a high level of sleepiness is accompanied by a high likelihood of falling asleep (Reyner & Horne, 1998). Anecdotal evidence suggests that, after a sleep-related motor vehicle accident, some people report that they did not fall asleep at the wheel and were not feeling sleepy before the crash (Horne & Reyner, 1999).

A second issue relates to a driver’s willingness to stop driving when sleepy. Regardless of whether a driver is aware of the risks involved with long distance driving and fatigue, a survey of Australian motorists’ knowledge and behaviour reported that, rather than stop driving, drivers are likely to try to fight fatigue when symptoms appear. This common reaction of ignoring sleepiness and continue to drive is extremely dangerous, leading to falling asleep at the wheel of the car and thus losing control of the vehicle. Surveys indicate between 14% and 22% of truck drivers admit to falling asleep at the wheel (Arnold et al., 1997; Hakkanen & Summala, 2000; NTSB, 1995). Drivers have also been shown to continue driving after brief episodes of sleep at the wheel. For instance, in a field study which monitored 80 truck drivers whilst driving at work during different shift schedules, two drivers had several periods of objectively-defined sleep, as identified by EEG, and 10% of drivers had several episodes of brief sleep on EEG recording (Miller, 1997). Despite falling asleep, drivers continued to drive after their sleep episodes (Miller, 1997). These studies indicate that some drivers may not only fail to recognise when they are significantly sleepy, but also do not act upon these subjective cues (i.e. by stopping driving).

There may be differences in individual’s susceptibility to sleepiness (Van Dongen, Maislin, & Dinges, 2004). For instance, some drivers often consider themselves to be safe to drive even when symptoms of severe sleepiness are present (Howard et al., 2004), whereas others rate themselves as too impaired to drive even when their performance has not deteriorated significantly (Arnedt et al., 2000). These findings suggest that drivers may be inaccurate when rating their own impairment before they decide to drive or take part in other tasks which require high levels of vigilance.
Previous studies have assessed subjects’ ability to self-monitor sleepiness when sleep deprived, using a range of subjective measures, including the Karolinska Sleepiness Scale (KSS) (Dorrian et al., 2000; Gillberg et al., 1994). Such measures ask how sleepy or alert subjects feel at that point in time, rather than measuring a propensity to fall asleep over an extended period of time. Field studies have anecdotally noted relationships between real-life incidents and subjective sleepiness (Connor et al., 2002; Torsvall & Akerstedt, 1987). For instance, in a study of train drivers, the driver with the greatest subjective sleepiness, measured by the KSS, had two incidents, one of failing to respond to a signal and another of failing to break (Torsvall & Akerstedt, 1987). There were no incidents with any of the other drivers. Similarly, Akerstedt and Gillberg (1990) evaluated levels of sleepiness in train drivers, truck drivers, and shift workers using both subjective and objective measures of sleepiness. The results showed that the KSS varied accordingly with increasing sleepiness, and was closely related to electrophysiological measures of sleepiness (Akerstedt & Gillberg, 1990). Interestingly, EEG changes were not apparent until subjective sleepiness scores (KSS) had reached a level of 7 to 9 (sleepy to extremely sleepy). Laboratory studies have also demonstrated that subjective sleepiness, measured by the KSS, is related to vigilance and reaction time performance (Gillberg et al., 1994) and objectively measured sleepiness (Akerstedt & Gillberg, 1990). The KSS will be used in the current thesis to determine the level of subjective sleepiness reported by participants following normal sleep and after sleep deprivation.

3.1.4 Sleepiness symptoms

Specific sleepiness symptoms have demonstrated promising results in terms of predicting performance deterioration following sleep deprivation (Gillberg et al., 1994). There have only been a few studies to date which have related specific symptoms of sleepiness to performance measures, and found progressive increases in symptoms rating across the night (Nilsson, Nelson, & Carlson, 1997), and strong relationships between ratings of sleepiness symptoms and performance (Gillberg et al., 1994). Nilsson et al. (1997) evaluated the relationship between drivers’ decisions to stop driving due to “fatigue” and 18 physical symptoms in 80 volunteer male drivers during a continuous drive. Drivers continued driving until they decided to stop because of “fatigue”, with drives lasting up to 4 hours. The symptoms varied from “dizziness” and “sore feet” to “muscles tense”, “drowsy” and “eyes strained”. The
symptoms “feeling drowsy” “eyes strained” and “sore feet” varied in a similar fashion with time and were closely related to each other statistically (Nilsson et al., 1997). These symptoms increased the most with driving time and were reported by 60% of drivers prior to stopping driving. One limitation of this study was that no assessment was made of the relationship between symptoms and performance or objective measures of sleepiness.

A second study by Gillberg et al. (1994) assessed changes in a sleepiness symptom frequency scores during one night of sleep deprivation, and related these to performance measures. The symptoms included “heavy eyelids”, “sand in your eyes”, “difficulties in focusing your eyes”, “irresistible sleepiness”, “difficulties in keeping your eyes open”, “difficulty focusing attention”, “difficulty concentrating” and “periods when you were fighting sleep”. Subjects were asked to rate the frequency of these symptoms, and symptom scores were summed to give a total score. The mean score (range 0 to 5) increased from 0.4 to 2.5 during the course of the night. Significant correlations of 0.5 to 0.7 between subjective measures of sleepiness and reaction time performance were observed in sleep deprived subjects (Gillberg et al., 1994). Symptom scores were more strongly related to performance than the KSS (r = - 0.79 compared to - 0.49). This study raised the possibility that specific sleepiness symptoms may provide better subjective assessment of performance deterioration than general sleepiness scales asking about degree of sleepiness and alertness. Both studies, however, grouped the sleepiness symptoms together to create an overall fatigue score, therefore it is not possible to determine the most useful or relevant sleepiness symptoms.

Field studies have also specifically examined sleepiness symptoms experienced by transport drivers. Summala et al. (1999) found that the most highly reported symptoms during an overnight long-distance real road driving task were muscles going numb, difficulty focusing, increased blink rate, lack of attention, apathy, stomach pain, and incoherent memory (Summala, Hakkanen, Mikkola, & Sinkkonen, 1999). Professional drivers, interviewed in a study by Norbakke et al. (2007), most frequently reported the symptoms “difficulty keeping the eyes open” (55% of respondents), “yawning”, “more frequent eye blinks”, “difficulty concentrating on driving”, and “body movements” prior to their last accident or the last time they were sleepy behind the wheel (Nordbakke & Sagberg, 2007). The current thesis will
examine a number of commonly reported sleepiness symptoms to determine the frequency that these are reported following sleep deprivation.

### 3.1.5 Decision making and judgment of performance

As outlined in Sections 3.1.3 to 3.1.4, sleep deprived drivers experience and recognise a range of sleepiness symptoms prior to falling asleep. Additionally, during night-driving, distinct environmental cues can also give a sleep deprived driver distinct immediate feedback on their declining performance, such as momentary loss of vehicle control (Baranski & Pigeau, 1997). However, sleepiness may also impair an individual’s ability to self-monitor and judge performance impairments (Dorrian et al., 2000). Despite knowledge of prior sleepiness, some drivers continue to drive. For instance, one study reported that three out of four drivers in one study reported that they continued to drive even when feeling too tired to drive (Nordbakke & Sagberg, 2007). They either overestimate their ability to fight off the symptoms of sleepiness, or don’t take the symptoms seriously enough.

Some studies have attempted to examine decision-making ability under conditions of sleep deprivation using validated, neurocognitive tests. Killgore et al. (2006) found that subjects were significantly impaired on the Iowa Gambling Task, a measure of ability to modify decisions under conditions of uncertainty, following 49.5 hours of sleep deprivation. As the sleep deprivation lengthened, subjects were less able to weigh the immediate benefits of short-term rewards against the greater cost of long-term penalties, a cognitive ability that is thought to rely heavily on the prefrontal cortex (Killgore, 2006). These findings suggest that frontal regions of the brain are vulnerable to disruptions by sleep loss, specifically those associated with conscious decision-making processes. Several caveats must be considered in that study, however. The type of task, involving making decisions about which deck of playing cards to choose, may not have reflected driving-related “decision-making” skills, but the sleep-deprived participants may have selected riskier decks to create some excitement during task performance. Additionally, these participants were motivated by monetary rewards. There are no studies to date assessing specific decision-making processes, in particular, in relation to driving-related decisions. It is not clear whether drivers are good at determining when they have reached a level of sleepiness that would increase their accident risk. Additionally, previous studies have not examined whether drivers would continue to drive despite significant objective or subjective
sleepiness. The current thesis will examine drivers’ decision to continue to drive in their current state, after a normal night of sleep or after sleep deprivation, to determine whether sleep deprivation affects the driver’s ability to make appropriate decisions.

3.1.6 Summary

The effects of sleep deprivation on subjective mood and sleepiness are relatively well established. Decline in mood ratings with hours awake is one of the most reliable changes measured. However, less research has been conducted assessing sleepiness symptoms experienced by sleep deprived individuals, particularly in relation to driving, or the decision-making process that individuals take when deciding whether they are safe to drive. This aspect is especially important, as drivers must self-monitor their own performance and sleepiness when driving, without direct performance feedback. Such information has important implications for road safety awareness campaigns and driver education.

3.2 The effect of sleep deprivation on on-road and simulated driving

There is a paucity of research assessing the effects of sleepiness on real-world driving, and no studies to date assessing the relationship between total sleep deprivation and on-road driving performance. On-road studies typically induce sleepiness in drivers by assessing performance during over-night driving, time-on-task effects or by restricting participants’ sleep the night prior to testing. Since there are no direct studies of sleep deprivation on on-road driving, studies using sleep restriction and night-time driving protocols will be described in this section.

Driving time-on-task effects and night-time driving are factors that can impair alertness and subsequent driving performance, particularly if the environment is monotonous (Thiffault & Bergeron, 2003). Truck drivers have increased accident rates with increasing drive time on real roads (Harris, 1977). Experimentally, there have been conflicting findings with regards to time-on-task effects on on-road driving performance. Both speed and lateral lane position increased across the night in one study (Riemersma et al., 1977), but not others (Summala et al., 1999). Summala et al. (1999) examined time-on-task effects in two professional drivers and two private drivers during a long-term night-time drive, using an instrumented car. There was no significant change in drivers lateral lane position over the course of the drive, nor
were there any specific effects of on-coming traffic to high frequency steering wheel inputs, contrary to expectations. This study was only performed on four participants, and therefore is not particularly representative of the population, however, drivers appeared to be able to maintain performance across the night relatively well.

Sleep restriction effects have also been examined in one study using an on-road driving task (Philip et al., 2003). Twenty-two healthy male participants drove in a normal car, equipped with a video camera, on a highway on two occasions; under sleep-deprived (two hours time-in-bed) and non-sleep deprived conditions. Overall, the number of inappropriate lane crossings increased eight-fold when subjects were restricted to two hours of sleep the previous night (Philip et al., 2003). Interestingly, there was a large inter-subject variability between subjects, with some drivers having no lane crossings and others having over 90 crossings, reflecting different susceptibilities to sleepiness on driving (Philip et al., 2003). These studies suggest that the length of time awake and previous hours of sleep has a much greater impact on driving performance than time-on-task effects. Regulations for professional drivers should thus integrate sufficient sleep and rest periods before and during work periods, as well as rest stops during the shift, to allow for necessary sleep.

In conclusion, sleepiness, induced by night-driving, time-on-task effects and sleep restriction can potentially lead to poorer on-road driving performance, with large inter-subject variations. However, these findings have only been demonstrated shown in a limited number of studies, using small subject numbers, with some studies assessing driving in situ, rather than in a controlled setting. Additionally, no studies to date have been conducted examining the specific effects of total sleep deprivation on on-road driving.

Conversely, sleep deprivation studies have predominantly utilised simulated driving tasks, as they have the ability to assess the impact of sleepiness on driving behaviours in a controlled, measurable, and safe environment, as outlined in Section 2.5.2. A number of driving simulators have been developed specifically to measure driving performance in sleepy drivers. These simulators often represent a monotonous driving scenario to unmask any hidden sleepiness. Most driving simulators are performed for around 30 minutes, as this amount of time produces sufficient time-on-task
decrements in performance following a period of sleep deprivation (Pizza et al., 2004).

Only two studies have specifically used a truck simulator to assess sleepiness and fatigue (as a consequence of long driving periods), targeting professional drivers (Gillberg, Kecklund, & Akerstedt, 1996; Stein, 1995). Gillberg et al. (1996) induced sleepiness in their participants by comparing night-time driving with day-time driving, using a 30-minute truck simulator. This small sample of drivers (N = 9) displayed significantly larger increases in variations in speed and lane position in the night condition, particularly towards the end of the driving task. Time-on-task fatigue effects have also been demonstrated in a sample of professional drivers using a truck simulator (Stein, 1995).

The majority of studies in this area have focused on car simulators, in non-professional drivers. One such task is the Aus Ed driving simulator, which simulates a monotonous, night-time drive commonly experienced by professional drivers. This task was specifically designed to be conducive to and test for fatigue and sleepiness, and measures aspects of driving such as speed and steering variations, braking reaction times and crash events (Desai et al., 2007). The AusEd driving simulator has been used in a number of previous studies, and has been shown to be sensitive to the effects of sleep deprivation (Howard et al., 2007; Desai et al., 2006), low dose alcohol (Howard et al., 2007; Vakulin et al., 2007; Banks et al., 2004), and obstructive sleep apnoea (Desai et al., 2006). Increased variations in lane position and speed on the AusEd driving simulator after 24-hours awake has been observed previously in professional drivers (Howard et al., 2007).

Periods of sleep deprivation between 24 hours and 60 hours awake show a clear qualitative decrement in driving-related skills and ability (Arnedt et al., 2000; Arnedt et al., 2001; Fairclough & Graham, 1999; Lenne, Triggs, & Redman, 1998; Thorne et al., 1999). The most consistent finding in the driving literature is the effect of sleep deprivation on variations in lane drift (Arnedt, Geddes, & Alistair, 2005; Arnedt et al., 2001; Lenne et al., 1998), both in lateral and longitudinal position on the road (Roge et al., 2003). One night of sleep loss appears to have significant detrimental effects on subjects’ ability to maintain their position in the centre of the road, and this effect has been demonstrated on various designs of simulator (Arnedt et al., 2005; Arnedt et al.,
Thus, this criterion has been established as an indicator of sleepiness-related performance (Pizza et al., 2004; Riemersma et al., 1977). Studies assessing between 24 hours and 36 hours of sleep deprivation have also demonstrated unnecessary speed decreases (Szlyk et al., 2002), or increases in variation outside the prescribed speed range (Arnedt et al., 2005; Arnedt et al., 2001; Lenne et al., 1998).

Another important outcome variable is off-road events, or “crashes”. The number of crashes increases with increasing hours awake from 36 hours to 60 hours of sleep deprivation (Peters et al., 1999). This study assessed drivers during the circadian low point in the early afternoon, therefore it is unclear whether this observed increased accident rate is due to the effects of extended wakefulness or circadian rhythms. Due to the nature of simulators, and their allowance of drivers to continue to drive immediately following a crash, it is impossible to make quantitative extrapolations from the data. Crash events on simulators are not as reliable or sensitive to sleep loss as other continuous measures (i.e. lane and speed deviations). The number of crashes on a simulated driving task would far exceed the absolute number that would occur in real-world settings, however, simulators provide important information about extreme driving events, and the ability to detect low-probably events (Peters et al., 1999).

Other studies have assessed sleepiness in drivers using different means of experimentally inducing sleepiness, such as shiftwork, partial sleep deprivation and time-on-task effects. Akerstedt (2005) assessed a small sample (N = 10) of shift workers after a normal night shift. Increased lane position variation (from 18 cm to 43 cm) increased number of incidents (two wheels outside the lane markings, 2.4 to 7.6 times) decreased time to first accident and increased subjective sleepiness were apparent during a two-hour drive (Akerstedt, Peters, Anund, & Keckland, 2005). This study highlighted the safety issue of night shift workers driving home the following morning after a shift.

The effects of partial sleep deprivation, or sleep restriction, on driving performance have also been examined, with comparable findings to those of sleep-deprived participants (Thorne et al., 1998). Studies have generally restricted sleep to between three hours and five hours time in bed on the previous night before testing (De Valck & Cluydts, 2001; Horne, Reyner, & Barrett, 2003; Rupp, Arnedt, & Carskadon,
Increases in lane drifting (De Valck & Cluydts, 2001, Horne et al., 2003; Rupp et al., 2003) and speed deviation (De Valck & Cluydts, 2001) relative to a control group have been found, with increased out of lane incidents reported in some (Rupp et al., 2003), but not all studies (Peters et al., 1999). Low numbers (N = 11 to 12) of young healthy participants may explain the discrepancy in these findings. Other studies (Horne & Baulk, 2004) have used larger samples, and found subjective sleepiness measures correlated with lane drifting following five hours time in bed, however testing was performed during the mid-afternoon therefore it is difficult to decipher whether these performance changes are due to sleepiness or circadian effects. In a large study (N = 66) of commercial drivers who were sleep restricted to three-hours per night for one week, accident rates increased and attentional decrements became apparent (Thorne et al., 1998). The effects of cumulative sleep deprivation appear to mostly reflect those of total sleep deprivation.

Studies examining the effects of acute sleep deprivation often do not only assess the detrimental effects of sleep loss on performance, but also circadian rhythm influences. A clear circadian modulatory effect has been observed on simulated driving performance, with improved performance during the late morning and early evening after a night without sleep (Lenne et al., 1998). Similarly, Moller et al. (2006) demonstrated significant diurnal fluctuations in speed and steering variability in the afternoon compared to the morning driving session. However, others (Horne & Baumber, 1991) have found no variations in performance on a 40-minute driving task across the day and evening. Studies examining daytime performance after a restricted nights’ sleep can evaluate the effect of acute sleep loss without any increased sleepiness or natural variations in performance due to circadian influences, and this is one factor which previous studies have not consistently controlled for. It is important to account for circadian effects in experimental studies. In order to assess the pure effects of sleep loss on performance data needs to be collected during circadian peak periods.

There is some debate regarding the length of the driving task and its ability to detect sleep-related changes in performance. Some authors argue that time-on-task effects cannot be demonstrated with a task as short as 30-minutes (Richter et al., 2005), however others have shown clear decrements with sleep loss (Gillberg et al., 1994), and restricted sleep (Gillberg et al., 1996) using a 30-minute task. Pizza (2004) also
reported time on task effects in a simulator task, with subjects’ performance deteriorating significantly over a 30-minute period. Thus, a 30-minute simulated driving task length will be utilised in the current thesis.

The majority of these studies have used relatively small participant numbers (N < 20), who are generally male, non-professional, young, healthy subjects (Akerstedt & Kecklund, 2001; Lyznicki et al., 1998; McCartt et al., 1996; Pack et al., 1995). Less research effort has been applied to professional or commercial drivers who have an increased risk of sleep-related accidents compared to other road users (McCartt et al., 2000).

3.2.1 Summary

The effects of sleep deprivation on simulated driving tasks are consistent with the well-identified night time peak of motor vehicle accidents. Sleep deprivation paradigms of as little as 24-hours result in increases in lane position variability, changes in speed variations, and increased crashes. Changes have also been shown in simulator task lengths of 30 minutes (Gillberg et al., 1994), and performance appears to be modulated by circadian effects, which should be taken into consideration when designing driving protocols. The effects of sleep deprivation on driving have only been examined in small numbers of participants, and have not been systematically examined in professional drivers.

3.3 The effects of sleep deprivation on neurocognitive domains related to driving

Changes in sleepiness due to sleep deprivation is associated with a variety of cognitive deficits (Banks & Dinges, 2007; Rogers, Dorrian, & Dinges, 2003; Kim et al., 2001). There appears to be differences in the types of cognitive task which are affected by sleep deprivation; some tasks appear to be more affected, while others are less susceptible to the effects of sleep loss. The literature examining the effects of sleep deprivation on the driving-related neurocognitive functions outlined in Chapter 2 is reviewed in Sections 3.3.1 – 3.3.4.
3.3.1 The effect of sleep deprivation on attention & vigilance

One of the most robust findings in the sleep literature is the effect of sleep deprivation on vigilance and the ability to sustain attention (Koslowsky & Babkoff, 1992; Murphy et al., 2006; Rogers, Dorrian, & Dinges, 2003). Slowing of reaction times and performance errors, in association with lapses in attention, have been demonstrated after as little as 18 hours awake (Dinges et al., 1997), and during the circadian nadir (Jewett, Dijk, Kronauer, & Dinges, 1999; Van Dongen & Dinges, 2003) Such changes can have significant effects on tasks that require motor co-ordination, speed and visual attention, such as driving. For instance, impaired vigilance has been associated with higher motor vehicle accident rates (Findley et al., 1995).

The predominant explanation for the sleep loss-related performance decrements has been the “lapse hypothesis” (Williams, Lubin, & Goodnow, 1959). Sleep-deprived participants are believed to perform at a relatively good level until a microsleep (a brief period of sleep) occurs, which in turn causes the occurrence of a lapse in attention (i.e. reaction times greater than 500 ms), or brief periods when no response occurs at all. The frequency and duration of microsleeps appear to increase as a function of sleep deprivation (see Section 3.3.2; Dinges et al., 1999; Howard et al., 2002).

Not all of the cognitive changes induced by sleep deprivation can be explained by the lapse hypothesis. Variation in psychomotor performance reflects more than just lapses in attention; it also includes normal timely responses, slowing of reaction times over time, and errors of commission (i.e. responding when no stimulus is present). For example, Williams (1959) demonstrated that the difference between fastest and slowest responses became greater as lapses increased in duration; and as lapses increased in frequency there was an associated increase in long reaction times in subjects who were sleep deprived for 72 hours (Williams et al., 1959). This suggested that sleep-deprived subjects are capable of performing at a similar level to their best reaction times of baseline testing during some trials (i.e. are able to compensate for their sleepiness to some extent), however there is a large increase in the duration of the longest reaction times. Therefore, over time the difference between subjects’ poorest performance and best performance becomes greater. This “state instability” hypothesis (Doran, Van Dongen, & Dinges, 2001) posits that as sleep loss increases, variability in performance increases as a function of the interaction between the
homeostatic drive for sleep and the endogenous circadian drive for wakefulness, and
the compensatory effort exerted by the participant. The effects of sleep deprivation on
sustained attention and vigilance will be explored in the current thesis, using a well-
validated measure of vigilance - the Psychomotor Vigilance Task.

3.3.2 The effect of sleep deprivation on visual processes

As described in Chapter 2, Section 2.3, microsleeps are brief periods of sleep which
can occur during sleep deprivation, and often involve slow eyelid closure. Importantly
for driving, responsiveness to environmental stimuli is impaired or completely absent
during a microsleep (Akerstedt, 1988). This can therefore result in accidents due to
failure to respond appropriately to hazards, such as avoiding obstacles, or adjusting
steering and speed. Assessment for microsleeps has also been used to objectively
measure sleepiness in sleep-deprived normal individuals on a driving simulator, and
has been shown to correlate negatively with simulated driving performance
(Wierwille & Ellsworth, 1994). Microsleeps also result in speed variability and an
increase in lane drift, which may result in road accidents (Riemersma et al., 1977).

A microsleep index should reflect impaired performance on objective tasks relevant to
the driving and ideally predict outcomes, such as accident risk. Field studies have
been relatively unsuccessful in demonstrating associations between measures of
microsleep and performance, despite microsleeps being present. Presumably many
periods of microsleep can occur before an episode results in an accident or other
measurable error in a field study (Lisper, Laurell, & van Loon, 1986). For instance, in
an on-road study by Summala and colleagues, drivers did not experience microsleeps,
or period of increased theta activity and slow eyelid closure, until they had been
driving for eight hours, and deprived of sleep for between 21 and 25 hours (Summala
et al., 1999). All microsleeps occurred in the morning, between 04:30h and 09:30h,
after being awake for 21.5 hours. One of the professional drivers completed the
driving task without experiencing any microsleeps, whereas one of the private drivers
had to stop the task for safety reasons having experienced several microsleeps just
prior to interrupting the task (Summala et al., 1999). This study highlights the
importance of further research in the proper detection of slow eye closure and
microsleeps. Overall, inattention and microsleeps can lead to drifting into an adjacent
lane or off the road, which are the most common type of sleep-related accidents
(Thiffault & Bergeron, 2003).
As mentioned in Chapter 2, Section 2.3, not all microsleep episodes are associated with eye closure. Therefore, other aspects of visual functioning may be impaired and contribute to road crashes in sleep deprived drivers. Chronic partial sleep deprivation and acute sleep deprivation contribute to deficits in visual functions (Dinges et al., 1997; Williamson et al., 1996). One specific aspect of visual attention that may relate to increased accident risk is ‘tunnel vision’. ‘Tunnel vision’ refers to a restriction in the functional field of view (Mackworth, 1965) (See Chapter 2, Section 2.3 for details). Impaired visual attention or visual field abnormalities may result in failure to detect a road hazard, particularly in the peripheral visual field, and are associated with increased road crash risk (Owsley et al., 1991; Rumar, 1990) and impaired simulated driving performance (Szlyk et al., 2002). This may help to explain motor vehicle accidents, particularly single vehicle incidents, involving driving off the road. Sleep loss and circadian rhythm disturbance appear to impair some aspects of visual functioning, however current findings from behavioural studies assessing peripheral vision neglect are conflicting. For example, sleep deprivation between 18 and 64 hours has been shown to cause a reduction in an individual’s ability to attend to the whole visual field in a number of laboratory studies (Mills et al., 2001; Roge et al., 2003; Russo et al., 2002; Russo et al., 2003; Russo et al., 1999). Prolonged monotonous tasks (such as driving) promote tunnel vision as well, so that sleep deprivation and driving together have a synergistic effect on visual field impairment (Roge et al., 2003). However, a more recent replication study failed to find this effect following 40 hours of wakefulness (Kendall et al., 2006). This contrary result is particularly important given that the data reported in the positive studies were derived from smaller samples (N < 10), and consisted of specific sample populations (air force pilots and younger drivers), which together with the negative study leaves the link between sleep deprivation and tunnel vision in some doubt. Additionally, tunnel vision has only been assessed using behavioural tasks, with no previous attempts to assess the related neural activity. Therefore, further studies employing larger more generalisable samples are required to determine whether acute sleep deprivation can cause reduced peripheral visual function. The current study will examine two aspects of visual functioning; firstly, microsleeps, by assessment of slow eyelid closures, during driving simulation; and secondly, peripheral field functioning, by examining behavioural performance and neural activity in the visual cortex (See Section 3.4.5.3 for details).
3.3.3 The effect of sleep deprivation on processing speed and reaction time

One night of sleep deprivation results in a significant detrimental effect on simple visual reaction time tasks of as short as ten minutes (Dinges et al., 1997), with some studies demonstrating negative effects after five minutes of testing (Glenville et al., 1978). Additionally, these decrements are evident despite these tasks providing constant feedback to participants regarding their on-going performance. It is likely that these effects are due to lapses in attention and vigilance, causing intermittent increases in reaction time, thereby increasing the overall mean response times (Doran et al., 2001). Alternatively, these changes may a direct result of slowing in information processing speed. As reported in Chapter 2, Section 2.5.5.3, the Digit Symbol Substitution Test (DSST) is a measure of information processing and motor speed. A decline in DSST performance has been observed in sleep restricted and total sleep deprivation (Van Dongen et al., 2003), in individuals with excessive sleepiness (Pack, Dinges, & Maislin, 2002), and following 19 hours of sleep deprivation (Williamson & Feyer, 2000). However, others have reported no change in DSST performance after one night of sleep deprivation (van Steveninck et al., 1999). The current study will examine changes in performance of a simple and choice visual reaction time task, and the speed of information processing following sleep deprivation.

3.3.4 The effect of sleep deprivation on executive functions

The prefrontal cortex (PFC) comprises around 30% of the total cortical mass, and has the highest metabolic rate of all cortical regions, thus it is believed to work the hardest during wakefulness (Beebe & Gozal, 2002). As such, the PFC requires the greatest recovery during sleep, and it is theorised that the PFC is the first brain region to suffer as a consequence of sleep loss, and is particularly sensitive to homeostatic pressure (Horne, 1993). The PFC is particularly vulnerable to one night of sleep deprivation in neuroimaging studies (Drummond & Brown, 2001; Thomas et al., 2000).

However, there have been conflicting findings regarding the impact of sleepiness on the performance of executive tasks. Complex cognitive tasks involving higher cognitive functions have often been regarded as insensitive to sleep deprivation (see Harrison & Horne, 2002 for a review) with some studies reporting no difference in
performance between sleep deprived and non-sleep deprived states (Binks, Waters, & Hurry, 1999). For instance, after one night of sleep deprivation, performance on the Stroop task was comparable to the control group, in both number of errors and time taken to perform the task. However, it was suggested that the tasks employed in this study were not sensitive enough to detect mild frontal lobe impairments associated with sleep deprivation (Binks et al., 1999). Additionally, the samples used were young participants, and may have been able to maintain attention and motivation during the task performance. Similarly, Sagaspe (2006) found no interference effect associated with sleep deprivation, however, this study did find a cognitive slowing in reaction times with sleep deprivation in the incongruent trials. It is thus believed that sleep deprivation may cause impairments in executive functions under more demanding circumstances (Sagaspe et al., 2006).

These findings, however, are contrary to those of other researchers, using different executive functioning tasks, including divergent and flexible thinking (Harrison & Horne, 1999), random number generation (Gottselig et al., 2006) novel language performance (Harrison and Horne; 1998), dichotic temporal order judgement (Babkoff, 2005), integrative functioning (Nillson, 2005), and grammatical reasoning (Lamond & Dawson, 1999). These impairments were independent of working memory and psychomotor vigilance; factors which were unaffected by sleep deprivation. These studies lend support to the theory that the PFC is adversely affected by, and therefore vulnerable to, sleep loss (Harrison & Horne, 2000).

The discrepancy between previous studies may be explained by the different methodologies employed, lengths of sleep deprivation utilised and the use of tasks which are thought to tap into different aspects of executive function (see Jones & Harrison, 2001 and Harrison & Horne, 2002 for reviews). Further, all of the previous studies have employed a between-subjects design, utilising a control group rather than a repeated-measures design. As such, it is currently unclear whether sleep deprivation significantly impairs executive functioning performance. The current thesis will examine whether performance of a well-validated measure of executive functioning is impaired after acute sleep deprivation. Impairments in higher-order functions may impact on a drivers’ ability to demonstrate flexible thinking and make behavioural judgements based on new information from the road scene.
3.3.5 Summary

Sleepiness due to sleep deprivation impairs a range of neurocognitive domains related to driving, including reaction times and vigilance, information processing, and some aspects of higher cognitive functioning (Akerstedt, 1988; Dinges et al., 1997; Russo et al., 1999; Williamson et al., 1996). Additionally, the concept of tunnel vision may provide some explanation for increased accident risk in sleep deprived drivers. To date, this aspect of visual functioning has not been adequately studied in sleep-deprived subjects, and there are currently mixed findings with regards to this phenomenon. Further, these aspects of driving-related performance have not been fully examined in professional drivers. Such impairments can have significant detrimental effects on driving.

3.4 The effect of sleep deprivation on psychophysiological techniques

It has been argued that neurocognitive findings do not easily explain many of the effects of sleep deprivation seen in the real-world setting (Roge, Kielbasa, & Muzet, 2002). As described in Chapter 2, Section 2.5.4, smaller, underlying neurophysiological changes may occur with sleep deprivation that cannot be assessed with overt behavioural measures. Additionally, although the neurocognitive aspects of functional impairment following acute sleep deprivation are relatively well established, the neurochemical underpinnings of these impairments are not known. Sleep loss causes changes in the levels of a range of neurotransmitters, including serotonin. Sleep deprivation can affect brain catecholamines, such as dopamine and noradrenalin (McCann et al., 1992). These neurotransmitters in turn can directly impact on cognitive functioning, which may explain the changes in performance demonstrated with sleep loss. Electrophysiological studies can provide some insight into the neurochemical systems that direct cognition. For example, the noradrenergic systems modulate sensory inputs to the cortex, which is believed to influence cognitive processing by enhancing the ability to discriminate between relevant and irrelevant sensory stimuli (McCann et al., 1992). For these reasons, electrophysiological techniques may provide additional insight into these underlying mechanisms and give a more detailed explanation of the effects of sleep deprivation.
3.4.1 The effect of sleep deprivation on event-related potentials (ERPs)

One way to examine the effects of sleep deprivation on cognitive functions related to driving is by using visual and auditory ERPs. In addition to quantifying the effects of sleepiness, ERPs’ provide insight into the associated altered brain activity following sleep deprivation (Broughton, 1982).

3.4.1.1 The effect of sleep deprivation on visual processing

As stated in Chapter 2, Section 2.5.3.2, driving is primarily a visual task. There have been a few, limited studies examining the effects of sleep deprivation on visual processing. Early visual sensory components of the ERP (around 70 msec to 90 msec post-stimulus) are influenced by attention and arousal levels in well-rested participants (Mangun & Hillyard, 1988; Morris et al., 1992), however there have been mixed findings with regard to visual ERPs and sleep deprivation. Some studies demonstrated effects on early, but not late components after up to 48 hours of sleep deprivation (Hord & Tracy, 1984; Krull, Smith, Sinha, & Parsons, 1993), whereas others demonstrated effects on later ERP components after 40 hours of sleep deprivation, related to slower reaction times (Corsi-Cabrera, Arce, Del Rio-Portilla, Perez-Garci, & Guevara, 1999). The latter study employed a task that involved foveal presentations, whereas Krull et al. (1993) utilised a task that covered the whole visual field. Hence, sleep deprivation may have differential effects on foveal and peripheral processing. Given that these studies did not report the time of day of testing, circadian factors may have altered the evoked responses in addition to the effects of sleep deprivation.

As described in Chapter 2, Section 2.5.4.2.1, a method used to assess the integrity of the early visual system is to examine the magnocellular and the parvocellular visual pathways (Farrag et al., 2002; Schechter et al., 2005). Only one study to date has examined the ERP response to magnocellular-weighted stimuli following sleep deprivation (Krull et al., 1993). Significant reductions in the occipital N100 latency following 22 hours of sleep deprivation were observed, with no change in amplitude. Reductions to the P100 component during early visual processing, particularly within the magnocellular visual system, have previously been implicated in attentional dysfunctions (Kim et al., 2006; Schechter et al., 2005). However, a differential effect of the magnocellular and parvocellular pathways was not examined in this study, and
is an area that may provide further insights into the effect of sleep deprivation on visual cognitive function (Mills et al., 2001; Rogers et al., 2003; Russo et al., 2002).

As stated in Chapter 2, Section 2.5.4.2.1, the mid-latency attentional component is believed to be a general characteristic of the spatial focusing of attention to stimuli, and is enhanced to attended-location stimuli (Hillyard & Anllo-Vento, 1998). Currently, there are no studies examining the effects of sleep deprivation on this attentional component.

The effects of sleep deprivation on later cognitive processes associated with visual stimuli have generally demonstrate a reduction in amplitude after participants are sleep-deprived for between 18 and 38 hours (Lee, Kim, & Suh, 2003; Morris et al., 1992; Tsai, Young, Hsieh, & Lee, 2005). These changes in P300 ERP are evident prior to developing behavioural impairment (Morris et al., 1992), thus, the P300 may be an early marker of sleepiness. After longer periods of sleep loss, behavioural responses occur, and these are correlated with the attenuated ERP amplitude (Lee et al., 2003). The change in this later complex are believed to be related to delays in information processing, rather than attentional problems (Lee et al., 2003). Some studies have also reported increased P300 latencies following sleep deprivation, which may indicate cognitive slowing associated with sleep deprivation (Morris et al., 1992).

Currently, there is conflicting data as to the effect of sleep deprivation on all components of visual processing. Sleep deprivation appears to influence the later components, with an associated decline in behavioural performance. The effects of sleep deprivation on these different stages in the visual information processing chain will be examined in the current thesis.

### 3.4.1.2 The effect of sleep deprivation on auditory processing

As outlined in Chapter 2, Section 2.5.4.2.2, auditory ERP analysis can also provide additional information about underlying neural processes related to driving. For example, auditory sensory gating, measured by the pre-pulse inhibition of the startle response, examines the ability of an individual to efficiently filter out extraneous sensory information and avoid overload, which is an important element of safe driving. Although this process is a very simple and primitive response, the magnitude
of the response can be modulated by different internal and external factors, such as diurnal rhythm (Davis & Sollberger, 1971). The effect of sleep deprivation on this response has not been examined in humans, therefore this study will examine this effect to see if there is any impairment in the startle response which may impair a sleep deprived driver’s ability to filter out information and reduce their effectiveness to drive safely.

Auditory change detection, measured by mismatch negativity (MMN), is another aspect of early neural processing that can affect driving performance. This “pre-attentive” process is intuitively believed to be independent of attention (Naatanen, 1990). However, attenuation of this component has been demonstrated in both objectively and subjectively defined sleepiness (Raz et al., 2001; Sallinen & Lyytinen, 1997), and other sleep-related measures, such as sleep onset (Campbell & Colrain, 2002; Pressman & Fry, 1989; Winter et al., 1995), circadian effects (Sallinen & Lyytinen, 1997), and exhaustion (Humphrey, Kramer, & Stanny, 1994). In one study, the change detection response was attenuated during a night of sleep deprivation, and that this paralleled behavioural performance (Sallinen & Lyytinen, 1997). However, this study was limited to the effect of sleep-time fatigue, induced by circadian rhythms, and did not address the effect of total sleep deprivation. MMN elicited by pitch deviants are still evident after acute periods of sleep deprivation up to 36 hours, however the amplitude of the change detection process is markedly attenuated (Raz et al., 2001). MMN, which is implicated in attentional switching to a change in unattended auditory stimuli, therefore appears to be vulnerable to sleepiness. Overall, these studies indicate that pre-attentive processes are not entirely immune to extended wakefulness, and indicate that sleep loss may degrade pre-attentive detection of environmental irregularities, and consequently may affect the reflexive shift of attention induced by these changes. However, these studies need to be replicated with larger samples in order to gain a better understanding of the effects of sleep deprivation on this process. Behaviourally, a decline in MMN is accompanied by an impaired awareness of the external environment, which may be detrimental to the task of driving.

The auditory P300 is elicited when an individual is required to make a decision based on the auditory information they are receiving. These processes are generally shown to be attenuated by drowsiness (Broughton, 1982), circadian rhythms (Higuchi, Liu,
Yuasa, Maeda, & Motohashi, 2001), sleep deprivation (Gosselin, De Koninck, & Campbell, 2005; Kaneda et al., 1999), and during light drowsy states (Koshino, Nishio, & Murata, 1993). Sleep deprivation studies have demonstrated amplitude reductions in the auditory P300 after 36 hours (Gosselin et al., 2005) and 24-hours (Kaneda et al., 1999) of sleep deprivation. This was argued to reflect a reduction in attentional capacity and central processing following sleep deprivation (Gosselin et al., 2005; Kaneda et al., 1999). The auditory P300 therefore appears to be a sensitive measure of attentional change following sleep loss.

3.4.1.3 Summary

There is a paucity of research examining the effects of sleep deprivation on electrophysiological measures of brain functioning. Although later visual and auditory EPR components appear to be adversely affected by sleep loss, early sensory components have not been examined in detail in sleep deprived subjects. The different components outlined above each have an important, differential relationship to driving, and therefore better clarification of the sleep deprivation effect on these processes may help to uncover aspects of driving which may be affected in sleepy drivers.

3.4.2 Functional neuroimaging measures of sleep deprivation

Impairments in cognitive performance demonstrated during sleep loss reported above suggest that some underlying brain physiological mechanisms are altered in sleep deprived subjects. Neuroimaging techniques, including functional MRI and positron emission tomography (PET), have been used to investigate the in vivo brain activity changes associated with neurocognitive abnormalities following sleep loss, during performance of a range of neurocognitive tasks (Chee & Chuah, 2007; Chee & Choo, 2004; Drummond et al., 2000; Drummond et al., 2004; Drummond, Gillin, & Brown, 2001; Habeck et al., 2004; Portas et al., 1998; Thomas et al., 2000; Wu et al., 1991).

The following sections will outline the current literature pertaining to the effects of sleep deprivation on neuroimaging, firstly describing task-related neural changes, then outlining studies which have examined the relationship between performance and neural activations, and describe the effect of task complexity and individual differences on neural responses following sleep deprivation.
Functional neuroimaging has shown that sleep deprivation reduces prefrontal metabolism and alters neurochemistry (Dorsey, 2000; Thomas et al., 1998), as well as affecting number of other regions associated with attention and vigilance (Thomas et al., 2000). The brain regions that display changed activity patterns after sleep deprivation are dependant on the type of task, so that different cognitive demands elicit differing cerebral responses to sleep deprivation. The first neuroimaging study of brain activity changes associated with sleep deprivation used PET and $^{18}$Fluorine-2-deoxyglucose (FDG); a marker for regional cerebral glucose metabolism (CMRglu) and neuronal synaptic activity (Wu et al., 1991). This study described significant global decreases in glucose metabolism following 32-hours of sleep deprivation during performance of a Continuous Performance Task, a visual vigilance task (Wu et al., 1991). A decrease in metabolic activity in the thalamus, basal ganglia and cerebellum was observed, suggesting that sleep deprivation dampens the brain’s rostrally projecting arousal mechanism (Wu et al., 1991). This was further supported by their findings of an association between decreased performance on a visual vigilance task and decreases in absolute regional metabolism in the thalamus and cerebellum, and relative metabolism in the temporal lobe (Wu et al., 1991). Although this study pioneered the literature on sleep loss and brain activation, the findings should be treated with caution as only eight subjects were recruited.

Thomas et al. (2000) used a more robust statistical approach to quantify global and regional brain activity during cumulative, extended sleep loss, at baseline, 24, 48 and 72 hours awake, in a larger sample (N = 17). A global deactivation of 8% in cerebral metabolic rate was demonstrated, with the orbitofrontal cortex showed the greatest decrease in glucose metabolism (Thomas et al., 2000). Additionally, relative deactivations in metabolic rate, greater than the global decrease, were demonstrated in the thalamus, and prefrontal and posterior parietal cortices (including the posterior cingulate and precuneus) following 24 hours of sleep deprivation during performance of a serial addition/subtraction task. The largest decrease was observed in thalamic regions; the only region in which the relative decrease was associated with changes in alertness. However, as sleep deprivation continued to 48 hours of wakefulness, rebound elevations in regional activations were observed in visual and motor areas (occipital cortex, fusiform gyri, cerebellar lobes, precentral gyrus and supplementary
motor cortex). Lateral occipital activation has been shown in previous studies of visual vigilance and working memory tasks at rest, as task difficulty increased and performance declined, and thus subjects’ effort to perform the task increased (Coull et al., 1996). Although the task did not become more difficult in the Thomas et al. (2000) study, it may have appeared to do so for these sleep deprived subjects. This view is supported by the association between a decline in task performance and decreased activation in the visual cortex. Additional regions of cortex therefore appear to be recruited in an attempt to sustain alertness, and maintain performance, reflecting voluntary control of attention; a theory has since been supported by a number of studies utilising functional MRI.

Increased activation of the thalamus (an important mediator of alertness) and prefrontal cortex (higher-cognitive processes) has been reported using fMRI during the performance of both simple, attention-related tasks, and complex cognitive tasks after sleep deprivation compared to non-sleep deprived states (Drummond & Brown, 2001; Drummond et al., 2000; Drummond et al., 1999; Portas et al., 1998). These changes reflect altered neuronal activity whilst performing the task, rather than activity at rest. Portas and colleagues examined neural activations during performance of a selective attention task in a small number of subjects (Portas et al., 1998). Arousal was modulated using one night of sleep deprivation and low levels of caffeine. Task duration was relatively short, and no significant differences between different arousal levels for attentional performance were observed. fMRI scanning showed an increased activation of the ventrolateral thalamus after 24-hours of sleep deprivation. Increased activation in the thalamic system during low arousal was hypothesised to be related to the effort of maintaining attention while performing the task, since no performance deficit was observed. This study did not utilise a repeated-measures design, and also had limited power (N = 5 in final analysis), thus these findings should be taken with caution.

Some (Chee & Choo, 2004; Drummond et al., 2004), but not all (Habeck et al., 2004), MRI studies have also reported increased frontal activation improvements during more complex task performance following sleep loss. For instance, Drummond and colleagues examined the effect of different task demands on brain activations following 35 hours of sleep deprivation and after a normal night of sleep (Drummond et al., 1999). Performance on a verbal learning task and an arithmetic task was
measured in 13 participants. After normal sleep, performance of the verbal learning
task, which is dependent on PFC involvement (Harrison, Horne, & Rothwell, 2000),
resulted in increased left PFC, premotor and temporal activations. After 35 hours of
sleep loss, participants showed a significant decline in free recall performance.
Significant brain activation was increased in discreet regions of the PCF, (left middle
frontal gyrus, right inferior frontal gyrus), and parietal lobes were observed, compared
to normal sleep. These regions are involved in working memory, short-term memory
storage and tasks with high cognitive load. There was a reduced activation in the
temporal lobes, however. During performance of the arithmetic task, activations were
observed in bilateral dorsolateral PFC, premotor, cingulate, visual regions and parietal
lobes following normal sleep. After sleep deprivation, however, only left superior
parietal lobe and left premotor area were significantly responsive to task demands.
Performance decrements were also noted, in line with the study by Thomas et al.
(2000) using the same task. Taken together, these studies suggest that sleep loss may
alter overall patterns of cerebral activation during task performance, and highlight the
task-specific nature of activation during sleep deprivation. This study provides
support for the PFC vulnerability hypothesis, but also indicates that other brain
regions may be similarly affected by sleep loss (e.g. parietal lobes).

A more complex, divided attention task was also shown to significantly increased
BOLD activation in both the PFC and parietal lobes, particularly in the right
hemisphere, after 35 hours of sleep deprivation, relative to rest, when performance
was well maintained during both sessions (Drummond & Brown, 2001). Similarly,
Strangman (2005) found increased activations associated with a shorter (3.2 minute),
but more complex, open-ended 3-D navigation task following 27-hours of
wakefulness. The most robust finding, demonstrated in all six participants, was an
increased activation in the posterior superior temporal gyrus following sleep
deprivation, compared to normal sleep (Strangman et al., 2005). This region was also
identified in the studies by Thomas (2000) and Drummond (2004). Other areas related
to visuospatial processing and spatial attention, including the right temporal lobes and
angular gyrus, were also significantly more activated after sleep deprivation. There is
some contention whether the region reported in the Strangman (2005) and Drummond
(2001) studies are accurate, since the STS and parietal regions align each other.
However, the study by Strangman et al. (2005) is limited by low study power (N = 6).
In contrast, it appears that performance of more simple tasks may not be as well preserved after sleep loss, and this may related to a decline in cerebral activation. For instance, arithmetic performance declined with sleep loss in the same participants, and the same task design and length, and this was associated with a relative decrease in activation in the PFC from normal sleep (Drummond et al., 2000). Working memory performance has been shown to decline with 30 to 48 hours of sleep deprivation, and this correlated with decreases activation primarily in the parietal region (Habeck et al., 2004; Mu et al., 2005). These findings suggest that sleep deprivation may affect retrieval of previously encoded objects, by disrupting perceptual processing, thereby reducing performance levels. These studies used significantly longer task duration (13 and 31 minutes respectively) which may have contributed to the decline in performance following sleep loss. These studies suggest that increased activation may aid task performance, whereas a decrease in neural recruitment is associated with a decline in performance. This has been further investigated using correlation analyses.

3.4.2.2 Relationship between neural activations, performance and sleepiness

The relationship between brain activation and cognitive performance following sleep deprivation has been examined to help elucidate whether this cerebral response actually assists performance following sleep loss. A number of studies in which performance has been maintained following sleep deprivation, have found associations between cerebral activation and cognitive performance (Drummond et al., 1999; Drummond et al., 2005). In Drummond’s (1999) study using a verbal learning task, better free-recall performance was correlated with activation within the bilateral parietal lobes, (known to be involved in verbal short-term memory), right temporal gyrus and left supplementary motor area. Further, activation in the left inferior frontal gyrus was positively correlated with higher subjective sleepiness ratings. Similarly, when subjects performed both verbal learning and arithmetic simultaneously, performance impairments were only modest, and there were associated increases in PFC and parietal regions (Drummond, Gillin et al., 2001).

In contrast, a decline in performance has been associated with reductions in neural activations following sleep deprivation. For instance, a small significant decrease in inferior frontal gyrus that was predictive of worsening recognition performance in one
study (Habeck et al., 2004), and prefrontal activation following sleep deprivation, and this was associated with a decrease in working memory performance (Chee & Choo, 2004). These findings suggest that task performance is dependent on sufficient neural recruitment, and is a compensatory response to increasing sleepiness and cognitive demands.

3.4.2.3 Relationship between task difficulty and neural recruitment

Whether additional cortical areas are recruited following sleep deprivation may also partly depend on the complexity of the task. Task difficulty has been shown to affect the level of activation in studies of well-rested participants, increases in activation as the level of complexity increases (Johnson & Zatorre, 2006; Loose et al., 2003). Similarly, neuroimaging studies in sleep-deprived subjects have also demonstrated this effect: increased task complexity is associated with increased activation in parietal, inferior frontal and dorsolateral prefrontal cortex (Chee et al., 2006; Drummond et al., 2005), and thalamic activation (Chee et al., 2006) following sleep deprivation. Increased activation of parietal and frontal regions were associated with better memory performance, indicating that these may be the regions of compensatory control following sleep deprivation (Chee et al., 2006). These findings extend the compensatory hypothesis, suggesting that brain regions are activated during sleep loss, and further regions are responsive during more difficult task demands when an individual is sleep deprived. Increased engagement of the frontal lobes with sleep deprivation may occur when a task is sufficiently complex to activate this region, such as when performing a divided attention task (Loose et al., 2003). Supporting this notion is the idea that complex cognitive tasks are relatively unaffected by sleep deprivation (Harrison & Horne, 2000).

3.4.2.4 Individual differences

Greater recruitment of attentional resources during task performance may occur in those individuals who have higher competency at the task (Gray, Chabris, & Braver, 2003) or more cognitive resources to begin with (Stern, 2002). However, it is also possible that an individual’s potential to recruit additional regions of the brain to assist performance may relate to more intrinsic factors, such as personality and sleepiness (Gray et al., 2005). For instance, there is a growing body of literature suggesting that sleepiness is heritable (Watson, Goldberg, Arguelles, & Buchwald,
2006), and that there are differences in individuals’ susceptibility to sleepiness and the effects of sleep deprivation on their performance (Van Dongen et al., 2004). Many neurocognitive studies of sleep loss have reported large variability in individuals’ responses to sleepiness (Lim, Choo, & Chee, 2007; Van Dongen et al., 2003), and this appears to be a relatively stable, trait-related phenomenon (Van Dongen et al., 2004). Subjects who are sleep deprivation-resilient activated the same areas both after normal sleep and after 30-hours of sleep deprivation, whereas those who were more vulnerable to the effects of sleep loss only recruit the prefrontal cortex during task performance (Mu et al., 2005). Similarly, cortical activation in a sample of 10 fighter pilots was significantly associated with fatigue vulnerability while performing a flight-simulator task after 37-hours awake (Caldwell et al., 2005). Some studies have also suggested a neural basis for these differences between individuals (Lim et al., 2007; Bell-McGinty et al., 2004). Differences in parietal activations between individuals who are sleep deprivation-resilient and vulnerable have also been shown after normal sleep (Chee et al., 2006; Mu et al., 2005). Lim et al. (2007) found that intra-individual variability of reaction times following one night of sleep loss was the most robust measure of subjects’ vulnerability to sleepiness, and this measure was associated with decreases in parietal activations from baseline to sleep deprivation. This finding is consistent with the “cognitive reserve” theory, which postulates that better cognitive resistance to sleep loss is attributed to having more cognitive resources to begin with, or the ability to engage other neural resources when required (Stern, 2002). Overall, it is still unclear which specific regions may be a good marker of sleep deprivation-vulnerability. These theories suggest that there may be some variability in the way individuals’ activate the “compensatory region” to influence performance when sleep deprived.

3.4.3 Summary

fMRI is one tool which can be used to identify regions of the brain where functional change has occurred as a result of sleep deprivation, and that the presence of increased regional activity may indicate an ability to compensate for the effects of sleepiness on performance and alertness. The findings of these studies suggest that additional regions of the cortex are recruited during sleep deprivation in order to help aid either alertness or cognitive performance directly. It is still unknown which region is the primary candidate for this response. Further, these regions may be
predetermined, or alternatively, the adaptive cerebral response may relate to cognitive demands (Drummond & Brown, 2001).

There is some suggestion that improved or maintained performance following sleep loss may depend on the ability of the brain to effectively recruit these additional regions. Increased activations of brain regions following sleep deprivation has been associated with better task performance, whereas decreased activation is associated with performance decline.

There are limited studies attempting to quantify the effects of total sleep deprivation on brain activity using neuroimaging techniques. The current fMRI literature is limited by a number of inconsistencies, which makes cross-study comparisons difficult, as well as by a lack of power. It is also limited in that there are differences between studies in terms of the tasks employed (arithmetic, working memory, verbal learning, visual attention, and reasoning), scanning parameters, lengths of sleep deprivation (between 24 and 72 hours), and analysis techniques. Thus, a firm conclusion relating the activity of the brain during periods of sleep loss is yet to be established. The current thesis will examine a the neural activation associated with an important aspect of driving - cross-modal divided attention - following sleep deprivation.

3.5 Aims and hypotheses of the current research

From this review of the literature, there are a number of issues relating to the effects of sleep deprivation on driving-related performance, which may be related to increased accident risk. The current thesis was designed to address and elucidate the reasons for increased crash risk in sleep-deprived drivers. The above review of the literature concluded that different aspects of the task of driving may be affected by sleep deprivation. These processes include introspective aspects of the driver, such as the driver’s awareness about their level of sleepiness, their ability to recognise symptoms of sleepiness and to make appropriate decisions regarding their fitness to drive during sleep loss. Studies of simulated and on-road driving have reported deficits on driving-related skills. Accident risk in sleep-deprived drivers may also be due to neurocognitive deficits or underlying neural processes outline in the literature review above. The overall aim of the current thesis, therefore, is to examine the
effects of acute sleep deprivation on a range of driving-related processes in professional drivers. The following experiments will aim to determine the effects of acute sleep deprivation on measures of behavioural disposition, simulated driving, and driving-related neurocognitive domains. Finally, in order to determine the underlying neural processes occurring with sleep deprivation, the current thesis also aims to examine the psychophysiological underpinnings of visual and auditory attentional-related neural processing following acute sleep deprivation, using ERPs and functional neuroimaging. As described in Chapter 1, Section 1.4.5, some professional drivers resort to using pharmaceutical means to help them stay awake during long-haul trips. The current thesis also aims to determine the effects of $d$-amphetamine, alone and in combination with acute sleep deprivation, on simulated driving performance, behavioural disposition, driving-related cognitive domains and visual and auditory neural processing.

Overall, the current thesis examined the following hypotheses:

- Whether sleep deprivation impacts on subjective measures of mood, sleepiness and performance;
- Whether sleep deprivation impacts on simulated driving performance;
- Whether sleep deprivation affects neurocognitive measures related to driving;
- Whether sleep deprivation affects electrophysiological measures of visual and auditory processing;
- Whether sleep deprivation alters neural processing during divided attention as measured by neuroimaging; and
- Whether $d$-amphetamine is an effective countermeasure of the effects of sleep deprivation.

More specific hypotheses will be outlined in the following three experimental chapters.
CHAPTER 4
EXPERIMENT 1

Chapter overview
This chapter presents an experiment that assessed the effects of 24-hours of sleep deprivation on driving-related processes. Firstly, the experiment examined how well professional drivers are able to perceive sleepiness symptoms and performance changes when sleep-deprived, and to make decisions to stop driving based on this information. Secondly, it assessed driving-related performance using both a simulated driving task, and neurocognitive tasks related to driving. Finally, it examined aspects of visual and auditory attentional processing that may explain impaired performance after sleep deprivation; specifically, the differential processing of visual stimuli presented to the foveal versus peripheral visual field; the differential processing of the sustained (parvocellular) versus transient (magnocellular) visual pathways; pre-pulse inhibition of the acoustic startle response; mismatch negativity (auditory change detection); and later cognitive processing to auditory and visual stimuli.

4.1 Introduction

As argued in Chapter 1, there appears to be a causal link between sleep deprivation and motor vehicle accidents, particularly accidents involving heavy vehicles. To date, there has been little research into the effects of sleep deprivation on driving-related performance in professional drivers. As outlined in Chapter 3, there are a number of facets of attitudinal and neurocognitive processes that are involved in the task of driving. Experiment 1 will attempt to uncover some of the driving-related processes which are affected in sleep deprived individuals, and whether drivers can accurately determine their level of sleepiness and fitness to drive safely.

Subjective sleepiness ratings increase significantly with acute sleep deprivation (Gillberg & Akerstedt, 1990). It has yet to be established whether drivers can accurately detect if their level of sleepiness has reached a point where it affects their ability to drive safely. This is because one explanation for the increased crash risk associated with sleep deprivation may be that sleepy drivers do not 1/ accurately make introspective evaluations of their degree of sleepiness or their ability to drive safely; and 2/ act upon these evaluations and make a decision to stop driving. The current
experiment will utilise a range of behavioural dispositional measures to examine subjective sleepiness, mood and dispositional aspects of driving, including Visual Analogue Mood Scale, the Karolinska Sleepiness Scale, the Sleepiness Symptoms Questionnaire, the Performance Questionnaire, and the Stop Driving questionnaire.

Simulated driving tasks are commonly used to examine driving-related performance during a task, as they are safe, inexpensive and have good face validity. Sleep deprivation and sleep restriction has been shown to cause a decline in on-road and simulated driving performance (Howard et al., 2007; Pizza et al., 2004; Welsh, Thomas, & Thorne, 1998; Thorne et al., 1998), which may explain the increase in accidents related to sleepiness. These changes have not been extensively examined in professional drivers, who are more exposed to the effects of sleep deprivation than non-professional drivers. The effects of one night of acute sleep loss have also not been examined, which is commonly experienced by this population of drivers. The AusEd simulated driving task will be utilised in the current experiment to determine the effects of sleep deprivation on driving performance. This simulated driving task is sensitive to performance changes due to sleep deprivation (Howard et al., 2007; Desai et al., 2006), circadian effects (Banks et al., 2005), and sleep disorders (Desai et al., 2006).

Sleep deprivation also results in increased sleep propensity and microsleeps (Corsi-Cabrera et al., 1992; Howard et al., 2002; Torsvall & Akerstedt, 1988). As reported in Chapter 2, the detection of microsleeps has important implications for driving safety and reducing sleep-related accidents. One promising method for detecting drowsiness is PERCLOS; video scoring of eye closure to assess the percentage of time that the eyes are closed (Wierwille & Ellsworth, 1994; see Chapter 3 for details). Manually scored PERCLOS using video recordings of the face has previously been validated as a predictor of drowsiness in sleep-deprived truck drivers during a simulated driving task (Wierwille & Ellsworth, 1994). Automated measures of eye closure, such as the Copilot (Grace et al., 1999), have not been well validated in sleep deprived subjects. The current experiment will use Copilot to assess slow eyelid closure following sleep deprivation.

Brief sleep episodes do not fully account for the performance decrements evident in sleep-deprived drivers (Akerstedt & Gillberg, 1990; Russo et al., 1999; Thorne et al.,
For example, in Welsh et al.’s (1998) study, microsleeps, or bursts of delta or theta activity in the EEG, only preceded 18% of crashes on a driving simulator; therefore they did not occur with sufficient frequency to explain the incidence of crashes (Welsh et al., 1998). Supporting this view, other studies have reported that drivers are awake and have their eyes open when they crash (Akerstedt & Gillberg, 1990). This suggests that other aspects of motor, perceptual, and/or cognitive processing may be impaired in sleepy drivers, accounting for the increased sleep-related accident risk. Sleep deprivation has a detrimental effect on a range of processes which are important for driving (see Chapter 2, Section 2.5 for details). A number of confounding factors make the interpretation of these studies difficult, such as the use of different tasks, and lengths of sleep deprivation. Therefore, to determine which functions related to driving are impaired in sleep-deprived drivers, this experiment employed a number of neurocognitive tasks that assess different components of neural processing that are considered essential for safe driving, and that may contribute to increased crash risk in drivers. Specifically, the current experiment employed the Psychomotor Vigilance Task to assess vigilance and visual attention; Critical Flicker Fusion test to assess psychophysiological arousal, Simple and Complex reaction time tasks to assess motor speed and reaction time performance; the Digit Symbol Substitution Task to assess information processing speed and motor performance; and the Stroop Task to assess executive functioning.

The behavioural response reported using neurocognitive tasks (e.g. increased reaction time or missed responses to peripheral visual signals) are the summation of a number of processes, from the initial encoding of information, to motor execution of the response and later cognitive processes, such as attention and memory. An alternative explanation for the discrepancy in the behavioural findings outlined above may be that only some processes are affected by sleep deprivation, and the tests utilised in behavioural studies may not be sensitive enough to detect abnormalities in the underlying cognitive processes. In addition, sleep-deprived individuals are often able to compensate for their sleepiness for the duration of the task, by recruiting cognitive reserve (Raz et al., 2001). One method of examining pre-attentive processes or automatic cognitive processes is with electrophysiological techniques.

As described in Chapter 2, Section 2.5.4.2, there are a number of visual and auditory ERPs that can be used to examine the integrity of the visual and auditory system.
Each ERP can examine specific components of visual and auditory processing, from early pre-attentive processes, to mid-latency attentional components, to later, higher-order processing components. Driving is primarily a visual task, and therefore two aspects of visual functioning were examined in the present experiment; the two primary visual pathways (parvocellular and magnocellular), and visual processing of the central and peripheral visual field. Other underlying driving-related neural processes can be extracted using auditory ERP measures. For instance, assessment of the acoustic startle reflex may give an indication of how sleep deprivation affects a driver’s ability to filter out irrelevant stimuli and focus on important information coming from the road scene. Mismatch Negativity is a measure of acoustic change detection; attenuation of this response has been demonstrated at sleep onset, during circadian nadir (Sallinen & Lyytinen, 1997) and following extended periods of sleep loss of up to 40 hours (Raz et al., 2001). However, these findings are yet to be replicated in larger samples, and with shorter periods of sleep deprivation (i.e. one night of sleep loss). Later cognitive processing can be measured using an auditory oddball tasks, which elicits a P300 waveform. Sleep deprivation of one night has been shown to attenuate the amplitude of the P300 response. These visual and auditory processes involve attentional processing, both pre-attentive and higher-order attentional processing, and will allow the examination of where along the information processing chain, attentional processing is being affected.

4.2 Aims

It is thus important to determine the effects of sleep deprivation on a number of dispositional, behavioural and electrophysiological measures. The present experiment was designed to determine whether there are changes in behavioural disposition following 24-hours of sleep deprivation; specifically, a) whether drivers can detect changes in sleepiness, mood and performance after sleep deprivation; and b) whether drivers can determine whether it is safe for them to continue to drive after sleep deprivation. Secondly, it aims to determine the behavioural effects of 24-hours of sleep deprivation on simulated driving performance, specifically, whether sleep deprivation increases a) lateral lane position variability, b) speed variability, c) braking reaction time and d) the number of crash events. Thirdly, it aims to determine the effects of sleep deprivation on driving-related processes, as measured by neurocognitive tasks related to driving. Finally this experiment aims to determine
whether sleep deprivation affects visual and auditory neural processes using ERP measures, specifically a) where along the information processing chain these potential deficits are occurring; b) whether there is a tunnel vision effect within a visual arc of 20° associated with sleep deprivation; c) using ERPs, where along the information processing chain these potential sleep-related tunnel vision deficits occur; d) whether sleep deprivation has a differential effect on the visual system under conditions designed to emphasise the parvocellular and magnocellular pathways e) whether sleep deprivation affects early auditory processing, measured by the acoustic startle response and mismatch negativity, and f) whether sleep deprivation affects later auditory processing, measured by the auditory oddball task.

4.3 Methods

4.3.1 Participants

4.3.1.1 Selection criteria

A sample of drug-naïve, licensed professional drivers was recruited from a pool of professional drivers previously involved in research at Austin Health, Melbourne, Australia, and through advertising in the Transport Workers Union newsletter and Trucking Life magazine. Inclusion criteria for participation was; a current heavy vehicle drivers licence, amphetamine-naïve, aged between 18 and 65 years, and English as a first language. Interested drivers were given a brief explanation of the study requirements and protocol, and were sent a more detailed information sheet. Drivers who agreed to participate were booked in for a medical examination.

4.3.1.2 Medical examination

All drivers underwent a medical examination with a registered Sleep Physician to ensure their fitness for the study. A set of screening questionnaires were used in the medical session to screen participants for any medical conditions, drug use, trait sleepiness and sleep disorders:

Medical Questionnaire - This questionnaire consisted of questions relating to general health, psychological health, height and weight, and blood pressure (Appendix C).
**Demographic Questionnaire** - This questionnaire consisted of questions regarding participants’ sex, age, height and weight, weekly alcohol intake, smoking behaviour, weekly hours driving for work, and general health questions (Appendix D).

**Drug use history questionnaire** – This questionnaire asked participants about their previous drug use of a number of substances, both licit (e.g. tobacco, caffeine and alcohol) and illicit (e.g. cannabis, ecstasy, cocaine, amphetamines). Questions relate to frequency, dosage and length of use of each substance (Appendix E).

**Drug Abuse Screening Test (DAST-20; Skinner, 1982)** - A 20-item self-reported questionnaire asked participants to answer in a "yes" or "no" format about previous psychoactive drug use. The DAST-20 provides a brief, simple, valid method for identifying individuals who are abusing psychoactive drugs; and yields a quantitative index score of the degree of problems related to drug use and misuse. It obtains no information on the various types of drugs used, or on the frequency or duration of the drug use. Individuals scoring ten or above are recommended to further investigate their drug use, therefore this was considered the cut off for exclusion in the current study (scores of 16 or greater are considered to indicate a very severe abuse or a dependency condition).

**The Epworth Sleepiness Scale (ESS; Johns, 1991, 1993)** - A self-reported measure of sleep propensity. This measure was used to identify participants who have excessive daytime sleepiness and/or had been experiencing a sleep disorder. Participants were asked to rate their likelihood of falling asleep or doze off in eight everyday situations. Possible total scores ranged from zero to 24, with higher scores indicating increased daytime sleepiness. Scores between zero and ten reflect normal sleepiness (Johns & Hocking, 1997), therefore participants with scores greater than ten were excluded from the study. The ESS has high internal consistency as well as test re-test reliability in healthy subjects (r = 0.82; Johns, 1991).

**Multiple Apnoea Prediction Scale (MAPS; Maislin et al., 1995)** – A screening tool for sleep disordered breathing. This questionnaire predicts sleep apnoea risk using a score between zero and one, based on body mass index and some sleep questions. A score of zero represents a low risk of sleep apnoea, and scores closer to one represent high risk. Participants with a MAPS score greater than 0.5 were excluded from the study.
The practitioner interviewed the participant on their medical and drug history, physical and mental health, any medical procedures or implants, smoking history, and obtained other physiological measures (i.e. weight, height, blood pressure). Drivers were excluded if they had a medical contraindication for the sleep deprivation protocol, including a history of cardiovascular disease, hypertension, epilepsy, diabetes, psychiatric illness or any other medical condition which could be exacerbated by sleep deprivation; a sleep disorder or sleep apnoea (as assessed by the MAPS and the ESS); pregnancy; participants who could not tolerate having no cigarettes in a 12-hour period, (drivers were asked to avoid smoking during the sleep deprivation session due to the possible stimulating effect); high-level caffeine users, defined as five or more caffeinated beverages per day (Lenne et al., 1998), as drivers were asked to refrain from drinking caffeinated beverages (cola, black tea, coffee, red bull) for 6 hours before each session until the conclusion of each session; and participants who had a visual impairment that does not correct with glasses. Based on this examination, the physician made a decision about whether the driver was fit to participate, and if they were deemed unfit, they were excluded from the sample.

### 4.3.1.3 Sample characteristics

Twenty professional truck drivers (1 female) were recruited for the study. Blood and urine samples taken during each session were analysed to verify that there was no recent drug use. One subject had detectable levels of THC (delta-9-tetrahydrocannabinol; cannabis) in their blood at the time of testing, therefore to explore this subject further, the urine sample from that session was examined. The sample revealed excessive levels of THC metabolites in urine. This toxicology data indicates that this subject was a heavy cannabis user, and we could not determine whether this participant’s performance during the study was due solely to sleep deprivation, or the combination of sleep deprivation with cannabis intoxication. Therefore, a decision was made to exclude this subject from further analyses throughout the study. All other participants were drug free at time of testing.

The final sample consisted of 19 participants (1 female), aged between 23 and 62 years (Mean age ± Std. dev. = 45.3 ± 9.1 years). All participants reported normal
hearing, normal or corrected-to-normal vision, and did not report any significant daytime sleepiness according to the ESS scores (Johns, 1993). The mean body mass index (BMI) of the sample was 30.9 (range 20.9 – 52.5), and the mean apnoea prediction score was 0.44, indicating a low likelihood of obstructive sleep apnoea. The average ESS score was 5.95. Of the 19 participants, six were left handed.

There was a large range of hours spent driving for work per week in the sample (range = 8 to 80 hours per week), with an average of 42.4 hours. On average, participants drank 3.6 caffeinated beverages per day and seven participants reported being smokers, averaging eleven cigarettes per day. The majority of participants reported drinking alcohol only socially (i.e. less than 5 alcoholic beverages per week; 80%). None of the participants had a current or past drug abuse problem at the time of testing, as assessed by the DAST (all scores below 4). Six participants reported being current (three) or past (three) users of cannabis. The current users reported using cannabis infrequently (no more than once per month). No other participants reported any previous illicit drug use.

4.3.2 Experimental Design

A repeated-measures, counter-balanced single-blind design was employed. Participants completed two treatment conditions; one following a normal night of sleep (no sleep deprivation; NSD) with placebo and one following 24-hours of sleep deprivation (SD) with placebo, separated by a one week wash-out period, to allow for the regulation of the participants sleep patterns following the sleep deprivation session. Time-of-day effects were controlled for by testing all participants at the same time of day to assess the independent impact of sleep deprivation alone on driving-related performance. Additionally, participants were tested in the mid-morning to avoid testing in the circadian nadir (i.e. 14:00h to 16:00h) where there may have been a negative effect of circadian cycle on performance. The period of 24 hours was chosen as it is a common, realistic level of deprivation which has ecological validity, and also allowed for a protocol to be carried out outside of the circadian nadir.

In order to be able to compare the results of Experiment 1 with the results of Experiment 3 in which drivers were administered d-amphetamine and placebo, drivers in the present experiment undertook an identical protocol as Experiment 3, including blood samples and capsule administration, however they were only administered
placebo capsules. Therefore, Experiment 1 was single-blinded (with regard to drug administration). This experiment was divided into three sections; simulated driving and behavioural disposition, driving-related cognitive assessment, and electrophysiological (ERP) assessment.

4.3.3 Procedure

Prior to conducting the study, ethics approval was obtained from the Swinburne University Human Research Ethics Committee and the Austin Health Human Research Ethics Committee. After agreeing to participate, drivers attended Austin Health for an initial screening session and medical examination to assess their fitness for the study by a practicing physician. Individuals who passed the medical examination and selection criteria were recruited as participants. Participants were provided with an information sheet outlining details of the research study (Appendix A), and when the participant had all questions answered and were satisfied with the requirements of the study, they gave written informed consent (Appendix B). All participants completed a demographics questionnaire (Appendix D), drug history questionnaire (Appendix E), the Epworth Sleepiness Scale (Johns, 1991) and the Multiple Apnoea Prediction Scale (Maislin et al., 1997). Participants were informed that they could withdraw from the study at any time. To reduce the impact of learning, drivers also practiced the neurocognitive tasks, and were given feedback on their performance.

Participants attended two experimental sessions in a counterbalanced order (see Appendix F for subject counterbalancing). For both experimental sessions, participants were blind to the drug treatment condition, which was placebo each time. Participants were told that they would be given a capsule which may or may not help their performance on the experimental tasks. Participants were asked to have their normal amount of sleep during the night prior to each session, and instructed to complete the sleep diary for the week prior to each study day. No caffeine (e.g. coffee, tea, cola, chocolate) or other stimulants were allowed from midday on the day prior to the session until the conclusion of the session. Participants were also asked to refrain from smoking throughout experimental sessions. Testing times during each session were identical in order to control for circadian variations on performance.

For the sleep deprivation (SD) session, participants were asked to wake at 07:00h on
the morning of their session and attend the sleep laboratory at 22:00h following a normal eight-hour day driving shift (Table 4.1). Participants stayed awake all that night until the following morning, monitored by the laboratory staff. During the night participants watched videos, read, or played games. The following morning at 07:00h, participants were taken by taxi to Swinburne University where the testing part of the study was carried out. Participants provided a urine sample and completed the SCL-90-R questionnaire. A light breakfast was then provided. Participants were then given a placebo capsule, and a blood sample was taken 120 minutes later. Participants then completed the simulated driving task and questionnaires, the neurocognitive tasks, and ERP tasks. The order of these three groups of tasks was counterbalanced between participants to avoid order effects. For the EEG battery, the order of the visual and auditory tasks was counterbalanced between participants. Where appropriate, alternate forms of the neurocognitive tasks and EEG tasks (TV task, Startle reflex, MMN, and Auditory Oddball Task) were presented to each participant. A second blood sample was obtained approximately five hours following capsule administration at the end of the session. Participants were provided with a taxi voucher for transport home.

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Task</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>&gt; 7 hours sleep</strong></td>
</tr>
<tr>
<td>1</td>
<td>07:00</td>
<td>Wake, complete SCL-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Normal day shift</strong></td>
</tr>
<tr>
<td>2</td>
<td>22:00</td>
<td>Attended the Sleep Laboratory</td>
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<tr>
<td></td>
<td>06:30</td>
<td>Taxi to Swinburne University</td>
</tr>
<tr>
<td></td>
<td>07:00</td>
<td>Urine sample, SCL-90</td>
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<tr>
<td></td>
<td>08:00</td>
<td>Breakfast</td>
</tr>
<tr>
<td></td>
<td>09:15</td>
<td>Administered capsules</td>
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<tr>
<td></td>
<td>11:15</td>
<td>Blood sample 1</td>
</tr>
<tr>
<td></td>
<td>11:30</td>
<td>Neurocognitive test battery</td>
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<td></td>
<td></td>
<td>Driving Simulation</td>
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<tr>
<td></td>
<td></td>
<td>EEG</td>
</tr>
<tr>
<td></td>
<td>14:15</td>
<td>Blood sample 2</td>
</tr>
<tr>
<td></td>
<td>15:00</td>
<td>End of session (Taxi home)</td>
</tr>
</tbody>
</table>

Table 4.1: Sleep Deprivation session timeline
The NSD sessions were identical to the SD sessions, differing only in that participants attended Swinburne University by taxi at 09:00h after a normal day shift followed by a normal nights’ sleep, instead of 24-hours sleep deprivation. Details are shown in Table 4.2.

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Task</th>
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<tbody>
<tr>
<td>&gt; 7 hours sleep</td>
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<tr>
<td>1</td>
<td>07:00</td>
<td>Wake</td>
</tr>
<tr>
<td></td>
<td>09:00</td>
<td>Taxi to Swinburne University</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine sample, SCL-90</td>
</tr>
<tr>
<td></td>
<td>09:15</td>
<td>Administered capsules</td>
</tr>
<tr>
<td></td>
<td>11:15</td>
<td>Blood sample 1</td>
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<tr>
<td></td>
<td>11:30</td>
<td>Neurocognitive test battery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Driving Simulation</td>
</tr>
<tr>
<td></td>
<td>14:45</td>
<td>Blood sample 2</td>
</tr>
<tr>
<td></td>
<td>15:00</td>
<td>End of session (Taxi home)</td>
</tr>
</tbody>
</table>

**Table 4.2: No Sleep Deprivation session timeline**

**4.3.3.1 Blood and urine samples**

One urine and two blood samples were taken from each participant during each session. A urine sample was taken at the start of each session as a screening tool to confirm that no substances were present prior to the session. Samples were taken in a small container, and refrigerated and collected at the end of the session. Urine was screened for seven major drug classes using Gas Chromatography Mass Spectroscopy (GC/MS). Blood samples were taken from each participant by a registered nurse or qualified phlebotomist. A medical doctor was also on call throughout the testing session. For each sample, 20 ml samples of blood were obtained using a syringe by venipuncture from the antecubital vein, and separated into two tubes (heparinised and sodium). Blood samples were immediately stored in a −20°C freezer and subsequently transported to a −70°C freezer at the conclusion of the study. Blood samples were analysed for seven major drug classes using the GC/MS method (Moeller & Kraemer, 2002). This method has been documented to be the most accurate technique for testing specific drug levels in blood.
4.3.4 Materials

4.3.4.1 Questionnaires

4.3.4.1.1 Symptoms Checklist 90 Revised (SCL-90-R; Derogatis, 1980)

The SCL-90-R is a 90-item self-report inventory designed to reflect the psychological symptoms patterns of community, medical and psychiatric respondents. This questionnaire asks participants to rate the frequency of 90 symptoms which they may have experienced over the past week, on a scale from zero “= not at all” to “five = frequently”. The SCL-90 R has received wide validation over a range of clinical and non-clinical samples (Croft, 2004).

4.3.4.1.2 Sleep Diary

This diary was completed in a retrospective fashion each morning for the week preceding their study day (Appendix H). The diary measured total sleep per night and sleep latency each night, and these were averaged across the week.

4.3.4.1.3 Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990)

The KSS is a single item scale which assesses state subjective sleepiness, which asks respondents to rate their current state of sleepiness on a 9-point scale. Phrases were anchored at numbers 1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy, but no difficulty staying awake, to 9 = extremely sleepy, fighting sleep. Possible scores ranged from zero to nine, with higher scores representing greater subjective sleepiness. The KSS is a well-validated measure, highly correlated with EEG and EOG measures of sleepiness (Akerstedt & Gillberg, 1990).

4.3.4.1.4 Sleepiness Symptoms Questionnaire (SSQ)

The SSQ is a self-administered questionnaire, which asks the respondent to rate how often they noticed eight symptoms of sleepiness occurring during the simulated driving task on a seven point Likert scale (1 = Not at all, 3 = Occasionally, 5 = Frequently, and 7 = Most of the time) (Appendix H). These symptoms were selected based on symptoms that are related to performance or sleepiness measures in previous studies (Gillberg et al., 1994; Herscovitch & Broughton, 1981; Itoi et al., 1993; Nilsson et al., 1997), together with symptoms rated for face validity by a panel of
drivers from the Transport Workers Union and sleep disorders experts. The eight symptoms were “struggling to keep your eyes open”, “vision becoming blurred”, “nodding off to sleep”, “difficulty maintaining correct speed”, “difficulty keeping in the middle of the road”, “mind wandering to other things”, “reactions slow” and “head dropping down”. A score for each item (between 1 and 7), as well as an overall summed score of all symptoms (between 8 and 56), were calculated, where higher scores represent increased sleepiness. The SSQ has been shown to correlate highly with the KSS (r = 0.81, Howard, et al., unpublished data), and was designed at the Sleep Disorders Unit at Austin Health, Melbourne, Australia.

4.3.4.1.5 Performance questionnaire

This single item scale was designed at Austin Health, Melbourne, Australia, to rate subjective task performance. Drivers are asked to rate their performance on the driving simulator compared to their “normal” driving performance on a scale from 1 = “significantly impaired” to 9 = “significantly improved” (Appendix I).

4.3.4.1.6 Stop driving questionnaire (SDQ)

This two-part questionnaire was used as a subjective measure of whether drivers felt they would stop driving in their current state (Appendix J). Participants were asked to decide whether they would continue to drive in two different, real-life situations; 1) a city drive; and 2) a protracted country drive. For each situation, possible scores ranged from 1 to 4 (1 = I would continue to drive, 2 = I would continue to drive only if pressured to do so, 3 = I would stop driving now even if under pressure to continue, to 4 = I would have stopped some time ago). The SDQ was designed at the Sleep Disorders Unit at Austin Health, Melbourne, Australia.

4.3.4.1.7 Visual Analogue Scale (VAS; Bond & Lader, 1974)

The VAS is a 16-item assessment of changes in a variety of affective states (Bond & Lader, 1974). Respondents were asked to rate the way they currently felt in terms of 16 given dimensions. The dimensions were presented as 100-mm lines, the two extremes of the emotion (e.g. ‘alert’ and ‘drowsy’) written at each end, and subjects
marked where they felt they ranked on each line. Scores on each scale were measured in millimetres from the left anchor to the line marked by the participant as corresponding to his/her current mood.

4.3.4.2 AusEd™ driving simulator (Woolcock Institute) and objective sleepiness measures

Driving performance was assessed on the AusEd driving simulator, a divided-attention driving task. The AusEd driving simulation task is a PC based programme designed to be conducive to, and test for, driver fatigue and sleepiness. The driving simulator is installed on a Windows NT workstation with steering wheel and pedals, and dual stereo computer speakers.

During the 30-minute task, the room lights were switched off to simulate a monotonous night time drive on a rural road, a driving environment that is very conducive to driver sleepiness. Participants viewed a full screen projection of the view from the driver’s seat of a car, and the driving scene displayed a dual-carriage rural road at night with common lane divisions and road edges marked with reflective posts. A small speedometer was displayed in the top left-hand corner of the screen, out of the line of sight of the road. This represents a divided attention task, as participants have to move their attention to the speedometer to check their speed throughout the drive. The participants were presented with a continuous country drive on a series of straight and curved roads, and were required to use a steering wheel and brake and accelerator pedals. Participants were instructed to maintain their position in the middle of the left-hand lane on the road (in accordance with Australian driving code), and to keep their speed between 60 and 80 kph. During the drive, ten slowly moving trucks appeared intermittently, driving in the same direction as the subject. Participants were instructed to brake as quickly as possible when they saw a truck appear in front of them (the truck appears dangerously close to the driver’s car). Continuous, low frequency (approximately 60 dB) simulated engine sounds were played through the computer speakers for the duration of the drive. Participants undertook a 5-minute practice drive prior to testing, to become familiar with the road layout and driving instrumentation (steering wheel and pedals).

The AusEd driving simulator measures several cognitive skills important for driving, including tracking ability, vigilance, divided attention and reaction time (RT).
Specifically, the following performance variables were used in this study:

**Velocity deviation:** ability to maintain a constant speed within 60 to 80 kph (deviation from the safe speed zone 60 to 80 kph). Higher scores represent larger deviation from the prescribed speed and decreased vigilance.

**Standard deviation of Lane position:** deviation from the median lane position during the drive (averaged every 40 milliseconds). Higher scores indicate larger deviations from the mean lane position and decreased vigilance.

**Mean reaction time (Mean RT), for braking episodes:** Computer scored RTs can be manually checked and any necessary corrections can be made using customised software prior to calculating final RT scores.

**Number of crashes:** Crashes were registered under three conditions; driving off the road, hitting the back of a truck, or remaining stationary for more than ten seconds.

Data was continuously recorded and saved to hard disk during the task. Following each session, the data was analysed using the AusEd analysis programme.

4.3.4.2.1 The Copilot (Carnegie Mellon Research Institute, Pittsburgh)

The Copilot is a device that measures slow eye closure, represented by the percentage of time that eyes are more than 80% closed (PERCLOS; (Grace et al., 1999). This video-based system uses two infrared illumination sources of different wavelengths that reflect off the retina. The Copilot calculates the difference between each light source ten times per second and calculates the percentage of time the eyes are closed, which is averaged over the prior minute (Grace et al., 1999). The device is designed to provide the driver with feedback if drowsiness reaches a certain threshold, by way of a visual gauge and an auditory tone, but this was deactivated in the present study. This small device was placed on the desk in front of the participant during the driving simulator task. Participants were asked to position the device until their eyes are visible in the small screen, and to minimise head movement during the task, to ensure that the device could detect slow eye closure throughout the whole task. Data was collected three times per second throughout the driving task, and saved to hard disk on the PC. The average percentage of eye closure for the session was calculated.
PERCLOS has been shown to be the most highly correlated with expert raters of drowsiness, with an r-value of 0.91 (Wierwille & Ellsworth, 1994).

4.3.4.2.2 Critical Flicker Fusion (CFF)

When a light is repeatedly turned on and off, it will be perceived as flickering. When it flickers at increasing frequency, it will eventually appear to fuse into a continuous light, even though it is actually still flickering. The threshold at which it is perceived as a steady light source is called the CFF threshold. This task is a well-established psychophysical threshold measure of attention and alertness, and has been used extensively as a measure of central nervous system arousal (Hindmarch, 1981). A decrease in the CFF threshold is indicative of a reduction in the overall integrative activity of the CNS (Hindmarch, 1981). During the task, participants looked through a one-metre long tube, where two red diode lights appeared in the position of the fovea. Participants are required to discriminate flicker from fusion, and vice versa, by responding to either the left or right button on the response box. Individual thresholds are determined by the psychophysical method of limits on four ascending (flicker to fusion) and four descending (fusion to flicker) scales (Woodworth & Schlosberg, 1958). The mean of these four ascending and descending presentations gives the threshold frequency in hertz. This task did not measure speed of reaction, but did provide the CFF frequency.

4.3.4.3 Neurocognitive tasks related to driving

A battery of neurocognitive tasks that test domains that have previously been found to relate to driving performance (see Chapter 3) were selected. These tasks were chosen as they assess skills or aspects of neurocognitive functioning that relate to driving performance, as well as being sensitive to the effects of sleep deprivation and fatigue in previous studies. This battery consisted of some computerised tasks, as well as one pen-and-paper task. Alternative forms of each task were used in each session where appropriate, to minimise order and learning effects.

4.3.4.3.1 Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985)

The PVT is a ten minute, computerised task that assesses sustained attention and reaction time, and requires continuous attention to detect randomly occurring stimuli.
(Dinges & Powell, 1985; Jewett et al., 1999). The PVT is a small hand-held box with two response buttons (right and left) below a display window. Participants were required to observe the display screen and press the right button (if right-handed) as quickly as possible in response to a small LED millisecond clock begin counting up from zero. Pressing the button stopped the clock, allowing the participant to read the reaction time. The interstimulus interval on the task varied randomly from two to ten seconds. The following outcome measures were used in the current study:

1. **Median reaction time (RT):** the elapsed time between the presentation of each number in the display window and the button pressing by the participant (measured in milliseconds). Higher scores indicate lower levels of sustained attention.
2. **Lapses:** Number of RTs greater than 500ms, or errors of omission.
3. Reciprocal (1/RT) of the slowest 10% of reaction times: the mean reaction time from the slowest 10% of reaction times. Lower scores indicate higher levels of sustained attention and faster reaction times. Increases in the duration of responses in the lapse domain (i.e: mean 1/RT from slowest 10% RTs per trial).
4. **Fastest 10% of RT:** shifts in optimum reaction times (i.e.: fastest 10% RTs per trial);

The main advantages of the PVT are that it is paced, non-stimulating, measurable, repetitive, provides immediate performance (RT) feedback to the subject, and is relatively long, which allows for fatigue-related responses to occur. Additionally, the PVT is free of aptitude and learning effects and is a reliable and sensitive to performance variations due to sleepiness (Ardmore et al., 2000; Doran et al., 2001; Dinges & Powell, 1985).

### 4.3.4.3.2 Simple reaction time (SRT)

This task measured simple reaction time in response to a single stimulus. The participant was instructed to press the YES response button as quickly as possible every time the word YES was presented on the screen. Fifty stimuli were presented with a varying inter-stimulus-interval of between 1 and 4 seconds. The outcome measure was the average reaction time to the stimuli (ms).
4.3.4.3.3 Choice Reaction Time (CRT)

This task is measures the processing time required to identify the correct stimulus (“yes” or “no”) and to respond accordingly. It assesses motor speed, and also involves an element of decision making in order to select the correct response. During this task either the word “yes” or the word “no” appeared on the screen, and participants were required to respond by pressing the corresponding button on the response box as quickly as possible. There were 50 trials with a varying inter-stimulus-interval of between 1 and 4 seconds. The outcome measure was the average reaction time to the stimuli (ms).

4.3.4.3.4 Digit Vigilance task

The Digit Vigilance task assesses the ability of an individual to focus and sustain attention, while also providing a measure of reaction time. A target digit was randomly selected and displayed to the right of the screen. A series of digits were presented in the centre of the screen at the rate of 2.5 digits per second. The participant was required to press the YES button as quickly as possible every time the digit in the series matched the target digit. The outcome measures were the average reaction time (ms), and the number of false positives (false alarms) made.

4.3.4.3.5 Digit Symbol Substitution Test (DSST)

The DSST is a timed, pen-and-paper task involving attention, working memory, skilled coordination and motivation. Participants were given a testing sheet, which displayed nine numbers at the top of the page, each with a corresponding nonsense symbol. Below these, 100 empty boxes with a number above each box are displayed. Participants were required to fill in as many blank boxes with each number’s corresponding symbol in 90 seconds. The total number of symbols correctly drawn out of 100 was recorded. Test-retest reliability of the DSST, which is a subtest of the WAIS-III, has produced high correlation coefficients, ranging from 0.82 to 0.88 (Matarazzo & Herman, 1984; Wechsler, 1981).
4.3.4.3.6 Colour Word Stroop

This task assessed frontal lobe function, specifically dorsolateral prefrontal cortical regions and anterior cingulate cortex (Petersen et al., 1999). Participants were presented a congruent and an incongruent trial, which were comprised of words in blue, red or yellow ink. The word set for the congruent trial consisted of the words “BLUE”, “YELLOW” and “RED” printed in the congruent colour (i.e. the word “BLUE” written in blue ink), and the incongruent trial consisted of the colour words printed in an incongruent colour (i.e. the word “BLUE” in yellow ink). Participants were instructed to read out aloud, as quickly as possible, the colour of the ink that the word was written in, ignoring the actual word. Time taken to read the whole page of words and the number of errors made for the congruent and incongruent trials were recorded.

4.3.4.6 Event-related potential task battery

EEG was used as an objective tool to study cortical processing while participants performed a computerised visual and auditory task battery. The task battery consisted of:

- **Pattern Reversal Task** – a measure of the magnocellular and parvocellular visual pathways.
- **Tunnel Vision Task** – a measure of the integrity of the peripheral and central visual fields.
- **Startle Reflex and Pre-pulse Inhibition Task** – a measure of sensorimotor gating, reflecting involuntary information processing.
- **Mismatch Negativity** – an objective measure of auditory discrimination, sensory memory, and involuntary attention.
- **Auditory Oddball Task** – a measure of general cognitive efficiency.

For each of the visual and auditory tasks, alternate forms were created and employed such that the subject did not perform the same version of the task twice. The order of administration of the auditory and visual sets of tasks, as well as the alternate forms, were counterbalanced and randomly assigned. All visual and auditory stimuli were generated using the NeuroScan Stim System (NeuroScan, Inc.). Visual stimuli were presented on a 17 inch LCD monitor. At the start of the ERP test battery, all subjects
were tested for any hearing problems, by responding with a button press to a series of tones, played through one ear at a time, ascending and descending in intensity from 8 to 32 dB SPL. No participant was excluded based on this test. From each task, different ERP components were derived, as described in Sections 4.3.4.6.1 – 4.3.4.6.5.

4.3.4.6.1 Pattern Reversal Task (PR)

The PR task has been employed to assess the magnocellular and parvocellular visual pathways separately (Alexander et al., 2005; Butler et al., 2001). In the present study, a fine black and white checkerboard pattern was used to emphasise the magnocellular pathway response. This had 28 squares, with equal numbers of black and white, with a check size of 1 cm$^2$, and a visual angle of 1.2° vertically and horizontally, with the mean luminance and contrast levels of the black/white stimulation 80 cd/m$^2$ and 75% respectively. A coarse red and green checkerboard was used to emphasise the parvocellular pathway response. Its check size was 4.5 cm x 5.5 cm, (a visual angle of 5.2° horizontally and 6.3° vertically), with the mean luminance and contrast levels of the red/green stimulation 21 cd/m$^2$ and 38% respectively. Each checkerboard reversed phase repeatedly at a rate of 2Hz. Attention was directed towards the centre of the screen with a blue fixation dot (8’ in diameter), such that participants were instructed to ignore the flashing checkerboard background, and to focus on the dot and respond quickly when it turned yellow (which it did for a duration of 500 ms, at random intervals of between 1000 ms and 4000 ms). The total duration of the task was four minutes.

4.3.4.6.2 Tunnel vision task (TV)

The TV task assessed central versus peripheral visual field processing. This task was designed to examine visual field processing at a 20° visual angle compared to fixation (Roge et al., 2003). Participants were asked to fixate on a small cross in the centre of the black screen. White squares (80%) and triangles (20%) were presented briefly in four locations along a horizontal plane, separately centrally (3.5° visual angle from fixation) and peripherally (20° visual angle from fixation) for the left and right hemifield. Stimuli were presented with equal probability at each position (5% at each position for triangles and 20% at each position for squares). Stimuli were displayed for a duration of 100 ms at random intervals between 820 ms and 1180 ms (mean =
The size of the squares was 1.9 cm x 1.9 cm (visual angle of 2.71°). The size of the triangles was 2.1 cm x 2.1 cm (visual angle of 2.99°). During the task, participants were instructed to respond only to triangles. Additionally, the numbers 0 to 9 were randomly presented over the fixation cross (this aspect of the task was used for another purpose that was independent of the present thesis and will not be described further here). However, subjects were instructed to ignore the numbers and focus on the shapes. A 30-second practice trial was given prior to each test session, and the task duration was 3.5 minutes.

4.3.4.6.3 Startle Reflex/Pre-Pulse Inhibition Task

This task examined sensorimotor gating. It consisted of a 70 dB SPL white-noise background against which a train of ‘startle’ stimuli were presented binaurally to participants through ear inserts. The task began with a one-minute acclimatisation period (of the white noise), followed by eight pulse alone (PA; habituation) trials. Following this, the main task consisted of eight pre-pulse (PP) and eight PA stimuli, delivered in a pseudorandom order. PA trials are those trials containing only a startle stimulus, and PP trials are those containing both a startle stimulus and a pre-pulse stimulus that preceded the startle stimulus by 60 ms. The SOA varied between 16 seconds and 24 seconds, with a mean of 20 seconds. PA stimuli were 40 ms (including <1ms rise and <1ms fall times) bursts of white noise presented at 108dB SPL, and ‘pre-pulse’ (PP) stimuli were PA stimuli that followed 20 ms (including <1 ms rise and <1 ms fall times) bursts of white noise presented at 80 dB SPL by 60ms.

During the startle protocol, visual stimuli were displayed on the monitor, in which a blue face appeared at random intervals, either with or without a nose. Participants were instructed to watch the monitor, and to press the response button when they saw a face with a nose. This visual task was designed to keep the participants’ focus away from the startling sounds during the task, and responses were not recorded (this visual discrimination task is hereafter referred to as the ‘visual face discrimination task’). Participants were told that they were going to hear a sequence of loud startling sounds, but to ignore them and continue with the task on the screen. The task took approximately nine minutes to complete.
4.3.4.6.4 Mismatch Negativity (MMN)

The MMN task examined auditory discrimination processes. This task involved the presentation of a series 80 dB SPL ‘standard’ and ‘deviant’ tones, presented via ear inserts. The deviant tones differed from the standard tones in duration only. Standard tones had a frequency of 1000 Hz and 50 ms duration (including 5 ms rise and 5 ms fall times), whereas deviant tones had a frequency of 1000 Hz and 100 ms duration (including 5 ms rise and 5 ms fall times). Tones were presented binaurally to the participant in random order (91% standards, 9% deviants). The task consisted of 511 standard tones and 50 deviant tones, with a variable SOA between 0.45 and 0.55 seconds. During these auditory presentations, the above Visual Face Discrimination Task was performed, with participants instructed to ignore the tones and focus on the visual task. The duration of the task was approximately seven minutes.

4.3.4.6.5 Auditory Oddball Task

The auditory oddball task examined higher cognitive processing associated with auditory stimulus processing. The task consisted of a series of target and non-target stimuli, presented in random order. These stimuli were delivered binaurally, via ear-inserts. The SOA varied between 750 ms and 1150 ms, with a mean of 950 ms. A total of 60, 1000 Hz target tones, and 390, 1100 Hz non-target tones were presented, where the overall probability of a target tone was 13% and a non-target tone was 87%. Stimulus tones were presented at 80dB SPL with a 50 ms duration (including 10 ms rise and fall times). Participants were instructed to press the response button as quickly and as accurately as possible to the low tone only. No response was required for non-targets. Accuracy and response time were recorded. The duration of the task was approximately seven minutes, and it was preceded by a 60-second practice task.

4.3.5 Data acquisition

EEG data were acquired using tin electrodes located at 30 scalp sites, plus one ocular site (below the left eye), referenced to the left mastoid, according to the International 10/20 System. An electrode was also placed at the nose (for subsequent mismatch negativity re-referencing). The ground electrode was located between FPz and Fz. All
data were continuously sampled at 500 Hz, with a 0.05 Hz to 100 Hz band pass. Impedances were below 5 kOhm at the start of each session.

4.3.6 ERP data analysis

Data were analysed using Neuroscan Edit 4.2 software (Neurosoft Inc., 1998). All data were EOG corrected (Croft & Barry, 2000) and re-referenced to common average (unless otherwise stated). Non-ocular artefacts were identified manually, and remaining segments removed if the recorded signal at any EEG electrode exceeded ±200µV, except for the Startle Reflex and Pre-pulse Inhibition responses.

4.3.6.1 Pattern Reversal task

Data were low pass filtered at 30 Hz (zero-phase shift, 12 dB slope) segmented (-100 ms to +460 ms post-stimulus), and baseline corrected using the pre-stimulus interval. Trials were averaged in the time domain, separately for the parvocellular and magnocellular stimuli for each session (NSD and SD). The early P100 and N100 components were analysed at Oz only, as this midline occipital site is where these electrophysiological components of interest display the greatest signal-to-noise ratio (Mangun & Hillyard, 1991). To determine each individual magnocellular and parvocellular amplitude, the SD and NSD sessions were averaged, and the most positive going peak within the window defined by the grand mean peak latency ± 30 ms was selected. Secondly, for each individual waveform for each subject, the P100 peaks were classified as the individual grand mean peak latency ± 15 ms. This procedure was repeated for the N100 peaks. The peak-to-peak amplitude for the P100 and N100 was used as it is less susceptible to noise. Overall, there were 180 trials for each of the PR ERPs.

4.3.6.2 Tunnel Vision task

Data were low pass filtered at 30 Hz (zero-phase shift, 12 dB slope), segmented (~200 ms to +800 ms post-stimulus), and baseline corrected using the pre-stimulus interval. Correct trials were averaged separately for the target (triangle) and non-target (square) stimuli.
The early sensory P100 and N100 components, attentional N100 and later P300 components were assessed. The electrodes used were Oz for the P100 and N100 peak-to-peak amplitudes of non-target responses, Fz for the N100 attentional peak-to-peak amplitudes for non-target responses (Hillyard & Anllo-Vento, 1998), and Pz for the P300 peak-to-peak amplitudes of target responses (Tsai et al., 2005). These sites were chosen as they are where the specific electrophysiological components have the greatest signal-to-noise ratios. Amplitudes and latencies for the TV task responses were detected by proprietary software routines and based on previously employed latency windows. These were the most positive peak in the window from 80ms to 140 ms for the P100 (Han et al., 2000), the most negative peak in the window from 120 ms and 180 ms for the N100 (Krull et al., 1993), the most negative peak between 140 ms and 200 ms for the attentional N100 (Hillyard & Anllo-Vento, 1998), and the most positive peak between 320 ms and 600 ms for the P300 (Han et al., 2000; Polich & Bondurant, 1997). After initial peak detection, waveforms were manually inspected to ensure that the peaks identified were genuine and preceded each other in correct order. The EEG epochs of the target trials with omitted responses were not included in the stimulus-locked ERP.

The outcome measures were average reaction time to targets, number of errors of omission, and percentage of errors of commission. Reaction time (RT) was recorded as the time between target onset and the first correct key press. Trials with RTs shorter than 200 ms and longer than the next stimulus onset were excluded from the analyses. Errors of omission were calculated as the number of missed responses to targets. Errors of commission were calculated as the percentage of actual responses in relation to the number of targets presented.

4.3.6.3 Startle Reflex/ Pre-pulse Inhibition

The startle reflex in the current study was measured using the EOG channel. The EOG data was filtered (band-pass 0.01-8 Hz, 12 dB slope) and segmented (−100 ms to +798 ms post-stimulus). Trials were averaged separately for the PP and PA trials for each session (NSD and SD). The PA and PP responses were operationally defined as the peak EOG response within the time window of 75 ms and 250 ms of the startle stimulus (Kumari, 1998). Individual trials were excluded if the response was not within 50 ms of the latency of the grand mean response for the same session.
Rejection criteria included a failure to have a steady baseline ±25 µV within the time window -200 ms to 40 ms, or if a participant blinked prior to the 75 ms time window. Participants were excluded if they had more than 50% trials rejected for a particular session.

Pre-pulse inhibition (PPI) was defined as the amplitude attenuation of the PP relative to the PA stimulus trials, according to the following formula: PPI = (PA-PP)/PA (Kumari, 1998; Hutchinson & Swift, 1999). PPI was calculated for each subject for the NSD and SD session separately.

4.3.6.4  Mismatch Negativity

MMN data were re-referenced to the nose, low pass filtered at 30 Hz (zero-phase shift, 12 dB slope) and segmented (–100 ms to +600 ms post-stimulus). Trials were averaged separately for each of the standard and the deviant stimuli, for the NSD and SD session separately. Previous studies (Näätänen, 1992) have documented a polarity inversion in MMN as it moves from anterior to posterior regions, and frontal regions contribute significantly to the generation of the MMN, therefore analysis was restricted to frontal sites (Fz, F3 and F4). To determine whether each individual subject elicited an MMN response, the SD and NSD sessions were averaged, and a MMN response was determined based on a polarity reversal at P7 and P8 (relative to frontal sites). The topography and latency were checked to ensure they were consistent with the grand mean. The MMN response was calculated by subtracting the standard stimulus ERPs from the corresponding deviant stimulus ERPs, thus resulting in a difference waveform. The difference between the waveforms elicited in the NSD and SD sessions was then quantified by calculating the integral of the area under the curve of each, over the interval from 100 ms to 200 ms for each subject separately (Sallinen & Lyytinen, 1997).

4.3.6.5  Auditory Oddball Task

Data were low pass filtered at 30 Hz (zero-phase shift, 24 dB slope) and segmented (–200 ms to +800 ms post-stimulus). Trials were averaged in the time domain for the NSD and SD session separately. As the N1/P2 complex has previously been reported to be elicited maximally from central sites (Barry, Kirkaikul, & Hodder, 2000), the Cz
electrode was used for this analysis. The N1/P2 complex was calculated for the non-target trials only. The N100 component was defined as the largest negative peak occurring within the latency window of 80 ms to 140 ms, and the P200 component was defined as the largest positive peak within the window of 140 ms to 250 ms (Polich & Bondurant, 1997). Peak amplitude was measured relative to the previous peak, and peak latency was measured from the time of stimulus onset. As the P300 is maximal over parietal scalp regions (Polich & Kok, 1995), the Pz electrode was used for analysis. Only target trials that received a correct response were included in the P300 averages. The P300 waveforms elicited in the NSD and SD sessions were quantified separately, by calculating the integral of the area under the curve of each, over the interval from 250 ms to 600 ms (Croft et al., 2003). Reaction times were measured as the time between the onset of the target tone and the first button press. Valid behavioural responses were classified as those within the response window of 100 ms to 900 ms. Response accuracy, error rate, and omission rate were calculated as percentage correct, erroneous, and omitted responses respectively.

4.3.7 Statistical analysis

4.3.7.1 Behavioural dispositional measures, simulated driving task, objective sleepiness measures, and neurocognitive tasks

Outliers of more than three standard deviations from the mean of any single variable were excluded from the analysis. Mood, as measured by the SCL-90-R, and sleep recorded for the week and night prior to each session was compared between sessions using Wilcoxon Signed Ranks tests. For the behavioural dispositional measures, data were not normally distributed and so non-parametric tests were used. In order to determine whether sleep deprivation affected measures of behavioural disposition, separate Wilcoxon Signed Ranks tests tested for differences between the NSD and SD session, with subjective sleepiness, performance, and sleepiness symptoms ratings as the dependent variables. For the Stop Driving questionnaire, chi-squared statistics were performed to determine whether there was a difference in the proportion of drivers who stated that they would continue to drive between the NSD and SD sessions, on a 1) short drive, and 2) a long country drive.

Some of the performance variables on the AusEd driving simulator and neurocognitive tasks were not normally distributed. Where possible these variables
were transformed to produce a normal distribution of data (see Table 4.3), and if not, non-parametric tests were used. For normally distributed data, changes in performance between the two sessions were testing with paired samples t-tests. For non-parametric variables, Wilcoxon Signed Ranks tests were used to assess the effect of sleep deprivation on performance variables. Linear regression analyses were performed to determine whether slow eye closure, as measured by PERCLOS, and PVT lapses were predictive of a) crashes and b) lateral lane position on the simulated driving task.

Table 4.3: Transformations of the behavioural dispositional measures, simulated driving and neurocognitive task variables

<table>
<thead>
<tr>
<th>Test</th>
<th>Variable</th>
<th>Transformation</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>Aus Ed variables</td>
<td>Lane position variation</td>
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<td>Parametric</td>
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<td></td>
<td>Mean braking RT</td>
<td>Log (MRT)</td>
<td>Parametric</td>
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<td></td>
<td>Speed variation</td>
<td>Log (speed)</td>
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<td></td>
<td>Number of crashes</td>
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<td>Non-parametric</td>
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<td>Objective Sleepiness</td>
<td>Critical Flicker Fusion</td>
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<td>PERCLOS</td>
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<tr>
<td>Neurocognitive tasks</td>
<td>PVT Median RT</td>
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<td>Parametric</td>
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<td></td>
<td>PVT lapses</td>
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<td></td>
<td>PVT Fastest 10% RT</td>
<td>Log(Fast10%RT)</td>
<td>Parametric</td>
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<td></td>
<td>PVT Reciprocal of slowest 10% RT</td>
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<td>Non-parametric</td>
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<td></td>
<td>Simple/ Choice/ Digit Vigilance</td>
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<td>Non-parametric</td>
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<td>mean RT</td>
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<td>Digit Vigilance Errors</td>
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<td>Stroop Time</td>
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<td>Stroop Errors</td>
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<td>Digit Symbol Substitution Task</td>
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<td>Subjective Sleepiness</td>
<td>KSS</td>
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<td>Subjective sleepiness</td>
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<td></td>
<td>Performance</td>
<td></td>
<td>Non-parametric</td>
</tr>
<tr>
<td></td>
<td>Subjective performance rating</td>
<td></td>
<td>Non-parametric</td>
</tr>
<tr>
<td></td>
<td>Subjective performance rating</td>
<td></td>
<td>Non-parametric</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Stop Driving</td>
<td></td>
<td>Non-parametric</td>
</tr>
</tbody>
</table>
4.3.7.2 ERP data

4.3.7.2.1 Pattern Reversal (PR) task

To reduce positive skews in the PR P100 and N100 peak amplitude distributions, data were transformed using the square root function. In order to determine whether there were differences in early sensory processes following sleep deprivation, as a function of pathway and ERP index, a three-way (Index: P100, N100; Session: SD, NSD; Pathway: Magnocellular, Parvocellular) repeated measures analysis of variances (ANOVA) was performed, where the dependent variable was the amplitude of the ERP component at Oz. Further, to determine whether there was any effect of sleep deprivation on the speed of processing of the above early sensory processes, parallel analyses were performed using latency instead of amplitude as the dependent variable.

4.3.7.2.2 Tunnel Vision (TV) task

To reduce positive skews in the TV P100 and N100 sensory peaks, and N100 and P300 attentional peak amplitude distributions, data were transformed using the natural log function. In order to determine whether there were differences in behavioural responses following sleep deprivation, two, two-way (Session: SD versus NSD; Field: Central versus Peripheral) repeated measures analysis of variances (ANOVA) were performed, where the dependent variables were 1/ reaction time to correct targets, 2/ the number of errors of omission, and 3/ the percentage of errors of commission. In order to determine whether there were differences in early sensory processes following sleep deprivation, as a function of visual field, a three-way (Session: SD versus NSD; Field: Central versus Peripheral; Index: P100, N100) repeated measures ANOVA was performed, where the dependent variable was peak amplitude of the ERP component. To determine whether there were changes in later attentional processes during the TV task following sleep deprivation, a two-way ANOVA (Session; Field) was performed, with the N100 peak-to-peak amplitude at Fz as the dependent variable. In order to determine whether there were later cognitive changes associated with sleep deprivation, the same analysis was performed for the P300 peak-to-peak amplitude at Pz. Further, to determine whether there was any effect of sleep deprivation on the speed of processing of the above early sensory and later cognitive processes, parallel analyses were performed using latency instead of amplitude as the dependent variable.
4.3.7.2.3 Startle reflex/ Pre-pulse Inhibition Task

To determine whether there was a pre-pulse response in the NSD session, a one-sample t-test was calculated. To determine whether there was a difference in the amplitudes of the pulse alone (PA) trials and pre-pulse (PP) trials between the NSD and SD sessions, two, one-way ANOVAs were performed, with PA and PP amplitudes as the dependent variable. To determine whether there was any effect of sleep deprivation on the speed of processing of the PA and PP trials, parallel analyses were performed using latency instead of amplitude as the dependent variables. To determine whether there was a difference between the NSD and SD sessions in the amplitude of pre-pulse inhibition (PPI), a Wilcoxon Signed Rank test was performed on the PPI amplitude data.

4.3.7.2.4 Mismatch Negativity

To determine whether there was a difference in the area under the curve (AUC) of the mismatch response between the NSD and SD session, a one-way (Session: NSD, SD) repeated measures ANOVA was performed on the AUC data.

4.3.7.2.5 Auditory Oddball Task

To determine whether there was a difference in the behavioural measures between the NSD and SD session, a directional t-test was performed predicting a reduction in response accuracy, slower RTs, and a higher error and omission rate in the SD session compared to the NSD session. To determine whether there was a difference in the N1 and P2 amplitudes at Cz between the NSD and SD sessions, two, one-way (Session: NSD, SD) repeated measures ANOVA was performed on the peak-to-peak amplitude data. To determine whether there was any effect of sleep deprivation on the speed of processing of the N1 or P2 complexes, parallel analyses were performed using latency instead of amplitude as the dependent variable. To determine whether there was a difference in the area under the curve of the P300 component between the NSD and SD session, a directional t-test was performed predicting a reduced activation of the P300 response in the SD compared to the NSD session.
4.4 Results

4.4.1 Mood and sleep prior to each session

There was no significant difference in mood ratings measured by the SCL-90-R, for the week prior to each session, between the NSD and SD sessions (p = 0.86). In the SD session, there no significant difference in mood ratings recorded in the morning prior of the SD session and ratings recorded the following morning after 24-hours awake (p = 0.78). The sleep diary results for the averaged hours of sleep each night for one week prior to each session did not differ between the NSD session (mean = 6.76 ± std. dev.= 0.99 hours) and the SD session (6.79 ± 1.14 hours; p = 0.55). Similarly, there was no difference in the number of hours sleep recorded on the night prior to the NSD session (6.68 ± 0.88 hours) and the SD session (6.90 ± 0.92 hours; p = 0.98).

4.4.2 Measures of behavioural disposition

The means, standard deviations and significance levels for the questionnaire data are displayed in Table 4.4. Two participants’ sleepiness symptoms questionnaire data from the NSD session were missing. Two participants’ VAS scores from the NSD session and three from the SD session were missing. Additionally, in the NSD session, two participants’ KSS and stop driving data, and one participant’s performance rating data was not recorded.

The total subjective mood rating, as measured by the VAS, was significantly higher at the end of the SD session when compared to the end of the NSD session (Figure 4.1). Specifically, the sub-scales drowsiness, lethargy and tension were rated more highly following 24-hours of sleep deprivation. Similarly, scores on the Karolinska Sleepiness Scale (KSS) were significantly higher in the SD session than the NSD session (Figure 4.1).

The overall rating of sleepiness symptoms questionnaire was also higher following 24-hours of sleep deprivation, compared to the NSD session (Figure 4.2). Specifically, the symptoms “struggling to keep eyes open”, “vision becoming blurred”, “difficulty keeping to the middle of the road”, “difficulty maintaining correct speed”, “mind wandering”, “reactions slow” and “head dropping down” were noticed at least “occasionally” during the driving session following sleep deprivation,
compared to very infrequently in the NSD session. For the performance ratings, participants rated their performance significantly lower during the SD session, compared to the NSD session.

Table 4.4 Means and standard deviations (Std. Dev.) for the questionnaires data for the no sleep deprivation (NSD) and sleep deprivation (SD) sessions.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>NSD N</th>
<th>NSD Mean ± Std. Dev</th>
<th>SD N</th>
<th>SD Mean ± Std. Dev</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (total)</td>
<td>43.24 ± 20.65</td>
<td>63.61 ± 19.92</td>
<td>Wilcoxon = -3.23, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alert – Drowsy</td>
<td>3.29 ± 2.54</td>
<td>6.69 ± 2.57</td>
<td>Wilcoxon = -2.54, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calm – Excited</td>
<td>2.24 ± 1.89</td>
<td>2.63 ± 2.09</td>
<td>p = 0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong – Feeble</td>
<td>2.88 ± 2.06</td>
<td>4.56 ± 2.13</td>
<td>Wilcoxon = -2.49, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear-headed – Muzzy</td>
<td>3.24 ± 2.14</td>
<td>6.50 ± 2.10</td>
<td>Wilcoxon = -2.71, p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-coordinated – Clumsy</td>
<td>3.12 ± 2.60</td>
<td>5.38 ± 2.42</td>
<td>Wilcoxon = -2.94, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energetic – Lethargic</td>
<td>4.12 ± 2.52</td>
<td>7.25 ± 1.24</td>
<td>Wilcoxon = -2.55, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contented – Discontented</td>
<td>1.88 ± 1.36</td>
<td>3.19 ± 2.14</td>
<td>Wilcoxon = -1.97, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troubled – Tranquil</td>
<td>2.12 ± 1.32</td>
<td>2.94 ± 1.98</td>
<td>p = 0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quick-witted – Mentally</td>
<td>3.76 ± 2.14</td>
<td>6.88 ± 1.89</td>
<td>Wilcoxon = -3.06, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relaxed – Tense</td>
<td>2.35 ± 1.37</td>
<td>4.25 ± 2.14</td>
<td>Wilcoxon = -2.38, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentive – Dreamy</td>
<td>2.88 ± 2.12</td>
<td>5.69 ± 1.78</td>
<td>Wilcoxon = -3.06, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proficient – Incompetent</td>
<td>3.00 ± 1.54</td>
<td>6.19 ± 2.23</td>
<td>Wilcoxon = -3.18, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy – Sad</td>
<td>2.12 ± 2.09</td>
<td>2.31 ± 1.58</td>
<td>p = 0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antagonistic – Amicable</td>
<td>2.41 ± 1.62</td>
<td>2.69 ± 1.96</td>
<td>p = 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interested – Bored</td>
<td>1.82 ± 1.07</td>
<td>3.25 ± 2.32</td>
<td>Wilcoxon = -2.50, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociable – Withdrawn</td>
<td>2.12 ± 1.32</td>
<td>3.81 ± 1.76</td>
<td>Wilcoxon = -3.03, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KSS</td>
<td>3.00 ± 1.97</td>
<td>7.53 ± 1.71</td>
<td>Wilcoxon = -3.54, p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td>4.39 ± 2.15</td>
<td>2.16 ± 1.77</td>
<td>Wilcoxon = -3.57, p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepiness Symptoms (total)</td>
<td>16.88 ± 7.30</td>
<td>28.05 ± 9.04</td>
<td>Wilcoxon = -3.14, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Struggling to keep eyes</td>
<td>1.71 ± 1.26</td>
<td>3.63 ± 1.61</td>
<td>Wilcoxon = -3.22, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision becoming blurred</td>
<td>1.94 ± 1.09</td>
<td>3.32 ± 1.60</td>
<td>Wilcoxon = -2.78, p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodding off to sleep</td>
<td>1.41 ± 1.23</td>
<td>2.37 ± 1.77</td>
<td>p = 0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty maintaining lane</td>
<td>2.88 ± 1.45</td>
<td>4.58 ± 1.30</td>
<td>Wilcoxon = -3.34, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty maintaining speed</td>
<td>3.35 ± 1.37</td>
<td>4.63 ± 1.38</td>
<td>Wilcoxon = -2.24, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mind wandering</td>
<td>2.06 ± 0.83</td>
<td>3.11 ± 1.41</td>
<td>Wilcoxon = -2.91, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactions slow</td>
<td>2.12 ± 1.17</td>
<td>3.74 ± 1.59</td>
<td>Wilcoxon = -3.14, p &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head dropping down</td>
<td>1.35 ± 0.86</td>
<td>2.74 ± 1.59</td>
<td>Wilcoxon = -2.51, p &lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4.1: Ratings for Karolinska Sleepiness Scale (KSS) and Visual Analogue Scale subscales in the No Sleep Deprivation (blue) and Sleep Deprivation (red) sessions. Error bars represent standard deviations; * = p<0.05.
Figure 4.2: Ratings of the eight Sleepiness Symptoms in the no sleep deprivation (blue) and sleep deprivation (red) sessions. Error bars represent standard deviations; * = p<0.05.

For the Stop Driving questionnaire, in which participants’ were asked if they would continue to drive in their current state, on a short city drive and a long country drive, the proportion of participants who stated that they would continue to drive is shown in Table 4.5. The same proportion of participants stated that they would continue to drive in the NSD session, on a short city drive and a long protracted country drive. For the SD session, only 22% of Participants said they would continue to drive in the city, and this dropped to less than 17% for a long drive, after being awake for 24 hours. There was a significant difference in the proportion of participants who stated that they would continue to drive on a short drive ($\chi^2 = 12.66$, p< 0.005) and on a long drive ($\chi^2 = 15.10$, p<.001) between the two session.
Table 4.5: Percentage of participants who stated they would continue to drive on a short city drive and long country drive, in the no sleep deprivation (NSD) and sleep deprivation (SD) session

<table>
<thead>
<tr>
<th></th>
<th>NSD session (%)</th>
<th>SD session (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short city drive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue to drive</td>
<td>82.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Long country drive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue to drive</td>
<td>82.4</td>
<td>16.7</td>
</tr>
</tbody>
</table>

4.4.3 Simulated driving task and objective sleepiness

Means and standard deviations of the Simulated Driving Task variables are displayed in Table 4.6. One participant’s driving simulator speed and lateral lane position data in the SD session could not be analysed due to technical problems, therefore this subject’s data was excluded from the analysis, leaving 18 participants overall. Six subjects in the NSD session and five from the SD session did not have PERCLOS data as there were problems downloading the data from the device. Three subjects (two in the NSD and one in the SD session) had unreliable CFF scores (abnormally high) so these subjects’ data were excluded from the CFF analysis.

The results of the driving simulator variables in each session are depicted in Figure 4.3. On the driving simulator, participants displayed significantly more speed variation and lane position variability in the SD session compared to NSD session. Participants were also significantly slower to brake in response to up-coming trucks when sleep deprived. There was no significant difference in the number of crashes during the driving simulator task between sessions. There was a significant difference in the average number of slow eye closures, as measured by PERCLOS during the driving task, between sessions, with a higher frequency of slow eye closure in the SD session.
Table 4.6: Means, Standard deviations (Std. Dev.) and minimum and maximum values from the simulated driving task variables in the no sleep deprivation (NSD) and sleep deprivation (SD) sessions

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>NSD min</th>
<th>NSD max</th>
<th>NSD (Mean ± Std. Dev.)</th>
<th>N</th>
<th>SD min</th>
<th>SD max</th>
<th>SD (Mean ± Std. Dev.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lane position (cm)</td>
<td>19</td>
<td>31.25</td>
<td>115.82</td>
<td>48.87 ± 19.11</td>
<td>17</td>
<td>31.74</td>
<td>124.04</td>
<td>60.39 ± 22.61</td>
<td>t(16) = -4.58, p&lt; 0.001</td>
</tr>
<tr>
<td>Speed deviation (km/h)</td>
<td>19</td>
<td>0.91</td>
<td>4.35</td>
<td>2.23 ± 0.97</td>
<td>17</td>
<td>1.31</td>
<td>8.92</td>
<td>3.25 ± 1.85</td>
<td>t(16) = -4.41, p&lt; 0.001</td>
</tr>
<tr>
<td>Mean braking RT (ms)</td>
<td>19</td>
<td>737.71</td>
<td>2954.22</td>
<td>1251.17 ± 451.33</td>
<td>18</td>
<td>951.44</td>
<td>3061.11</td>
<td>1454.16 ± 474.07</td>
<td>t(17) = -3.14, p&lt; 0.01</td>
</tr>
<tr>
<td>Std. Dev. Braking RT (ms)</td>
<td>19</td>
<td>86.68</td>
<td>1356.26</td>
<td>331.68 ± 318.80</td>
<td>18</td>
<td>116.70</td>
<td>1715.07</td>
<td>633.74 ± 506.55</td>
<td>Wilcoxon = -2.64, p&lt; 0.01</td>
</tr>
<tr>
<td>Crashes</td>
<td>19</td>
<td>0.00</td>
<td>1.00</td>
<td>0.16 ± 0.38</td>
<td>18</td>
<td>0.00</td>
<td>1.00</td>
<td>0.20 ± 0.41</td>
<td>p = 1.00</td>
</tr>
<tr>
<td>PERCLOS</td>
<td>13</td>
<td>0.01</td>
<td>3.34</td>
<td>0.74 ± 0.90</td>
<td>14</td>
<td>0.14</td>
<td>8.06</td>
<td>2.18 ± 2.33</td>
<td>Wilcoxon = -2.12, p&lt; 0.05</td>
</tr>
<tr>
<td>CFF</td>
<td>16</td>
<td>32.00</td>
<td>45.00</td>
<td>37.38 ± 3.46</td>
<td>16</td>
<td>26.00</td>
<td>49.00</td>
<td>35.44 ± 5.63</td>
<td>p = 0.15</td>
</tr>
</tbody>
</table>

RT = reaction time; CFF = Critical Flicker Fusion task; PERCLOS = percentage slow eye closure per hour.
Figure 4.3: Mean responses of the AusEd driving simulator variables a) mean braking reaction time, b) average lane position variation, c) average speed variation; d) crashes and e) percentage of slow eye closure (PERCLOS) in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions. Error bars represent SEMs; * = p <0.05; # = p <0.01
4.4.4 Neurocognitive measures

Means and standard deviations of the neurocognitive task variables are displayed in Table 4.7. Due to equipment issues, the PVT was not completed by one participant, leaving 18 participants in total for the PVT analysis, and three subjects’ Stroop data was missing, leaving 16 participants in total for the Stroop analysis. The results of the PVT variables in each session are depicted in Figure 4.4. Median RT and the fastest 10% of reaction times were significantly faster in the NSD session compared to the SD session. There was a significant increase in the number of PVT lapses (reaction times greater than 500 ms) following 24-hours of sleep deprivation. The slowest 10% of reaction times also increased significantly in the SD session compared to the NSD session, indicating a worsening of performance. There was a significant increase in mean Simple RT performance when participants were sleep deprived, compared to the NSD session (Figure 4.5a). Similarly, sleep deprivation significantly slowed mean Choice RT performance (Figure 4.5c). For the Digit Vigilance task, although participants were slower in reacting to targets in the SD session, this was not significant, nor was there any significant difference in false alarms between sessions (Figure 4.5b). The number of correct symbols completed in the DSST task did not differ significantly between sessions (Figure 4.5f). For the Stroop Task, there was no significant difference between the sessions in the number of errors or time to complete the congruent trial (Figure 4.5d), or the incongruent trials (Figure 4.5e). To examine whether eye closure and PVT attentional lapses were predictive of crashes and lane position on the driving simulator, linear regression analyses were performed. After sleep deprivation, slow eye closure predicted 53% of the variance in crashes \(F(1, 11) = 12.47; p<0.05\), and 40% of the variance in lateral lane position \(F(1, 11) = 7.28, p<0.05\). PVT lapses were not predictive of any driving simulator variables.
Table 4.7 Means, Standard Deviations (Std. Dev.), and minimum and maximum values for the neurocognitive tasks in the no sleep deprivation (NSD) and sleep deprivation (SD) sessions

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSD</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>PVT Median RT</td>
<td>18</td>
<td>199.00</td>
<td>267.00</td>
</tr>
<tr>
<td>PVT Lapses</td>
<td>18</td>
<td>0.00</td>
<td>11.00</td>
</tr>
<tr>
<td>PVT Fastest 10% RT</td>
<td>18</td>
<td>172.31</td>
<td>224.86</td>
</tr>
<tr>
<td>PVT Slowest 10% RT</td>
<td>18</td>
<td>1.29</td>
<td>3.43</td>
</tr>
<tr>
<td>Mean Simple RT</td>
<td>18</td>
<td>205.06</td>
<td>291.02</td>
</tr>
<tr>
<td>Mean Choice RT</td>
<td>18</td>
<td>374.27</td>
<td>512.76</td>
</tr>
<tr>
<td>Digit Vigilance RT</td>
<td>18</td>
<td>356.26</td>
<td>457.27</td>
</tr>
<tr>
<td>Digit Vigilance False Alarms</td>
<td>18</td>
<td>.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Congruent Stroop Time</td>
<td>16</td>
<td>20.04</td>
<td>42.95</td>
</tr>
<tr>
<td>Congruent Stroop Errors</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incongruent Stroop Time</td>
<td>17</td>
<td>49.92</td>
<td>95.68</td>
</tr>
<tr>
<td>Incongruent Stroop Errors</td>
<td>17</td>
<td>.00</td>
<td>8.00</td>
</tr>
<tr>
<td>DSST</td>
<td>19</td>
<td>40</td>
<td>99</td>
</tr>
</tbody>
</table>

PVT = Psychomotor Vigilance Task; RT = reaction time; DSST = Digit Symbol Substitution Task
Figure 4.4: Psychomotor Vigilance Task variables a) median reaction time, b) lapses, c) fastest 10% of reaction times and d) reciprocal of the slowest 10% of reaction times in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions. Error bars represent SEMs; * = p <0.05; # = p <0.01.
Figure 4.5: Mean responses for a) Simple reaction time, b) Digit Vigilance reaction time, c) Choice reaction time, d) Congruent Stroop time e) Incongruent Stroop time and f) Digit Symbol Substitution Task in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions. Error bars represent SEMs; * = p <0.05; # = p <0.01
4.4.5 Visual & Auditory ERPs

4.4.5.1 Pattern Reversal Task

Two participants’ data for both the early sensory peaks were excluded as the peaks could not be detected in the NSD session, and one participant’s data was excluded as the peaks could not be detected in the SD session. Means and standard deviations for the early sensory peak-to-peak amplitudes and latencies, for magnocellular and parvocellular evoked responses in each session, are shown in Table 4.8. Grand averages of the magnocellular and parvocellular pathways, for the SD and NSD sessions, are shown in Figure 4.6.

Early visual processing – P100 and N100

There was no significant effect of sleep deprivation on the magnocellular N100 amplitude (F(1,15) = 0.40, p = 0.54), however there was a trend towards an effect of sleep deprivation on the P100 amplitude of the magnocellular pathway (F(1,15) = 3.99, p = 0.06), with amplitude reduced with sleep deprivation. There was no significant main effect of sleep deprivation on the P100 amplitude (F(1,15) = 0.03, p = 0.86), nor on the N100 amplitude (F(1,15) = 0.11, p= 0.74) for the parvocellular pathway. For the parvocellular pathway, there was a significant main effect of sleep deprivation on the P100 latency (F(1,15) = 8.57, p < 0.05), with sleep deprivation prolonging latency. There was no significant main effect of sleep deprivation on the P100 latency of visual evoked responses of the magnocellular pathway (F(1,15) = 0.57, p = 0.46), nor on the N100 latency (F(1,15) = 0.26, p = 0.62). There was no significant effect of sleep deprivation on the N100 latency of the parvocellular pathway (F(1,15) = 0.16, p= 0.69).
Table 4.8: Means and standard deviations (Std. Dev.) of the amplitude and latency for the early sensory peak-to-peak amplitudes and latencies, for the foveal and peripheral ERPs in response to the Tunnel vision (TV) task, and for the magnocellular and parvocellular pathway responses in the Pattern Reversal (PR) task in the Sleep Deprivation (SD) and No Sleep Deprivation (NSD) sessions.

<table>
<thead>
<tr>
<th></th>
<th>NSD Amplitude (uV)</th>
<th>NSD Latency (ms)</th>
<th>SD Amplitude (uV)</th>
<th>SD Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TV task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P100 sensory (Oz)</td>
<td>2.48 ± 1.42</td>
<td>117.63 ± 15.23</td>
<td>2.31 ± 1.64</td>
<td>126.11 ± 21.12</td>
</tr>
<tr>
<td>Foveal</td>
<td>1.78 ± 0.94</td>
<td>113.58 ± 21.85</td>
<td>1.84 ± 1.24</td>
<td>122.74 ± 18.78</td>
</tr>
<tr>
<td>Peripheral</td>
<td>1.85 ± 1.32</td>
<td>167.44 ± 11.08</td>
<td>1.97 ± 1.19</td>
<td>167.00 ± 10.41</td>
</tr>
<tr>
<td>N100 sensory (Oz)</td>
<td>1.99 ± 1.32</td>
<td>170.44 ± 19.13</td>
<td>1.60 ± 1.13</td>
<td>163.31 ± 20.41</td>
</tr>
<tr>
<td>Foveal</td>
<td>2.11 ± 1.81</td>
<td>131.00 ± 17.69</td>
<td>2.97 ± 2.18</td>
<td>139.53 ± 16.75</td>
</tr>
<tr>
<td>Peripheral</td>
<td>4.25 ± 3.44</td>
<td>139.58 ± 13.74</td>
<td>3.75 ± 2.76</td>
<td>146.00 ± 16.62</td>
</tr>
<tr>
<td><strong>PR task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P100 (Oz)</td>
<td>5.48 ± 3.18</td>
<td>470.94 ± 60.72</td>
<td>3.67 ± 3.13</td>
<td>475.28 ± 57.96</td>
</tr>
<tr>
<td>Magnocellular</td>
<td>4.52 ± 3.22</td>
<td>477.06 ± 65.99</td>
<td>4.07 ± 2.93</td>
<td>480.39 ± 48.29</td>
</tr>
<tr>
<td>Parvocellular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N100 (Oz)</td>
<td>3.43 ± 2.12</td>
<td>101.94 ± 16.88</td>
<td>2.77 ± 1.58</td>
<td>104.81 ± 15.82</td>
</tr>
<tr>
<td>Magnocellular</td>
<td>5.83 ± 3.45</td>
<td>108.06 ± 4.77</td>
<td>5.71 ± 2.52</td>
<td>101.38 ± 5.43</td>
</tr>
<tr>
<td>Parvocellular</td>
<td>2.35 ± 2.26</td>
<td>148.69 ± 17.67</td>
<td>1.73 ± 1.55</td>
<td>146.88 ± 20.54</td>
</tr>
<tr>
<td></td>
<td>3.66 ± 3.30</td>
<td>136.69 ± 13.58</td>
<td>3.77 ± 2.69</td>
<td>145.31 ± 21.59</td>
</tr>
</tbody>
</table>
Figure 4.6: Grand Averaged ERPs for the Magnocellular and Parvocellular Stimuli for No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions. Note: N = 16.
4.4.5.2 Tunnel Vision Task

Means and standard deviations for the P100 and N100 sensory amplitudes, N100 attentional amplitudes and P300 amplitudes, for foveal and peripheral evoked responses in each session are shown in Table 4.8.

Behavioural measures

Four participants were unable to complete the task correctly, therefore there were 15 participants overall in the statistical analyses results for the behavioural data. Mean RTs to targets, and errors of omission and percentage error of commission are displayed in Table 4.9. Participants responses were significantly slower to targets in the SD session compared to the NSD session (F(1,14) = 14.03, p<0.01). No overall effect on RT was found for visual field position (F(1,14) = 0.03, p = 0.86), nor was there an interaction of visual field position and sleep deprivation (F(1,14) < 0.01, p = 0.97). Participants made significantly more errors of omission in the SD session compared to the NSD session (F(1,14) = 5.84, p<0.05), however, there was no effect of visual field position (F(1,14) = 1.46, p = 0.25) and no interaction of visual field position and sleep deprivation on errors of omission (F(1,14) = 0.35, p = 0.56). No overall effect of errors of commission was found for visual field position (F(1,14) = 1.71, p = 0.21), sleep deprivation (F(1,14) = 3.43, p = 0.09), nor was there an interaction of visual field position and sleep deprivation (F(1,14) = 0.22, p = 0.65).

Table 4.9: Means and standard deviations (Std. Dev.) for reaction time (RT) to targets, and errors of omission and commission in the foveal and peripheral visual field separately, for the Sleep Deprivation (SD) and No Sleep Deprivation (NSD) sessions

<table>
<thead>
<tr>
<th></th>
<th>RT (ms) (Mean ± Std. Dev.)</th>
<th># Errors of omission (Mean ± Std. Dev.)</th>
<th>% Errors of commission (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSD: foveal</td>
<td>455.19 ± 29.51</td>
<td>1.33 ± 1.88</td>
<td>9.07 ± 3.02</td>
</tr>
<tr>
<td>NSD: peripheral</td>
<td>456.50 ± 47.17</td>
<td>2.00 ± 2.42</td>
<td>9.17 ± 2.95</td>
</tr>
<tr>
<td>SD: foveal</td>
<td>490.91 ± 52.37</td>
<td>3.40 ± 2.7</td>
<td>7.27 ± 2.41</td>
</tr>
<tr>
<td>SD: peripheral</td>
<td>492.83 ± 48.58</td>
<td>3.67 ± 2.16</td>
<td>7.45 ± 2.83</td>
</tr>
</tbody>
</table>
Early visual processing – P100 and N100

Grand averages of the foveal and peripheral early visual ERPs in the SD and NSD sessions are shown in Figure 4.7. Three participants’ data for the N100 early sensory could not be identified in the NSD session. There was a significant visual field effect for the amplitude of the P100 complex ($F(1,18) = 5.67, p<0.05$), with larger peaks at the fovea. No significant effect was found for sleep deprivation on the P100 complex ($F(1,18) = 0.33, p = 0.57$), and this did not interact with visual field ($F(1,18) = 0.15, p = 0.70$). The P100 latency was not significantly affected by visual field position ($F(1,18) = 3.63, p = 0.07$), sleep deprivation ($F(1,18) = 0.68, p = 0.42$), or the interaction of sleep deprivation and visual field ($F(1, 18) = 0.01, p = 0.92$). There was no significant effect of visual field position ($F(1,15) = 0.21, p=0.65$), sleep deprivation ($F(1,15) = 0.59, p = 0.45$), or interaction between sleep deprivation and visual field ($F(1,15) = 1.17, p = 0.30$) on the N100 amplitude. There was no significant effect of visual field position ($F(1,15) = 0.94, p = 0.76$), sleep deprivation ($F(1,15) = 2.08, p = 0.17$), or the interaction of sleep deprivation and visual field ($F(1,15) = 2.54, p = 0.13$) on the N100 latency.

![Figure 4.7: Grand Averaged ERPs in response to Foveal and Peripheral Visual Field Stimuli in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions.](image)

Note: N = 16
Attentional components – N100

Grand averages of the foveal and peripheral N100 attentional components in the SD and NSD sessions are shown in Figure 4.8. Larger amplitudes were evoked in response to peripheral compared to foveal stimuli for the attentional N100 complex at Fz (F(1,18) = 10.02, p<0.01; Figure 4.8). No significant effect was found for sleep deprivation on the N100 amplitude (F(1,18) = 0.40, p = 0.54), and this did not interact with visual field position (F(1,18) = 1.91, p = 0.18). There was a significant reduction in the N100 latency to peripheral compared to foveal evoked responses (F(1,18) = 5.23, p<0.05). There was no effect of sleep deprivation on the N100 latency (F(1,18) = 2.83, p = 0.11), and this did not interact with visual field position (F(1,18) = 0.20, p = 0.66).

Figure 4.8: Grand Averaged ERPs in response to Foveal and Peripheral Visual Field Stimuli in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions. Note: N = 19
Grand averages of the foveal and peripheral later cognitive processes, in the SD and NSD sessions are shown in Figure 4.9. One participants’ data for the P300 peaks was excluded, as the P300 peak could not be identified for the NSD session. There was no significant effect of visual field position on the P300 amplitude (F(1,17) = 0.72, p = 0.79; Figure 4.9). The P300 amplitude was significantly reduced in the SD session compared to the NSD session (F(1,17) = 5.07, p<0.05), however this did not interact with visual field position (F(1,17) = 2.98, p = 0.10). There was no significant effect of visual field on P300 latency (F(1,17) = 0.22, p = 0.65), sleep deprivation (F(1,17) = 0.20, p = 0.66), or interaction between sleep deprivation and visual field position (F(1,17) = 0.00, p = 0.98).

Figure 4.9: Grand Averaged P300 ERPs on response to Foveal and Peripheral Visual Field Stimuli in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions
4.4.5.3 The Startle reflex/ Pre-pulse Inhibition Task

One participant was excluded due to problems with the headphones during the task. Four other participants were excluded as they had more than 50% trial rejections in either session, leaving a total of 14 subjects for the final analysis. The amplitude and latencies for the pulse alone (PA) and pre-pulse (PP) trials for each session are shown in Table 4.10.

A significant PP amplitude was evident in the NSD session \( t(13) = 2.89, p<.05 \). There was no difference in the PA trials between the NSD and SD sessions for amplitude \( F(1,13) = 1.15, p = 0.30 \) or latency \( F(1,13) = 0.64, p = 0.44 \). Similarly, there was no difference in PP response between the NSD and SD sessions, for both amplitude \( F(1,13) = 1.00, p = 0.33 \) or latency \( F(1,13) = 0.37, p = 0.55 \).

<table>
<thead>
<tr>
<th></th>
<th>NSD</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± Std. Dev</td>
<td>Mean ± Std. Dev</td>
</tr>
<tr>
<td>PA amplitude</td>
<td>56.11 ± 52.90</td>
<td>45.62 ± 49.00</td>
</tr>
<tr>
<td>PA latency</td>
<td>111.36 ± 13.74</td>
<td>118.93 ± 38.15</td>
</tr>
<tr>
<td>PP amplitude</td>
<td>24.32 ± 31.46</td>
<td>17.08 ± 28.13</td>
</tr>
<tr>
<td>PP latency</td>
<td>113.29 ± 42.04</td>
<td>121.71 ± 43.56</td>
</tr>
</tbody>
</table>

Table 4.10: Means and standard deviations (Std. Dev) of the amplitude and latencies of the pulse alone (PA) and pre-pulse (PP) responses to the acoustic startle in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions.
The percentage of the pre-pulse inhibition (PPI) observed in each session is depicted in Figure 4.10. There was no significant difference in the percentage of PPI between the NSD and SD sessions (p = 0.47).

![Figure 4.10: Percentage of pre-pulse inhibition (PPI) in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) session](image)

**4.3.5.4 Mismatch Negativity**

The means and standard deviation of the area under the curve data at Fz, F3 and F4, for each session are displayed in Table 4.11. Seven participants’ data were excluded as a clear peak was not able to be distinguished in their NSD session, leaving 12 subjects in the final analysis. There was a trend-level difference between the NSD and SD session, with a smaller area under the curve (AUC) in the SD session compared to the NSD session (F(1, 11) = 19.33, p = 0.07; Figure 4.11). There was no significant main effect for laterality (p = 0.24), nor was there an interaction between laterality and session (p = 0.12).
### Table 4.11: Area under the curve (AUC) data for Mismatch Negativity responses at the three frontal sites in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions

<table>
<thead>
<tr>
<th></th>
<th>NSD (Mean ± Std. Dev.)</th>
<th>SD (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fz AUC</td>
<td>-2.37 ± 1.71</td>
<td>-1.11 ± 1.29</td>
</tr>
<tr>
<td>F3 AUC</td>
<td>-2.03 ± 1.62</td>
<td>-0.77 ± 1.07</td>
</tr>
<tr>
<td>F4 AUC</td>
<td>-1.83 ± 1.35</td>
<td>-1.23 ± 1.58</td>
</tr>
</tbody>
</table>

![Figure 4.11: Grand Averaged ERPs for MMN at the Fz scalp site in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions](image-url)
4.4.5.5 Auditory Oddball Task

Behavioural data, amplitude and latencies for the N1 and P2 complexes, and P300 area under the curve results are displayed in Table 4.12. Two subjects were excluded as the task did not run properly during their NSD sessions, leaving 17 subjects for the N1-P2 and behavioural analyses.

A higher number of errors of omission (t(16) = -2.06, p<0.05), and a lower percentage of correct responses (t(16) = 2.08, p<0.05) was observed in the SD session when compared to the NSD session. There was no effect of sleep deprivation on mean RT (p = 0.79), standard deviation of RTs (p = 0.49), or false alarms (p = 0.50)

Table 4.12: Means and Standard deviations (Std. Dev.) of the behavioural and electrophysiological responses for the Auditory Oddball Task in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions

<table>
<thead>
<tr>
<th></th>
<th>NSD (Mean ± Std. Dev.)</th>
<th>SD (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors of Omission</td>
<td>4.35 ± 3.95</td>
<td>7.59 ± 6.72</td>
</tr>
<tr>
<td>False alarms/ errors</td>
<td>4.06 ± 5.20</td>
<td>3.71 ± 4.61</td>
</tr>
<tr>
<td>Correct responses (%)</td>
<td>88.02 ± 10.88</td>
<td>79.09 ± 18.26</td>
</tr>
<tr>
<td>Mean Reaction Time (ms)</td>
<td>429.24 ± 50.78</td>
<td>432.84 ± 64.46</td>
</tr>
<tr>
<td>Std. Dev of Reaction Time</td>
<td>126.76 ± 60.09</td>
<td>115.76 ± 56.15</td>
</tr>
<tr>
<td>N1 peak to peak amplitude (uV)</td>
<td>4.33 ± 2.02</td>
<td>4.47 ± 3.13</td>
</tr>
<tr>
<td>N1 latency (ms)</td>
<td>91.88 ± 12.25</td>
<td>92.82 ± 8.28</td>
</tr>
<tr>
<td>P2 peak to peak amplitude (uV)</td>
<td>4.03 ± 3.23</td>
<td>4.11 ± 3.63</td>
</tr>
<tr>
<td>P2 latency (ms)</td>
<td>169.24 ± 22.84</td>
<td>176.12 ± 20.68</td>
</tr>
<tr>
<td>P300 Area Under the Curve</td>
<td>3.55 ± 2.65</td>
<td>2.37 ± 2.37</td>
</tr>
</tbody>
</table>
Figure 4.12 depicts the N1-P2 ERP response to the auditory oddball task from the Cz electrode site. There was no significant difference in N1 amplitude ($F(1, 16) = 0.06$, $p=0.81$) or latency ($F(1, 16) = 0.02$, $p=0.89$), between the NSD and SD sessions. Similarly, there was no significant difference in P2 amplitude ($F(1, 16) = 0.02$, $p=0.89$) or latency ($F(1, 16) = 0.19$, $p=0.19$), between the NSD and SD sessions.

Figure 4.12: Grand Averaged ERPs for N1P2 complex of the TTI response at the Cz scalp site in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions.
One additional subject was excluded from the P300 analysis as they did not exhibit a clear P300 in the NSD session, leaving 16 subjects in total for the P300 analyses. The P300 responses at Pz in each session are shown in Figure 4.13. A directional t-test supported our hypothesis that there would be a reduction in the P300 area under the curve in the SD session compared to the NSD session ($t(15) = 1.98, p<0.05$). Behaviourally, participants displayed more errors of omission ($t(16) = -2.06, p<0.05$), and a lower percentage of correct responses ($t(16) = 2.08, p<0.05$) in the SD session when compared to the NSD session. There was no effect of sleep deprivation on mean RT ($p = 0.79$), standard deviation of RTs ($p = 0.49$), or false alarms ($p = 0.50$).

Figure 4.13: Grand Averaged ERPs for the P300 complex of the Auditory Oddball response at the Pz scalp site in the No Sleep Deprivation (NSD; blue) and Sleep Deprivation (SD; red) sessions.
4.5 Discussion

The current experiment examined the effects of 24-hours of acute sleep deprivation on a range of driving-related neural processes in a sample of professional drivers. This experiment aimed to examine the effects of sleep deprivation on driving-related processes using different measures and techniques. It is unclear whether drivers are unaware of their level of sleepiness, are not recognising symptoms of sleepiness, or are poor at making decisions regarding their fitness to drive during sleep loss. Accident risk in sleep-deprived drivers may also be due to small changes in driving performance or neurocognitive deficits. Changes in driving performance during sleep deprivation may also relate to deficits in the underlying neural processes, therefore that psychophysiological underpinnings of visual and auditory attentional-related neural processing was also examined in the present experiment.

4.5.1 The effects of sleep deprivation on behavioural disposition

Significantly higher ratings of subjective sleepiness and sleepiness symptoms, and impaired mood were observed following 24-hours of sleep deprivation compared to after normal sleep. In line with previous studies (Akerstedt & Gillberg, 1990; Gillberg et al., 1994), the current experiment demonstrated a progressive increase in subjective sleepiness, measured by the KSS, in professional drivers after 15 to 20 hours awake. This finding was also corroborated by ratings on the VAS; participants’ ratings of drowsiness, lethargy and tension all increased with sleep deprivation.

There was also a progressive increase in the frequency of specific symptoms of sleepiness and subjective ratings of driving impairment during acute sleep deprivation. The specific symptoms which were reported occasionally or frequently throughout the driving task after sleep deprivation included “struggling to keep eyes open”, “vision becoming blurred”, “difficulty keeping to the middle of the road”, “difficulty maintaining correct speed”, “mind wandering”, “reactions slow” and “head dropping down”. Although these specific symptoms have not been used in previous studies, these findings are consistent with other studies which have reported increases in specific sleepiness symptoms including: “dizziness”, “muscles tense”, “feeling drowsy” and “eyes strained” (Nillson et al., 1997); “heavy eyelids”, “sand in your
“tired eyes”, “difficulties in focusing your eyes”, “irresistible sleepiness”, “difficulties in keeping your eyes open”, “difficulty focusing attention”, “difficulty concentrating” and “periods when you were fighting sleep” (Gillberg et al., 1994). Nillson et al. (1997) clustered 18 symptoms into groups that displayed similar trends across the sleep deprivation session, and found that “tired eyes” and “feeling drowsy” increased most with driving time. Increasing sleepiness symptom frequency has also been reported during one night of sleep loss (Gillberg et al., 1994). Eight symptoms were recorded including ocular symptoms (e.g. “difficulty in keeping your eyes open”), and difficulty with maintaining attention and fighting sleep. In this study, the average of all symptoms was reported, rather than changes in individual symptoms. A cluster of symptoms including “tired eyes” and “feeling drowsy” were most commonly noticed and increased to the greatest degree prior to stopping driving. Symptom scores predicted between 50% and 60% of the variance in performance scores, however, it is unknown which sleepiness symptoms were most valid in their prediction. Similar symptoms (difficulty keeping eyes open, yawning, increased reaction time and difficulties concentrating on the driving) have also been reported by drivers immediately prior to falling asleep behind the wheel, or in people who were afraid of falling asleep during actual on-road driving (Nordbakke & Sagberg, 2007; Summala et al., 1999). Drivers appear to recognise physiological signs and symptoms that indicate to them that they are tired and potentially impaired in their performance, supporting previous studies which suggest that sleepiness is perceived by an individual well before he or she is overcome by sleep (Horne & Baulk, 2004; Akerstedt, 1988). Strong associations have been reported between increasing sleepiness and an increase in the number of incidence on a driving simulator (Reyner & Horne, 1998). Conversely, other studies report that people may fail to appreciate that a high level of sleepiness is accompanied by a high likelihood of falling asleep (Reyner & Horne, 1998). Anecdotal evidence suggests that, after a sleep-related motor vehicle accident, some drivers may report that they did not fall asleep at the wheel, and were not feeling sleepy before the crash (Horne & Reyner, 1999). However, the results from the current experiment suggest that after one night of sleep deprivation, subjective measures of physiological symptoms of sleepiness are recognised by sleepy drivers.
It is important for drivers to then act upon this information and stop driving when they have reached a significant level of sleepiness and/or performance impairment. In the current experiment, drivers could recognise that their performance was impaired when sleep deprived compared to after normal sleep. Further, the majority of drivers also stated that they would stop driving in their current state after 24-hours of sleep deprivation. There were a small proportion of drivers who stated that they felt safe to continue to drive after sleep deprivation, despite a significant decrease in driving performance in the sleep deprivation session. The sample of professional drivers used in this study commonly experience fatigue and sleepiness associated with sleep deprivation and driving for long hours. Therefore, they are used to experiencing the symptoms associated with sleep loss, and to determine when they are safe to drive. However, experienced drivers may also over-estimate their ability to drive safely because they are more confident about their driving ability compared to non-professional drivers. This may explain why a few drivers in the current study reported that they felt safe to continue to drive. Some people are less susceptible to sleepiness, and thus the particular drivers who stated that they would continue to drive may not have had the same level of performance deterioration following sleep loss compared to those who stated that they would stop driving. Overall, however, the results of the performance data would suggest that these drivers would experience significant driving-related performance deterioration following 24-hours of sleep deprivation, and thus would not be safe to drive after this period of time without sleep. The current sample of drivers appeared to be able to make good introspective decisions about their ability to continue to drive safely, which supports previous literature examining the association between subjective and objective (EEG) sleepiness (Horne & Baulk, 2004). Subjects who have less driving experience and knowledge of their limits for driving safely may not have been as accurate in detecting their ability to drive safely compared to professional drivers in the current study.

One of the limitations of laboratory studies is that participants are likely to rate or detect sleepiness and mood differently to what they would report or how they would act in real-world situations. Driving simulators pose less pressure and distractions compared to real driving, and therefore our drivers’ estimates of whether they would continue to drive in their current state are likely to be conservative. Despite this, some participants may over-report sleepiness due to being questioned about it and being...
made more aware of it, whereas others may under-report or not notice their sleepiness as adequately, since they are in a low-risk laboratory environment that does not have the same motivational factors nor threat when compared to real-world driving situations.

Subjective ratings are inherently difficult to interpret, and lack the objectiveness of cognitive tasks. However, it is important to examine these introspective aspects of driving in fatigued subjects, as it provides some insight into the decision-making processes of drivers when they are driving under the conditions of sleepiness and sleep deprivation. It appears, from these findings, that drivers can recognise their sleepiness and mood changes associated with staying awake for an extended period, which supports previous literature suggesting that people are able to make relatively good introspective decisions about their ability to continue to drive safely (Horne & Baulk, 2004; Reyner & Horne, 1998b). However, how they respond to these signals may differ between individuals, since a small proportion of drivers stated that they would continue to drive after a significant period of sleep deprivation. A better understanding of what symptoms are recognised by drivers’ and their relationship to performance deterioration under different conditions is important in educating drivers about specific symptoms to be wary of whilst driving, because they may indicate significant deterioration in driving ability, or imminent sleep onset.

4.5.2 The effects of sleep deprivation on simulated driving

Overall, performance on the simulated driving task was significantly impaired following one night of sleep deprivation compared to after normal sleep. Specifically, lane drifting, variations in speed, and braking reaction times all increased with sleep loss, whereas crash events did not differ between conditions. The effect size for detecting a difference in lateral lane position on the driving simulator between the NSD and SD sessions in this experiment was 0.56. Further, this was observed in a sample of professional drivers who are very experienced drivers, and whom are often exposed to conditions of sleep deprivation in their working life. This is the first study to look at these changes in professional drivers.
The higher average steering deviation scores following sleep deprivation indicated a decreased level of vigilance for this performance measure. Consistent with previous studies using the AusEd driving simulator (Banks et al., 2004; Howard et al., 2007; Vakulin et al., 2007), the current experiment found significant increases in lane drift with sleep loss. This is one of the most robust findings reported with sleep deprivation, and has implications for on-road driving. For instance, the changes demonstrated in the current study are consistent with the epidemiological literature of observed increases in night time crash risk. Variation in lane position has been shown to increase with impaired daytime alertness both on road (O’Hanlon et al., 1995; Philip et al., 2005; Ramaekers & O’Hanlon, 1994), and in simulator settings (George, 2000; George, Boudreau, & Smiley, 1996; Lenne, Triggs, & Redman, 1997; Reyner & Horne, 1998a), and is an indicator of sleepiness-related performance impairment (Arnedt et al., 2001; Arnedt et al., 2000; O’Hanlon, 1974; O’Hanlon, 1984). The present experiment has demonstrated that these changes are also observed following acute periods of sleep deprivation, in professional drivers who commonly experience sleep deprivation. This suggests that changes in lateral lane position may be a sensitive and useful indicator of changes in driving performance in drowsy drivers, and further research into automated methods of detecting variations in lateral lane position during on-road driving is warranted.

Larger variations in speed in the AusEd driving task, found in the sleep deprivation session, are consistent with a reduced ability to divided attention between maintaining correct lane position and checking the speedometer in the top left hand corner of the screen in order to maintain the correct speed. Previous studies have also noted significant speed decreases and variations outside the prescribed speed range with sleep loss, both of which are indicative of unsafe driving (Brookhuis et al., 2003).

No difference in crash events between sessions was demonstrated in the current experiment. Previous studies found increased crashes in subjects who were sleep deprived for 36 to 60 hours (Welsh et al., 1998; Thorne et al., 1998). Whilst the current study design resulted in deterioration in other aspects of driving performance, the degree of sleepiness experienced by the drivers may not have been enough to increase crash risk. This may have been due to the positive circadian effects during the morning period, despite having been awake for 30 hours.
The use of a laboratory based driving task may affect the drivers’ decision-making and levels of sleepiness. It has been noted that driving simulators can produce premature performance and sleepiness impairment when compared to real driving (Philip et al., 2005). Some studies have reported that longer periods of task are required to see any sleep deprivation effects (Richter et al., 2005), however the 30-minute task in the current experiment, following one night of sleep deprivation, was sufficient to observe decrements in performance. Performance on skills required for driving (e.g. reaction time and vigilance tasks) after this period of sleep loss has been demonstrated to be equivalent to performance at a BAC of 0.08% to 0.10% (Dawson & Reid, 1997; Williamson et al., 2001). Driving at these BAC levels is reported to increase accident risk more than twofold (Dunbar, Penttila, & Pikkarainen, 1987), with the implication being that acute sleep deprivation may increase accident risk to a similar degree.

A clear standard for objective measurement of sleepiness in awake active individuals has not emerged. For tasks such as driving, such a measure would need to be capable of detecting brief periods of inattention (O'Hanlon & Beatty, 1977). The current experiment utilised the Copilot – a promising automated measure of objective sleepiness as assessed by slow eye closure. Slow eyelid closure occurs prior to sleep onset, and has been used as a method for indicating sleepiness in active individuals (Santamaria & Chiappa, 1987). As expected, slow eye closure significantly increased while participants were driving on the simulator when sleep deprived in the current experiment. Previous studies investigating the effects of sleepiness on simulated driving and attention tasks have generally found an increase in eye closure duration (using a variety of methods) with increasing hours awake and a lowering of attentional capacity (Morris & Miller, 1996). Strong relationships have also been described between PERCLOS and simulated driving performance (r values of 0.40 to 0.78) using different methods for measuring PERCLOS (Dingus et al. 1987; Wierwille, 1999). Grace (1999) conducted a driving simulation study examining 16 commercial driving license holders to assess the effectiveness of drowsiness feedback on performance, driver alertness and behaviour (Grace et al., 1999). Although there were significant between-subject variations in drowsiness and consequently in the
number of warning alerts, drowsiness feedback reduced drivers’ drowsiness levels and improved performance.

Periods of inattention of even a few seconds would be long enough to result in an accident on the road (O’Hanlon & Beatty, 1977). Methods that can measure brief periods of sleepiness or related performance impairment in drivers include driver-related measures (eye closure, EEG) or vehicle measures (variations in speed or lane position). These methods have the potential to be utilised as drowsiness alerting devices, however further research is needed to validate the Copilot and other ocular monitoring devices designed to assess fatigue and sleepiness.

In summary, although it is difficult to relate simulated driving performance to actual driving, this study provides insight into the effects of sleepiness on different skills essential to driving, such as reaction time, steering control, and speed variability. This study also highlights the potential use of automated slow eyelid closure measures as an indicator of sleepiness in drivers, however this requires further validation and support. In terms of real-world driving, if an individual cannot react quickly enough in a dangerous situation (e.g. braking in response to a car in front of them), this can potentially lead to an accident. Similarly, if a driver experiences a microsleep and runs off the road (two factors which the current study demonstrated in the PERCLOS and driving simulator lane deviation findings) they may not be able to respond quickly enough to avoid a crash. It is generally a combination of the impairments noted above that would ultimately lead to a road accident.

4.5.3 The effects of sleep deprivation on neurocognitive tasks related to driving

A range of cognitive tasks related to driving were examined in the current experiment, to determine which functions are affected by sleep deprivation. Performance on sustained attention tasks (Psychomotor Vigilance Task (PVT)), and simple reaction time tasks (Simple and Choice Reaction time) were all significantly affected by 24-hours of sleep deprivation. These are motor tasks involving vigilance and attention, and performance on such tasks has been shown to decline with sleep loss (Koslowsky & Babkoff, 1992; Rogers et al., 2003; Dinges et al., 1997). The effect size for detecting a difference in PVT median RT between the NSD and SD sessions in this
experiment was 0.53. As described in Chapter 3, sleep loss-related performance decrements may be explained by the “lapse hypothesis” (Williams et al., 1959), which suggests that sleep deprived participants can perform at a relatively good level until a microsleep occurs, which in turn causes the occurrence of a lapse in attention or brief period when no response occurs at all. The frequency and duration of microsleeps appear to increase as a function of sleep deprivation, as demonstrated in this, and previous studies (Dinges et al., 1999; Howard et al., 2002). This is reflected by an increase in the number of PVT lapses in sleep-deprived subjects in the current study. Lapses in attention may cause decreased performance, which is reflected by increased lapses on the PVT after sleep deprivation.

Some tasks were unaffected by sleep loss in the current experiment. No effect of sleep deprivation on the Digit Symbol Substitution Task was found, suggesting that information processing speed and motor control were not affected by sleep loss. This finding is contrary to previous studies (Williamson & Feyer, 2000), which may be due to differences in how the task was administered. Previous studies have measured the time taken to complete the symbol sheet, which is different to how it was performed in the current experiment (complete as many symbols as possible within two minutes). Similarly, although a trend-level increase in reaction time was demonstrated, the current experiment observed no significant effect of sleep loss on the Digit Vigilance task, in both the number of lapses in attention during this task, and the average reaction time. It is possible that the length of both of these tasks was too short to induce any sleep loss effects, since significant sleep-deprivation effects were observed in the longer PVT. Previous studies have reported that simple tasks shorter than 10 minutes are able to be sustained by sleep deprived subjects, and it is not until after the 10-minute period that sleep-deprivation effects are observed (Bonnet, 1989; Lee & Klietman, 1923). The PVT is known to be unaffected by aptitude and learning, and is sensitive to the effects of sleep loss. Other neurocognitive tasks used in the current thesis may be influenced by aptitude and therefore this may have affected the results and made the task “insensitive” to sleep loss. Overall, professional drivers in the current experiment were able to maintain their performance on these short, motor-related performance measures even after one night without sleep. The effect size for detecting a difference in Digit Vigilance RT between the NSD and SD sessions in this experiment was 0.57. In order for an effect size of 0.57 to be significant with an alpha
of 0.05% and a power of 0.8 it is estimated that 20 subjects would be required. This indicates that the trend-level sleep-deprivation effect observed on this task may have reached significance with a larger sample.

The Colour-word Stroop task was unaffected by sleep deprivation in the current experiment, suggesting that executive functioning was insensitive to sleep loss in these drivers. Although this is opposed to the body of neuroimaging and cognitive literature highlighting prefrontal decrements in sleep deprived participants (Harrison et al., 2000; Thomas et al., 2000), there have been mixed findings with respect to the effects of sleepiness on the Stroop Task more specifically in previous studies. Consistent with Binks (1999) and Sagaspe (2006), the current study did not find an interference effect associated with sleep deprivation. Binks, however, used a control group as opposed to a repeated-measures design. Sagaspe (2006) used a relatively young sample (< 26 years), and the task was repeated a number of times, thus, practice effects may have masked sleep deprivation effect. The current study has produced the same results as these previous studies, utilising a repeated-measures design. Contrary to the current findings, however, Sagaspe (2006) demonstrated a cognitive slowing in reaction times with 36-hours of sleep deprivation in the incongruent trials. Although our null finding may be a true effect, it is also possible that this version of the Stroop Task was not sensitive enough to detect subtle changes in prefrontal activity induced by sleep loss, or perhaps a period of 24-hours was not long enough to induce such changes. Previous literature examining the effects of sleep loss on higher cognitive functioning has reported that such tasks may be insensitive to sleep loss (Harrison & Horne, 2002). The novel aspect of these tasks keeps the participant alerted and maintaining attention throughout the task. Alternatively, drivers may have been able to compensate for their sleepiness to some extent since the task was relatively short, and there is also some suggestion that experimenter-paced tasks may be more sensitive at detecting sleep loss effects. However, overall this finding indicates that 24-hours of sleep deprivation had little effect on tasks related to PFC functioning, at least in the short term, in this sample of professional drivers.

In summary, decrements in sustained attention were observed in the drivers in this experiment following 24-hours of acute sleep deprivation, whilst normal function was maintained on short tests of executive function. It is unlikely that the lack of
significant difference was due to a learning effect on these tasks; all participants received substantial training on each of the neurocognitive tasks prior to commencing the experimental sessions. Additionally, alternate forms were used, and the sessions were counterbalanced, thereby reducing any order effect on the results. Many performance tests that have been shown to be “sensitive” to sleep loss are relatively simple and straightforward, and once administered during sleep deprivation, they can become dull and tedious (Harrison & Horne, 1988). Most individuals have the capacity to perform reasonably well under the most trying of sleep loss circumstances provided they are sufficiently stimulated or motivated, and the task is not overly complex (Walsh & Lindblom, 1997). A powerful determinant of lapsing and decreased performance in a sleepy person is the duration of the task (Dinges & Kribbs, 1991). The longer the task duration, the greater likelihood that performance will show evidence of impairment early in sleep deprivation (Dinges & Kribbs, 1991).

There is a wide range of individual differences between people’s abilities and susceptibility to sleep loss. Some of the participants may have been able to cope with their sleepiness and perform well, whereas others may have been more affected. There is some evidence that people who perform poorly on particular tasks after sleep loss tend to always perform poorly on those tasks, however they may perform well on a different type of task (Van Dongen, 2006). This reflects an intra-individual stability of performance during sleep deprivation. It would have been interesting to examine those who were poor performers and those who were good performers, and see if the types of tasks (or cognitive domains) were similar in each group. Unfortunately this type of analysis was difficult due to low subject numbers.

4.5.4 The effect of sleep deprivation on visual and auditory ERPs

The underlying mechanisms related to behavioural impairment following acute sleep deprivation were explored further utilising tasks performed in conjunction with collecting ERPs. In both auditory and visual tasks, early sensory processes remained unaffected by sleep loss, whereas later processes and behavioural responses appeared to be more vulnerable.
4.5.4.1 *The effects of sleep deprivation on the magnocellular and parvocellular visual pathways*

Sleep deprivation was related to slower processing of more-detailed visual information, requiring higher spatial resolution, observed as a longer P100 latency for the parvocellular pathway. A trend-level effect of sleep deprivation on the magnocellular pathway, which represents fast, transient, crude processing of visual information, was also shown. Both these findings suggest that sleep deprivation may differentially affect visual processing at this level, which is potentially dangerous for driving.

4.5.4.2 *The effect of sleep deprivation on the Tunnel Vision task*

The present experiment observed a slowing of reaction time (Dinges et al., 1997; Lisper & Kjellberg, 1972), and increases errors of omission (Doran et al., 2001; May & Kline, 1987; Murphy et al., 2006) following sleep deprivation, which is consistent with previous studies. These behavioural findings were not associated with changes in early visual processing ERP components elicited during the Tunnel Vision (TV) task, nor the attentional components indexed by the N100, however, a significant reduction in the P300 component was observed. No difference in visual processing in response to central and peripheral stimuli was observed, contrasting the tunnel vision hypothesis. This sleep deprivation-related behavioural change was not explained by alterations in early visual processing, but appears to be related to effects on later, higher-order, cognitive processing.

This experiment did not reveal any interaction between sleep deprivation and visual field position using the behavioural data. This is in agreement with the study by Kendall et al., (2006) in which no behavioural TV effect was observed following 40-hours of wakefulness. However, it contrasts with recent behavioural evidence suggesting that sleep deprivation causes a tunnel vision-type effect, with deficits in responses to stimuli in the peripheral visual field (Russo et al., 2003). It is unclear whether there were problems with these previous studies. This contrary result is particularly important given that the data reported in the positive studies was derived
from smaller samples (N < 10), and consisted of specific sample populations (air force pilots and younger drivers), which together with the negative study leaves the link between sleep deprivation and tunnel vision in some doubt. Alternatively, this TV effect may have been too small to be detected by altered behavioural responses in our sample.

No significant effect of sleep deprivation on the sensory P100/N100 complex to foveal compared to peripheral stimuli was found. This is in contrast to the tunnel vision hypothesis, and neuroimaging studies that report decreased activation to peripheral targets when the central task had high cognitive load (Schwartz et al., 2005). This lack of effect in the present study does not appear due to a failure to achieve the experimental manipulation, as a reduction in the early visual ERPs to peripheral compared to central stimuli was found (independent of sleep deprivation). This indicates that the position of the stimuli on the screen was appropriate to produce differential sensory processing to central and peripheral stimuli (neuronal firing rate is reduced in response to visual stimuli that fall outside the foveal region).

Similarly, for mid-latency attentional processes, sleep deprivation did not influence the visual field position effect. The N100 attentional amplitude, however, was larger for peripherally presented stimuli than for centrally presented stimuli, with a slower latency for peripheral compared to central stimuli, independent of sleep deprivation. Attending to stimuli in a particular location in the visual field typically elicits a larger ERP amplitude compared to unattended locations. For example, Hoshiyama, et al., (2001) found an enhanced P100 response to foveal stimuli when attention was directed to the foveal region, and this response was suppressed to peripheral stimuli. Furthermore, Hillyard et al., (1998) demonstrated a posterior N100 enhancement elicited by cueing to peripheral stimuli. They suggest that this enhancement may reflect orientation and engagement of attention to relevant stimuli locations. In the current study, subjects were asked to attend to stimuli presented both foveally and peripherally in a relatively demanding task. Thus, larger N100 attentional amplitude to peripheral compared to foveal stimuli may reflect an increase in recruitment of attentional resources in order to attend sufficiently to peripheral targets. Overall, this effect was not influenced by sleep deprivation, suggesting that preconscious attention
is not affected by sleep deprivation, or does not demonstrate differential visual field deficits induced by sleep deprivation.

Significant reductions in later cognitive processing following 24-hours of sleep deprivation were found in the current study (reduced P300 amplitude), indicating that this may be the stage at which the behavioural deficits first occur. This supports previous sleep deprivation studies that found that later components showed a progressive and linear reduction in amplitude and lengthening of latency with 40 hours of sleep deprivation, while the amplitude and latency of the early and middle components remained unchanged (Corsi-Cabrera et al., 1999). This finding suggests that higher cognitive processes, such as motivation and conscious deployment of attentional resources, are affected by sleep deprivation, as a reduction in P300 amplitude is believed to be associated with a decrease in attention (Lisper & Kjellberg, 1972). Furthermore, these deficits were also evident in the slowing of behavioural responses to stimuli in the sleep-deprived state. For instance, the reduction in P300 amplitude may reflect a reduction in vigilance, which, in turn, would prolong reaction times. Similarly to previous studies (Kingshott, Cosway, Deary, & Douglas, 2000; Tsai et al., 2005) we did not observe any P300 latency changes with sleep deprivation. It is possible that a longer period of sleep deprivation would delay P300 latencies, and that one night of experimental sleep loss was insufficient to elicit such changes.

Finally, although a reduced P300 amplitude was found following sleep deprivation, there was no visual field effect, suggesting that there was not a TV effect in terms of higher order cognitive processes. Thus, sleep deprivation appears to be associated with a general decline in visual attention. An overall effect of visual field position is apparent with reduced early sensory processing and an increased attentional requirement for peripheral stimuli, however, these TV effects are not exacerbated by sleep deprivation. This suggests that sleep loss has a general effect on attentional allocation to visual stimuli on a global level, with no specific effects on the location of the stimuli.

The underlying mechanisms that produce these sleep deprivation-related behavioural deficits, and subsequent reduction in P300 amplitude, are not clear. Since there were
an increased number of errors of omission following sleep deprivation in the current study, the lapses hypothesis may explain these findings (Broadbent, 1953). Inattention during the task led to some stimuli being missed by participants, which is for example, similar to failing to stop at a red light. However, this theory does not fully explain the increase in reaction time with sleep deprivation. In addition, the task duration was such that it was expected that most participants would be able to maintain wakefulness throughout the test period. Therefore, it is unlikely that the reduction in the P300 amplitude induced by sleep deprivation in the current study is due to microsleeps, since when missed responses were excluded from the analysis, a significant reduction was still demonstrated. Finally, it is often hard to distinguish whether P300 changes are due to habituation, circadian factors or sleep deprivation. For example, the P300 amplitude is greater in the morning compared to the afternoon (Wesensten et al., 2002). All of the testing performed in the current study was at the same time of day, minimising circadian influences.

There are a few possibilities as to why a peripheral visual field effect was not found following sleep deprivation in the current study. The visual angle used for the peripheral stimulus in the current paradigm was 20 degrees from fixation, as reported by Roge, et al., (2003), however a wider visual angle may still induce an effect on behavioural and electrophysiological responses. It may be argued that subjects in the current study did not fixate in the centre of the screen throughout the whole task, thereby reducing the foveal ERP response. However, this appears an unlikely explanation, since ERP responses were larger to centrally-presented stimuli than to those presented to the periphery. It is possible that a paradigm of 24-hours of sleep deprivation may have been insufficient to produce peripheral visual changes. The current study did, however, demonstrate behavioural and ERP changes with 24-hours of sleep deprivation. It is possible that a TV effect might be observed with longer periods of extended wakefulness or if testing were performed during the circadian nadir period. Additionally, the length of the TV task may have been too short to elicit such changes, as our participants may have been able to maintain their performance at a relatively high level for that short period when sleep deprived. Performance deficits on RT tasks have been reported with task lengths of ten minutes (Dinges et al, 1997). However, it would be expected that the underlying early neural mechanisms would
still be apparent in the ERP data, despite the ability of participants to compensate for their sleepiness, which was not demonstrated in the current study.

It is difficult to generalise the findings of the current study to more complex tasks such as driving. We have assessed a simple reaction time task, and these findings cannot be extrapolated across all the other neurocognitive components of the complex, integrated task of driving a motor vehicle. These findings do, however, allow insight into the specific effects of sleep deprivation on both the visual behavioural responses, and underlying electrophysiological brain changes associated with a visual task, which is an important aspect of driving. These findings suggest that sleep-related accidents may not be caused by peripheral field neglect, but rather there may be a reduction in the efficiency of later cognitive processing which affect the processing of visual stimuli from the driving scene.

4.5.4.3 The effects of sleep deprivation on the Startle Reflex/Pre-pulse Inhibition

There was no effect of sleep deprivation on the acoustic startle response in the present study. It is difficult to interpret these findings in terms of previous research, since this component of neural processing has not been previously examined in sleep-deprived individuals. The startle response has previously been measured in subjects immediately upon waking, during which time individuals experience a period of grogginess, or sleep inertia, and can be associated with impaired performance (Horner, et al., 1997). This study reported that the response to the startle stimuli alone were similar during different waking states, however, the pre-pulse response was smaller upon waking from non-REM sleep compared to established wakefulness (Horner, et al., 1997). The authors suggest that sleep inertia is associated with a reduced gating of motor responses to sensory inputs. No effect of sleep loss on pre-pulse inhibition was observed in the current experiment. This suggests that underlying neural processing that occurs in response the acoustic startle are different during sleep inertia compared with sleep deprivation. Since the startle response in a pre-attentive mechanism, it is not surprising that it was insensitive to sleep deprivation. In terms of driving, a reduction in PPI following sleep deprivation may impair a driver’s ability to
filter out intrusive stimuli from the driving environment, thus overloading their attentional capacity and reducing their ability to drive safely.

### 4.5.4.4 The effect of sleep deprivation on Mismatch Negativity

The current study found a trend-level reduction in the Mismatch Negativity (MMN) response following sleep deprivation. The cognitive mechanisms underlying MMN are believed to be pre-attentive. Indeed, the response is usually elicited while participants are not attending to the stimuli (i.e. their attention is directed to another task, such as the visual task in the current study). Thus, it is not unexpected that sleep deprivation would not greatly affect this pre-attentive response. This is in contrast to previous reports of an attenuation of the MMN response following both objectively and subjectively defined sleepiness (Raz et al., 2002; Sallinen & Lyytinen, 1997). These studies, however only reported an attenuation of the response in clear sleepiness, with severely affected behavioural response, using longer periods of sleep deprivation (36 hours). Closer inspection of the Raz et al. (2002) study, however, indicates that this effect was only significant for large (10%) deviants. The current finding suggests that the fronto-temporal subcomponent of MMN, which is implicated in involuntary attention switches towards sound changes in unattended auditory stimuli (Näätänen, 1990), may be vulnerable to sleepiness. Thus, a reduction in this response may have implications for safe driving, and may reflect deficits in an individual’s ability to pre-consciously discriminate auditory changes in the road environment.

### 4.5.4.5 The effects of sleep deprivation on the auditory oddball task

The area under the curve of the P300 potential over parietal regions was significantly attenuated following sleep deprivation, however, earlier processes (N1 and P2 complexes) remained unaffected. This is consistent with previous reports of a reduced P300 amplitude following 18 hours (Morris et al., 1992), 24 hours (Tsai et al., 2005) and 38 hours (Lee et al., 2003) of extended wakefulness, as well as after fragmented sleep (Kingshott et al., 2000). The amplitude of the P300 component is believed to reflect the deployment of attentional resources (Picton, 1992). Thus, a reduction in this component indicates that participants in the current study were less attentive to
target stimuli following sleep deprivation. Previous studies using sleep deprivation paradigms of less than 24-hours have failed to report any cognitive changes associated with the P300 response, and suggest that the reduction in P300 amplitude was therefore due to participants’ drowsiness rather than a reflection of cognitive decline (Morris et al., 1992). Conversely, the current experiment observed a significant increase in errors of omission, or lapses in attention, following sleep deprivation, consistent with previous studies (Lee et al., 2003). This suggests participants who were sleep-deprived were more likely to miss correct responses compared to when they were well-rested. Lapses in attention are very common in sleep deprived individuals, as demonstrated in the PVT results in Section 4.4.4. The reduced P300 found in the current study may therefore reflect a change in vigilance and attentional processing, which in turn increases lapses in attention.

Earlier components, including the N1 and P2 early auditory processes, were unaffected by sleep deprivation. The absence of attenuation of these components across the sessions indicates that sleep deprivation did not affect the initial encoding of the auditory stimuli in the auditory cortex, but later processing associated with the P300. This is also reflected in the TV task results reported in Section 4.5.4.2, in which the early sensory components were unaffected, thus suggesting that the effects of sleep deprivation on visual and auditory processing occurs at later, attentional and cognitive stages.

The P300 amplitude measured in the afternoon can be smaller than that measured in the morning (Geisler & Polich, 1990; Wesensten, Badia, & Harsh, 1990). This may be due to circadian factors, food intake and body temperature, however the impact of each are poorly understood. The current study attempted to overcome and circadian influences on performance by testing subjects at the same time each session. The ERPs were performed at approximately 10:30h, during which time participants would have passed the circadian nadir, and would be performing at a relatively high level. Despite this, we still did see a significant effect of sleep loss on the P300 complex.

Brief periods of inattention during driving can potentially have serious consequences if a driver misses traffic signs, or briefly runs off the road or into oncoming traffic. Taken together, these behavioural and electrophysiological findings suggest that the
brain is susceptible to lapses in attention following even only one night of sleep loss, which may greatly impact on their ability to drive safely.

4.6 Conclusion

The causes of sleep-related motor vehicle accidents, from a behavioural and psychological perspective are still under investigation. The findings from the present experiment suggest that a period of acute sleep deprivation can lead to a deterioration of a number of driving-related processes, which in turn may affect in individuals’ ability to drive safely. Psychological, physiological and performance-related indicators of sleepiness were well recognised by the professional drivers in the current experiment, suggesting that such introspective measures should continue to be promoted as warning signs for drowsy drivers. This is consistent with limited previous studies examining symptoms of fatigue, and reports by real-world drivers during actual on-road driving (Nordbakke & Sagberg, 2007; Summala et al., 1999).

Driving-related performance changes were observed after one night of sleep loss in the present experiment. Detection of early performance measures, such as increases in lateral lane deviations, may provide an indication of impairment which may be significantly detrimental to an individuals’ ability to drive safely. Currently, lane position monitors are one measure of on-road driving performance which can alert a driver when there is a significant increase in lane crossings, which may ultimately reduce road accidents in the real-world setting.

Electrophysiological findings in the current experiment suggest that pre-attentive processing, in both the visual and auditory modality, remain largely unaffected by sleep loss, whereas later, cognitive processes appear to be more vulnerable to the effects of sleep loss. Because the P300 is sensitive to sleep deprivation, it is less affected by motivation, and is associated with cognitive impairment and slowing of neural processing, it may prove to be a useful marker of sleep deprivation. The deterioration in performance observed in this study is likely to be purely due to the sleepiness effects caused by sleep deprivation and not circadian factors, since testing occurred at the same time for each participant and outside of the circadian nadir.
CHAPTER 5
EXPERIMENT 2

Chapter overview

Driving is a complex task which requires the drivers to constantly divided his or her attention between different sensory modalities. It is unknown how sleep deprivation impacts on the neural processing underlying divided attention. This chapter describes an experimental study which examined changes in functional magnetic resonance imaging (fMRI) neural activation following sleep deprivation, during selective and divided cross-modal attention tasks. The study involved two experimental sessions; one session following a normal night of sleep, and one session following 27-hours of sleep deprivation. During each fMRI session, participants completed a cross-modal divided attention task (visual and auditory). The effects of sleep deprivation, compared to normal sleep, on behavioural responses and neural activation during selective and divided attention are described.

5.1 Introduction

Driving is a complex task, involving constant division of attention between different sensory modalities. The detrimental effect of sleep deprivation on cognitive functioning, including driving, has been well documented (Dawson & Reid, 1997; Mitler et al., 1997). As reported in Experiment 1, sleep deprivation has a detrimental impact on a number of driving-related processes. Behaviourally, sleep deprivation impairs attention and vigilance, resulting in increased reaction times, lapses in attention, and microsleeps, even after only one night without sleep (Dorran, 2001; Jewett, 1999). An early effect of sleep deprivation is impairment of performance on tasks requiring sustained and divided attention (Bohnen and Gaillard 1994; Jewett et al., 1999; Van Dongen et al., 2003; Van Dongen et al., 2004). This ability is an important part of most day-to-day functioning as real-world tasks often include simultaneous attending to, or monitoring of, multiple sources of information. One real-world example is driving, during which attention is divided between visual, proprioceptive and auditory inputs from the road environment (Anstey et al., 2005;
McKnight & McKnight (1999). Thus, impaired divided attention may be a contributing cause of sleep-related accidents following sleep deprivation.

Behavioural and electrophysiological studies have limitations (see Chapter 2, Section 2.4.5.3 for details). To overcome some of the limitations involved with EEG and ERPs, such as reduced spatial resolution, functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have been introduced to some research paradigms. In particularly, sleep researchers have utilised these techniques to help clarify brain regions that are affected in sleep deprived individuals.

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique which measures the blood-oxygenated level dependent (BOLD) response to brain activation during the performance of a cognitive task (see Chapter 2, Section 2.4.5.4). This allows examination of changes in cortical activation associated with performing the task and varying the conditions under which the task is performed, although it does not assess the baseline levels of activation. Functional neuroimaging studies have examined the effect of selectively attending to one sensory modality over another, and dividing attention between two modalities, on brain activation in well-rested participants, but not following sleep deprivation (Johnson & Zatorre, 2006; Loose et al., 2003). Selective attention refers to the ability to focus attention on one source of information, in the face of competing or distracting stimuli, while divided attention refers to the ability to simultaneously monitor multiple tasks or task demands. Cross-modal divided attention refers to instances when attentional resources are allocated to two or more sensory modalities simultaneously (e.g., visual and auditory). Selectively attending to one modality increases activity in the corresponding primary and secondary sensory cortices, with a simultaneous decrease in activity in the unattended modality sensory regions (Johnson & Zatorre, 2006; Loose et al., 2003). When attention is divided between both visual and auditory modalities simultaneously and task difficulty remains constant, increased BOLD activity is observed in prefrontal areas that is not evident when selectively attending to either modality alone (Johnson & Zatorre, 2006; Loose et al., 2003). Prefrontal regions thus appear to be important for executive control, and it is thought that this is by actively integrating the activity
of multiple sensory inputs so that both can be attended to simultaneously and with a
time sharing regime (Courtney et al., 1998; Dove et al., 2008; Loose, 2000). These
studies generally report that behavioural performance does not differ across
conditions, however, those participants who demonstrated the best performance
during divided attention also recruited more sensory cortex during the task (Johnson
& Zatorre 2006). Prefrontal recruitment may also occur if the task-switching is more
cognitively demanding (MacDonald et al. 2000), and therefore this needs to be taken
into account when designing cross-modal divided attention tasks.

Functional neuroimaging studies using PET and fMRI report that sleep deprivation
reduces prefrontal metabolism and alters neurochemistry (Dorsey, 2000; Thomas et
al., 1998; Wu et al., 1991), and diminishes performance on measures sensitive to
prefrontal cortex functioning such as tasks of executive function and divided attention
(Durmer & Dinges, 2005; Harrison & Horne, 1999; Nilsson et al., 2005; Pilcher &
Huffcutt, 1996). Positron emission tomography studies have shown that baseline
levels of cortical neuronal activity are globally reduced following sleep deprivation
(Thomas et al., 2000). However, the neural correlates of selective and divided
attention tasks during periods of extended wakefulness have not been clearly
identified. One study has examined neural activation during simultaneous
performance of two tasks (arithmetic and verbal learning) (Drummond et al., 2001).
After 35 hours of sleep deprivation, compared to after normal sleep, there was a
significant increase in BOLD activation in both the PFC and parietal lobes,
particularly in the right hemisphere, during simultaneous performance of the two
tasks. This occurred in addition to the activations demonstrated during performance of
each task alone. These regions have previously been shown to be involved in verbal
learning, as well as attentional processing. There were only modest impairments in
performance following sleep loss. The authors hypothesised that the recruitment of
attention-related brain regions (prefrontal cortex) indicate that more sensory
monitoring and attention was required to maintain performance of the experimental
task after sleep deprivation than after normal sleep. Further, recruitment of additional
regions of the cortex in the parietal lobe was associated with lower levels of
impairment in arithmetic performance, suggesting that this may be compensatory
aiding task performance in the sleep deprived state, when attentional resources are
limited. These findings were interpreted by the authors as the result of the brain
recruiting additional regions of the cortex during performance of tasks where attentional resources are limited, and that this compensation aided performance in the sleep deprived state. These studies suggest that fMRI can be used to identify regions of the brain where functional change has occurred as a result of sleep deprivation, and that the presence of increased regional activity may indicate an ability to compensate for the effects of sleepiness and harness additional attentional resources (Drummond et al., 2001).

However, the increased PFC activation during sleep deprivation may not purely reflect divided attention, as the complex cognitive tasks utilised in the Drummond study also involve higher cognitive processes such as working memory and semantic processing, and thus the task is somewhat different to the cross-modal divided attention tasks described above. Therefore, a clear understanding of the brain’s response to cross-modal, sensory divided attention, particularly when there is increased demand on attentional resources, such as when sleep deprived, has not yet been achieved. Further, the tunnel vision hypothesis was not supported by the visual ERP results in Experiment 1, therefore Experiment 2 will examine whether sleep deprivation impacts performance when two different sensory tasks are performed simultaneously. Since divided attention is an important aspect of the driving task, deficits in divided attention performance, or in the associated underlying neural processing during sleep deprivation, may have a detrimental effect on driving performance.

5.2 Aims

The aim of the current study was to compare cortical activation associated with performing visual and auditory selective attention tasks, both separately and simultaneously, in rested and sleep deprived states. Based on previous divided attention studies in non-sleep deprived participants, it was hypothesised that a) cortical activation would be seen in task-related, sensory regions during selective attention, and b) additional areas of cortex will be activated during a divided attention tasks were compared to either task alone. Secondly, we hypothesised that c) activation within these additional sensory areas would be further enhanced and new cortical
activations seen in parietal regions, when the sleep deprived state was compared to the well-rested state.

5.3 Methods

5.3.1 Participants

5.3.1.1 Selection Criteria

A sample of drug-naïve, licensed professional drivers was recruited. To be included in the study, drivers had to hold a current heavy vehicle drivers licence, to have never previously used amphetamine-type stimulants, to be aged between 18 and 65 years, and to speak English as their first language. Participants were recruited from a pool of professional drivers previously involved in research at Austin Health, Melbourne, Australia, and through advertising in the Transport Workers Union newsletter and Trucking Life magazine. Due to difficulties recruiting professional drivers for this study, non-professional drivers, who had a full drivers licence, were also allowed into the study. Interested individuals were given a brief explanation of the study requirements and protocol, and were sent a more detailed information sheet. Drivers who agreed to participate were booked in for a medical examination.

5.3.1.2 Medical Examination

Participants were provided with an information sheet outlining details of the research study, and when the participant had all questions answered and were satisfied with the requirements of the study, they gave written informed consent (see Appendices K and L for the Participant Information Sheet and Consent Form). Participants were informed that they could withdraw from the study at any time. All participants completed a demographics questionnaire (Appendix D), drug history questionnaire (Appendix E), the Epworth Sleepiness Scale (Johns, 1991) and the Multivariate Apnoea Prediction Scale (Maislin et al., 1997). Refer to Chapter 4 Section 4.4.4.1 for details of the screening questionnaires.

The practitioner interviewed the participant regarding their medical and drug history, physical and mental health, medical procedures or implants, their smoking history,
and obtained other physiological measures (i.e. weight, height, blood pressure). The selection criteria for the present experiment were the same as for Experiment 1 Chapter 4. Participants were excluded if they were shift-workers, had symptoms suggestive of a sleep disorder, any significant daytime sleepiness according to the Epworth Sleepiness Scale scores (ESS; Johns, 1991), a history of illicit drug use, other medical conditions that contraindicated sleep deprivation or may affect neuronal function (e.g. psychiatric illness, epilepsy), could not tolerate abstinence from cigarettes for up to 12-hours, or if they consumed five or more caffeinated beverages per day. Participants were also excluded if they returned a positive urine test for illicit drugs. Based on this examination, the physician made a decision about whether the driver was fit to participate, and if they were deemed unfit, they were excluded from the sample.

5.3.1.3 Sample characteristics

Fifteen healthy males were recruited for the study, however three participants were excluded due to image artefacts and excessive motion. This left a final sample of 12 healthy males, aged between 27 and 56 years (M = 42.6, Std. Dev. = 9.6 years). Due to difficulties with recruitment, two of the drivers were non-professional drivers. All participants reported normal hearing and normal or corrected-to-normal vision. Professional drivers drove on average 36.8 hours for work per week, and the non-professional drivers drove on average 8.5 hours per week. The mean ESS score was 5.1, indicating low levels of daytime sleepiness. Two of the participants were left handed.

5.3.2 Experimental Design

A repeated-measures, counter-balanced, single-blind design was employed. Participants completed two treatment conditions; one following a normal night of sleep (no sleep deprivation; NSD) with placebo and one following 27-hours sleep deprivation (SD) with placebo, separated by a one week wash-out period, to allow for the regulation of the participants sleep patterns following the sleep deprivation session. Time-of-day effects were controlled for by testing all participants at the same time of day to assess the independent impact of sleep deprivation alone on driving-related performance. Additionally, participants were tested in the mid-morning to
avoid testing in the circadian nadir (i.e. 14:00h to 16:00h) where there may have been a negative effect of circadian cycle on performance. The period of 27-hour was chosen as it is a common realistic level of deprivation which has ecological validity, and also allowing for a protocol to be carried out outside of the circadian nadir (10:30h). In order to be able to compare the results of Experiment 2 with the results of Experiment 1, drivers undertook an identical protocol as Experiment 1, including placebo capsule administration, and was therefore single blinded.

5.3.3 Procedure

Prior to conducting the study, ethics approval was obtained from the Swinburne University Human Research Ethics Committee and the Austin Health Human Research Ethics Committee. After agreeing to participate, drivers attended Austin Health for an initial screening session and medical examination to assess their fitness for the study by a practicing respiratory physician.

Participants attended two experimental sessions in a randomised counterbalanced order. They were asked to complete a sleep diary for the week prior to each study day, in which they recorded the duration of sleep each night, and caffeine and alcohol intake. Caffeine, alcohol or other stimulants were not allowed from 12:00h on the day prior to the experimental session until the conclusion of the test session. Participants were asked to wake at 06:30h on the morning of each testing day, and ensure their normal (at least seven hours) sleep on the night prior to testing.

During the no sleep deprivation session (NSD), participants attended the Sleep Laboratory at 08:00h after a normal night of at least seven hours sleep and a normal breakfast without caffeine. Participants completed the Symptoms Checklist (SCL-90-R) mood questionnaire and provided a urine sample for drug screening purposes. A battery of subjective sleepiness (Karolinska Sleepiness Scale (KSS; Akerstedt & Folkard, 1996) and mood (Profile of Moods States (POMS; McNair, Lorr, & Droppleman, 1992 and Visual Analogue Scale (VAS)) questionnaires were rated prior to the scan. At 08:30h, a placebo capsule was administered to the participants. At 10:30h, participants underwent an fMRI scan at the Brain Research Institute, Austin
Health, and completed the subjective sleepiness and mood questionnaires again after the scan.

During the sleep deprivation session (SD), woke at 07:00h on the morning of the sleep deprivation night, and completed the SCL-90-R. Participants were asked to remain awake all day, and attend the Austin Health Sleep Laboratory at 22:00h, following a normal work-shift. Participants stayed awake all night until the following morning, and were monitored by the laboratory staff. During the night participants watched videos, read, or played games. At 06:30h they were given a light breakfast without caffeine, provided a urine sample for drug screening purposes, and completed the battery of questionnaires as reported in the NSD session. At 08:30h, a placebo capsule was administered to the participants. The functional MRI scan was undertaken as in the NSD session at 10:30h, and following the scan, participant completed the subjective sleepiness and mood questionnaires again after the scan.

5.3.3.1 Imaging Procedure

The Magnetic Resonance Imaging (MRI) scans were carried out on a 3-Tesla GE Signa LX MRI scanner (General Electric, Milwaukee, WI, USA) with a birdcage quadrature coil at the Brain Research Institute, Melbourne, Australia. Two data sets were acquired to provide high-resolution anatomical images. The first was a T1-weighted 3D fast spoiled gradient recovery sequence (TR = 13.8 ms; TE = 2.7 ms; TI = 500 ms; flip angle = 20°; FOV = 25 x 25 cm; 512 x 512 matrix) with contiguous coronal slices of 2 mm thickness. The second of which was a fast spin-echo T2 weighted sequence (TR = 7500 ms; TE = 80 ms; TI = 500 ms; ETL: 18; FOV = 22 cm; 384 x 256 matrix). A total of 40 slices (3.2 mm thickness with 0.2 mm gap) were acquired at a tilted-axial plane, matched to the fMRI acquisition plane.

Functional magnetic resonance images (T2*-weighted) were acquired using a gradient-recalled echo-planar imaging sequence (TR = 3.2 s; TE = 40 ms; flip angle = 75°; FOV = 22 cm, 64 x 64 matrix). 40 slices were acquired in a 30 degree tilted-axial plane, 3.2 mm thickness with 0.2 mm gap. In each scanning session, 168 volumes were acquired continuously as 40 interleaved axial slices (3.2 mm thickness, 0.2 mm
gap) at an oblique angle to the axial plane (tilt angle = 30 degree). An oblique acquisition angle was employed to enable whole brain imaging, i.e., including the cerebellar cortices. The initial four functional images collected were discarded prior to the first fixation epoch to eliminate initial magnetisation effects.

5.3.3.2 Urine samples

A urine sample was collected from each participant at the beginning of each session to screen for recent drug use. A medical doctor was also on call throughout the testing session. Samples were taken as described in Experiment 1 (Refer to Section 4.3.3.1 for a full description).

5.3.4 Materials

5.3.4.1 Questionnaires

A battery of sleepiness symptoms and mood questionnaires were completed by the participants prior to and following the MRI scan. The Sleepiness and performance questionnaires used in the current experiment were the same as those used in Experiment 1. These included the Symptoms Checklist 90 Revised (SCL-90-R; Derogatis, Rickels, & Rock, 1976), Performance questionnaire (Appendix I), the Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990), the Sleepiness Symptoms Questionnaire (SSQ; Appendix H), Stop driving questionnaire (Appendix J), and the Visual Analogue Rating Scale (VAS; Bond & Lader, 1974). Refer to Chapter 4, Section 4.3.4.1 for full description of the questionnaires.

In addition, The Profile of Mood States (POMS; McNair et al., 1992) was administered. The POMS is a 65-item self-administered questionnaire that provides an index of six mood dimensions over the preceding seven day period: tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment. A Total Mood Disturbance score is obtained by summing all six factor scores. All indices of internal consistency are satisfactory (tension-anxiety K-R20 = .91, depression-dejection K-R20 = .95, anger-hostility K-R20 = .92, vigour-

5.3.4.2 Experimental task

The experimental task was a cross-modal divided attention task that used visual and auditory stimuli presented in an epoch-based block design, and was based on previous cross-modality studies that used auditory and visual stimuli simultaneously (Loose et al., 2003). In the design of a cross-modal divided attention task, there is a trade-off between maintaining task difficulty, and applying equal stimulus energy during the task. Since we are interested in targeting sensory regions to examine neural modulation in response to attention in the current study, we have chosen to apply a paradigm in which subjects are exposed to the same number of stimuli, during the divided attention blocks of the task compared to the selective attention blocks. The limitation of this approach is that the divided attention task will have more targets than the selective attention task. Any activation observed outside of the sensory areas during divided attention may therefore be an accumulation of both the task-switching component of the task, and an increase in task difficulty. This design, however, has the benefit of applying equal stimulus energy to participants during all task blocks, which is an important aspect of functional neuroimaging task designs.

During the task, visual stimuli (white “M” and “W” on black background) were projected onto a screen using an LCD projector, and the images were viewed via mirror positioned approximately 11 cm above the participant’s eyes on the head coil. Auditory stimuli were played through Bilsom headphones (two sinusoidal pure tones, 1500 Hz and 500 Hz, 16 bit stereo at 44.1 kHz). Each stimulus was presented for 300 ms, in an oddball-type paradigm with a variable interstimulus interval ranging from 400 ms to 1000 ms.

The task consisted of four 20-second conditions (baseline, visual, auditory, and divided) that were each presented eight times in a randomised presentation sequence lasting 9 minutes and 10 seconds. For each participant, a stimulus for each of the visual and auditory modalities was randomly selected as the target stimulus (or stimuli) for each condition. Targets were presented with a 20% probability, and the
participant’s task was to press a response button to targets on an MR compatible keypad that was held with their dominant hand.

At the start of each block, instructions were displayed on the screen for four seconds, explaining what was required for that particular block. For the baseline block, participants were instructed to fixate on a cross-hair on the screen and press the response pad on every exhalation and ignore the sounds and letters; for the visual blocks, participants were instructed to fixate on the cross-hair and press the right response button every time their visual target (either an M or a W) appeared on the screen and to ignore the sounds; for the auditory block, participants were instructed to fixate on a cross-hair and press the left response button when they heard their target tone (either a 1500 Hz or 500 Hz tone) and to ignore the letters that appeared on the screen; and for the divided attention blocks, participants were instructed to fixate on the cross-hair and press the right button when the target letter appeared on the screen, and press the left button when the target tone was heard. A 30-second rest period was given halfway through the nine-minute task. A two-minute practice session was completed in a mock scanner before each session to minimise practice effects during testing, and to familiarise participants with the scanning environment.

5.3.5 Image Processing

Pre-processing and statistical analysis of functional images were carried out using SPM2 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). For each data set (participant-wise and session-wise), image data were first realigned to the first functional image acquired and a mean image created. Structural images (T1 and T2) were then co-registered to the first functional image for respective sessions, and then normalised to the T2 and T1 templates supplied with SPM2. These templates define the standardised stereotaxic space specified by the Montreal Neurological Institute (MNI space). The parameters of the structural T2 transformation were subsequently applied to functional image (T2*-weighted) data. These realigned and normalised functional images were then spatially smoothed using a Gaussian kernel (FWHM 12 mm).
5.3.6 Statistical analyses

5.3.6.1 Behavioural and questionnaire data

Mood, as measured by the SCL-90-R, and sleep recorded for the week and night prior to each session was compared between sessions using Wilcoxon Signed Ranks tests. Questionnaires were completed prior to and after the MRI scan in each session. There was no significant difference between any questionnaire responses reported pre- or post-scan in either session. There is some evidence that the fMRI scanning environment can induce sleepiness (Drummond et al., 2001), therefore to obtain the most accurate measure of participants’ sleepiness at the time of testing, pre-scan data was examined. Paired-samples t-tests were performed to determine whether there was a significant difference in subjective sleepiness (KSS) and mood (POMS and VAS) between the NSD and SD sessions. Behavioural performance was assessed as errors of omission and commission during each of the response blocks. Two, two (session: NSD, SD) by three (task block: visual, auditory, divided) repeated measures ANOVAs were performed to assess the difference between the task blocks in each session. Post hoc analyses were performed using paired-wised comparisons. A p-value of 0.05 was accepted as significant for all behavioural and questionnaire analyses.

5.3.6.2 Imaging data

At the first level of analysis, functional images for the NSD and SD sessions were modelled separately for each participant using epoch-based general linear modelling. After high-pass filtering (128 s), time-series image data were entered into a multiple regression model where the onset and duration of task blocks were modelled as separate boxcar regressors convolved with a canonical haemodynamic response function (SPM2), predicting BOLD intensity changes for each condition (visual selective attention, VS; auditory selective attention, AS; and divided attention, DA). Note however, that the baseline condition was not modelled and thus constituted an implicit task baseline. The six motion parameters (three translational and three rotational) defining the realignment of each functional image were entered into the
model as covariates of no interest to account for residual BOLD variance that was
correlated with head motion.

Auditory and visual stimuli were presented during all blocks, but attentional resources
were actively engaged only in the VS, AS and DA tasks. In order to determine the
neural correlates of selective attention to a particular modality, it was necessary to
compare with another block in which attention was actively engaged. Therefore to
examine the sensory cortices modulated by the selective attention condition, we
examined BOLD intensity changes in the attended compared to unattended modality,
where sensory stimulation was equal in both conditions (Johnson & Zatorre 2006).
Therefore, the contrasts of interest were 1) visual selective attention is greater than
auditory selective attention in the NSD session (VS > AS), and 2) auditory selective
attention is greater than visual selective attention in the NSD session (AS > VS). To
examine whether there was differential activation when participants were attending to
a single modality, compared to both modalities simultaneously, divided attention was
compared to both selective attention conditions (VS and AS) for the NSD and SD
sessions (DA > (VS + AS)/2); note that in this comparison, the parameter estimate for
divided attention was compared to the average of the selective attention conditions at
each voxel.

Group level statistics were generated using random effects models. To examine
BOLD intensity changes related to visual selective attention, auditory selective
attention and divided attention, the contrast images derived from the first level of
analysis for the VS > AS, AS > VS and DA > SA from the NSD session were entered
into separate one-sample t-tests. To examine the effect of sleep deprivation on divided
attention, the DA > (VS + AS)/2 from the NSD and SD sessions were entered into a
paired t-test. Statistical significance was evaluated using a cluster extent method.
Because the pattern of activation at a given voxel is not independent (i.e. is highly
correlated with activity at contiguous voxels), rather than looking for significance at
the voxel level and apply a stringent correction for multiple comparisons, cluster-level
threshold, based on random Gaussian field was used (Friston et al., 1994), in which
the smoothness of the data is taken into account. Statistical parametric maps were
height thresholded at $t = 3.09$ and significant clusters are reported ($p < .05$, corrected
for multiple comparisons at the cluster level).
In order to determine the relationship between BOLD activation and performance, regression analyses were performed between SD session behavioural data (errors of omission change scores from the NSD session to account for individual differences), subjective sleepiness (KSS) and significant activation (as determined above) in brain regions in the SD session. Although there are limitations with this technique, we adopted the same approach as Drummond et al. (2001) to allow for comparison between studies. A region of interest approach was used, for areas which were significantly activated during SD and NSD sessions separately. For each region of interest we produced an average parameter estimate for the whole region for each person. These values were entered into the regression analysis.

5.4 Results

5.4.1 Mood and sleep prior to each session

There was no significant difference in subjects Symptoms Checklist scores for the week prior to each session, between the NSD session and the SD session (p = 0.23). In the SD session, there no significant difference in mood ratings recorded in the morning prior of the SD session and ratings recorded the following morning after 24-hours awake (p = 0.89). The sleep diary results for the averaged hours of sleep each night for one week prior to each session, did not differ between the NSD session (mean = 7.21 ± std. dev. = 0.83 hours) and the SD session (7.16 ± 0.71 hours; p = 0.88). Similarly, there was no difference in the number of hours sleep recorded on the night prior to the NSD session (6.85 ± 2.03 hours) and the SD session (7.13 ± 0.98 hours; p = 0.39).
5.4.2 Questionnaire data

The means and standard deviations of the questionnaire data in each session are displayed in Table 5.1. KSS scores were higher in the SD compared to the NSD session. Total mood scores from the VAS were significantly higher in the SD session compared to the NSD session. For the VAS subscales, participants rated the scales drowsy, feeble, muzzy, clumsy, lethargic, mentally slow, dreamy, sad and bored significantly higher in the SD session compared to the NSD session (Table 5.1). The POMS Fatigue and Confusion subscales were significantly higher in the SD session compared to the NSD session, whereas the Vigour subscale was significantly higher in the NSD session. There was no effect of session on the depression, tension or anger subscales.
Table 5.1: Means and standard deviations (Std. Dev.) of the questionnaire data in the no sleep deprivation (NSD) and sleep deprivation (SD) sessions.

<table>
<thead>
<tr>
<th></th>
<th>NSD</th>
<th></th>
<th>SD</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ±</td>
<td>N</td>
<td>Mean ±</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Std. Dev.</td>
<td></td>
<td>Std. Dev.</td>
<td></td>
</tr>
<tr>
<td>SCL-90</td>
<td>12</td>
<td>18.83 ± 20.14</td>
<td>12</td>
<td>26.25 ± 26.82</td>
<td>NS</td>
</tr>
<tr>
<td>VAMS: total score</td>
<td>12</td>
<td>41.08 ± 22.92</td>
<td>12</td>
<td>73.16 ± 16.56</td>
<td>t(11) = 4.87, p&lt; 0.001</td>
</tr>
<tr>
<td>alert/drowsy</td>
<td>12</td>
<td>2.83 ± 1.95</td>
<td>12</td>
<td>7.67 ± 1.23</td>
<td>t (11) = -7.13, p&lt; 0.001</td>
</tr>
<tr>
<td>calm/excited</td>
<td>12</td>
<td>2.75 ± 1.86</td>
<td>12</td>
<td>3.42 ± 2.57</td>
<td>NS</td>
</tr>
<tr>
<td>strong/feeble</td>
<td>12</td>
<td>2.00 ± 1.21</td>
<td>12</td>
<td>4.75 ± 1.60</td>
<td>t (11) = -5.94, P&lt;.001</td>
</tr>
<tr>
<td>muzzy/clear-headed</td>
<td>12</td>
<td>2.53 ± 2.15</td>
<td>12</td>
<td>6.25 ± 2.14</td>
<td>NS</td>
</tr>
<tr>
<td>well-co-ordinated/clumsy</td>
<td>12</td>
<td>2.83 ± 2.25</td>
<td>12</td>
<td>5.08 ± 2.50</td>
<td>t (11) = -3.04, P&lt;.05</td>
</tr>
<tr>
<td>lethargic/energetic</td>
<td>12</td>
<td>3.42 ± 2.43</td>
<td>12</td>
<td>8.18 ± 1.33</td>
<td>t (11) = -5.17, P&lt;.001</td>
</tr>
<tr>
<td>Contented/ discontented</td>
<td>12</td>
<td>2.25 ± 1.82</td>
<td>12</td>
<td>3.42 ± 2.78</td>
<td>NS</td>
</tr>
<tr>
<td>troubled/tranquil</td>
<td>12</td>
<td>3.25 ± 2.60</td>
<td>12</td>
<td>2.92 ± 2.39</td>
<td>NS</td>
</tr>
<tr>
<td>mentally slow/ quick-witted</td>
<td>12</td>
<td>3.75 ± 2.05</td>
<td>12</td>
<td>6.50 ± 2.15</td>
<td>T (11) = -6.65, P&lt;.001</td>
</tr>
<tr>
<td>tense / relaxed</td>
<td>12</td>
<td>2.33 ± 1.56</td>
<td>12</td>
<td>3.08 ± 2.43</td>
<td>NS</td>
</tr>
<tr>
<td>attentive/ dreamy</td>
<td>12</td>
<td>1.92 ± 1.24</td>
<td>12</td>
<td>5.92 ± 2.39</td>
<td>T (11) = -4.90, P&lt;.001</td>
</tr>
<tr>
<td>incompetent/ proficient</td>
<td>12</td>
<td>3.00 ± 1.90</td>
<td>12</td>
<td>3.92 ± 2.15</td>
<td>NS</td>
</tr>
<tr>
<td>happy/ sad</td>
<td>12</td>
<td>1.25 ± 0.45</td>
<td>12</td>
<td>2.92 ± 1.50</td>
<td>T (11) = -3.46, P&lt;.01</td>
</tr>
<tr>
<td>antagonistic/ amicable</td>
<td>12</td>
<td>2.83 ± 2.08</td>
<td>12</td>
<td>3.50 ± 1.62</td>
<td>NS</td>
</tr>
<tr>
<td>interested/ bored</td>
<td>12</td>
<td>2.20 ± 1.08</td>
<td>12</td>
<td>3.58 ± 2.27</td>
<td>T (11) = -2.28, P&lt;.05</td>
</tr>
<tr>
<td>withdrawn/ sociable</td>
<td>12</td>
<td>2.33 ± 2.02</td>
<td>12</td>
<td>3.67 ± 2.46</td>
<td>NS</td>
</tr>
<tr>
<td>POMS total</td>
<td>12</td>
<td>2.08 ± 29.00</td>
<td>12</td>
<td>20.08 ± 14.27</td>
<td>T (11) = -2.17, p=0.05</td>
</tr>
<tr>
<td>POMS tension</td>
<td>12</td>
<td>4.75 ± 4.43</td>
<td>12</td>
<td>5.00 ± 3.05</td>
<td>NS</td>
</tr>
<tr>
<td>POMS depression</td>
<td>12</td>
<td>4.50 ± 7.31</td>
<td>12</td>
<td>3.92 ± 3.05</td>
<td>NS</td>
</tr>
<tr>
<td>POMS anger</td>
<td>12</td>
<td>3.67 ± 6.71</td>
<td>12</td>
<td>3.00 ± 4.92</td>
<td>NS</td>
</tr>
<tr>
<td>POMS vigour</td>
<td>12</td>
<td>18.92 ± 5.87</td>
<td>12</td>
<td>11.92 ± 7.29</td>
<td>T (11) = -3.77, p&lt;0.01</td>
</tr>
<tr>
<td>POMS fatigue</td>
<td>12</td>
<td>4.08 ± 4.64</td>
<td>12</td>
<td>12.58 ± 6.11</td>
<td>T (11) = -3.79, p&lt;0.01</td>
</tr>
<tr>
<td>POMS confusion</td>
<td>12</td>
<td>3.92 ± 3.45</td>
<td>12</td>
<td>7.50 ± 4.30</td>
<td>T (11) = -2.33, p&lt;.05</td>
</tr>
<tr>
<td>Karolinska Sleepiness Scale</td>
<td>12</td>
<td>3.33 ± 1.88</td>
<td>14</td>
<td>7.58 ± 1.16</td>
<td>T (11) = -9.92, P&lt;.001</td>
</tr>
</tbody>
</table>
5.4.3 Behavioural data

Table 5.2 displays the means and standard deviations of the divided attention task data. Figure 5.1 depicts the results of the divided attention task in each session. Three participants’ data were excluded in the SD session, and one in the NSD session due to technical problems related to the task, leaving 10 and 11 participants in the final analysis of the behavioural data, respectively.

There was a significant main effect of block type for errors of omission between the visual, auditory and divided attention task blocks ($F(1.78, 16) = 11.44, p< 0.005$). Post hoc analysis indicated that there were significantly more errors of omission recorded in the divided attention blocks compared to both the auditory ($p<0.01$) and the visual blocks ($p<.005$). There was no significant effect of session for errors of omission ($p = 0.20$). There was a significant main effect for task block for errors of commission ($F(1.64, 14.74) = 4.40, p< 0.05$). Post hoc analysis indicated that there were significantly more errors of commission from the divided attention blocks compared to the visual attention blocks ($p > 0.01$). There was no effect of session for errors of commission.

Table 5.2: Means and Standard deviations (Std. Dev.) of the errors of omission and commission in each task block in the No Sleep Deprivation (NSD) and Sleep Deprivation (SD) sessions

<table>
<thead>
<tr>
<th></th>
<th>NSD N</th>
<th>NSD (Mean ± Std. Dev.)</th>
<th>SD N</th>
<th>SD (Mean ± Std. Dev.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>visual errors of omission</td>
<td>11</td>
<td>0.55 ± 0.69</td>
<td>10</td>
<td>0.90 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td>visual errors of commission</td>
<td>11</td>
<td>2.91 ± 2.21</td>
<td>10</td>
<td>1.80 ± 2.44</td>
<td>NS</td>
</tr>
<tr>
<td>auditory errors of omission</td>
<td>11</td>
<td>1.18 ± 1.08</td>
<td>10</td>
<td>3.50 ± 5.76</td>
<td>NS</td>
</tr>
<tr>
<td>auditory errors of commission</td>
<td>11</td>
<td>2.09 ± 2.26</td>
<td>10</td>
<td>2.30 ± 3.40</td>
<td>NS</td>
</tr>
<tr>
<td>divided errors of omission</td>
<td>11</td>
<td>3.91 ± 1.58</td>
<td>10</td>
<td>6.10 ± 5.43</td>
<td>NS</td>
</tr>
<tr>
<td>divided errors of commission</td>
<td>11</td>
<td>1.27 ± 1.35</td>
<td>10</td>
<td>1.10 ± 2.13</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 5.1: Errors of omission during the three different task blocks (visual, auditory and divided) for the no sleep deprivation and sleep deprivation sessions separately. There was a significant difference between all task blocks in the no sleep deprivation session. There was no significant difference between the no sleep deprivation and sleep deprivation sessions for any task block. Error bars represent SEM; * p<0.05.

5.4.4 Functional activations

The anatomical locations, Brodmann’s areas (BA), cluster size, and peak voxel t-scores of significant clusters of activation for the comparisons of interest after normal sleep are displayed in Table 5.4.

5.4.4.1 Selective attention with no sleep deprivation

When attention was directed to the visual targets, significantly more activation was observed in the right middle frontal gyrus (BA 10/11), right hypothalamus, and bilateral middle temporal gyrus (BA 21/38) when compared to auditory selective
attention (Figure 5.2). Activation was also observed in the visual regions of the lateral occipital gyrus and precuneus, however these regions only reached voxel-level significance. When attention was directed to the auditory targets, increased activation was evident in bilateral superior temporal gyri (BA 22), right inferior frontal gyrus (BA 47) and the left cerebellum when compared to visual selective attention (Figure 5.2).

5.4.4.2 Divided attention versus selective attention with no sleep deprivation

When compared to activation during selective attention, increased activation was observed in the right middle frontal gyri (BA 6/9) and left superior frontal gyri (BA 6/9), bilateral inferior parietal lobe (BA 40) and the left cerebellum during divided attention (Figure 5.3A).

5.4.4.3 Divided attention versus selective attention with sleep deprivation compared to normal sleep

At the cluster level analysis for this comparison, no clusters survived the criteria for significance outlined in the methods section. However, there were a number of regions in which activation was greater than the T height threshold defined. These voxel-level activations are reported in Table 5.5.

Areas of increased activation (voxel-level) after normal sleep compared to sleep deprivation included the right superior temporal gyrus (BA 38), left cerebellum, parahippocampal gyrus (BA 36), limbic lobe (BA 20), and left middle frontal gyrus (BA 8). Following 27 hours of sleep deprivation, there was increased activation of the bilateral precuneus (BA 31), right superior temporal gyrus (BA 22), and right culmen (cerebellum) during the divided attention task, compared to the activation observed after normal sleep (Figure 5.3B).

Results from the regression analysis indicated that there were no significant associations between any brain regions activated during divided attention in the NSD
or SD sessions, and divided attention performance. Further, there were no associations between brain activations and subjective sleepiness measures in the SD session.

Table 5.3: BOLD activation in the visual vs. auditory, auditory vs. visual, and divided vs. selective comparisons after normal sleep.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Cluster</th>
<th>L/R</th>
<th>Region</th>
<th>BA</th>
<th>Peak voxel T-value</th>
<th>Coordinates (MNI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significant Clusters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD: Visual vs. Auditory</td>
<td>R</td>
<td>MTG</td>
<td>21</td>
<td>7.83</td>
<td>42, 12, -42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>MTG</td>
<td>38</td>
<td>4.47</td>
<td>-40, 2, -34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>MFG</td>
<td>10</td>
<td>3.44</td>
<td>6, 62, 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>MFG</td>
<td>11</td>
<td>7.19</td>
<td>22, 30, -18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Hypothalamus</td>
<td>7.63</td>
<td>6, -6, 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-significant clusters of interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD: Auditory vs. Visual</td>
<td>R</td>
<td>Lateral Occipital gyrus</td>
<td>18</td>
<td>4.29</td>
<td>26, -94, -18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Precuneus</td>
<td>39</td>
<td>4.32</td>
<td>34, -66, 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>STG</td>
<td>6.11</td>
<td>-62, -26, 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>Cerebellum</td>
<td>5.45</td>
<td>-28, -68, -32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>IFG</td>
<td>47</td>
<td>5.10</td>
<td>46, 30, -4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>Lingual gyrus</td>
<td>18</td>
<td>4.95</td>
<td>16, -76, -10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>IPL</td>
<td>4.88</td>
<td>-12, -92, 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Significant Clusters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD: DA vs. SA</td>
<td>R</td>
<td>Cerebellum</td>
<td>7.76</td>
<td>32, -64, -32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>SFG</td>
<td>7.17</td>
<td>-24, 8, 74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>SFG</td>
<td>5.82</td>
<td>-44, 38, 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>MFG</td>
<td>6.50</td>
<td>38, 48, 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>MFG</td>
<td>5.98</td>
<td>54, 12, 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>IPL</td>
<td>4.52</td>
<td>-44, -46, 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>IPL</td>
<td>4.80</td>
<td>42, -42, 44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L = left; R = right; B = bilateral; NSD = no sleep deprivation; DA = divided attention, SA = selective attention (visual + auditory); SFG = superior frontal gyrus; MFG = middle frontal gyrus; IPL = inferior parietal lobule; STG = superior temporal gyrus; MTG = middle temporal gyrus; BA = Brodmann’s area; MNI = Montreal Neurological Institute. Cluster-level significance of p<0.05 (corrected for multiple comparisons).
Figure 5.2: Axial views of brains showing comparative activations during performance of visual selective attention compared to auditory selective attention (hot colouring) and auditory selective attention compared to visual selective attention (cold colouring) after normal sleep.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Cluster</th>
<th>L/R</th>
<th>Region</th>
<th>BA</th>
<th>Peak voxel T-value</th>
<th>Coordinates (MNI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSD &gt; SD: DA vs. SA task</strong></td>
<td>80</td>
<td>L</td>
<td>Parahippocampal gyrus</td>
<td>36</td>
<td>6.06</td>
<td>-36, -26, -28</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>R</td>
<td>Limbic Lobe</td>
<td>20</td>
<td>4.66</td>
<td>34, -14, -38</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>R</td>
<td>STG</td>
<td>38</td>
<td>4.50</td>
<td>32, 20, -30</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>L</td>
<td>Cerebellum</td>
<td></td>
<td>3.98</td>
<td>-18, -36, -30</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>L</td>
<td>MFG</td>
<td></td>
<td>3.42</td>
<td>-4, 50, 50</td>
</tr>
<tr>
<td><strong>SD &gt; NSD: DA vs. SA task</strong></td>
<td>178</td>
<td>R</td>
<td>Precuneus</td>
<td>31</td>
<td>8.64</td>
<td>20, -58, 26</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>L</td>
<td></td>
<td></td>
<td>5.29</td>
<td>-18, -58, 34</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>R</td>
<td>STG</td>
<td>22</td>
<td>6.37</td>
<td>46, -58, 16</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>R</td>
<td>Culmen</td>
<td></td>
<td>5.63</td>
<td>14 -38 -24</td>
</tr>
</tbody>
</table>

L = left; R = right; B = bilateral; NSD = no sleep deprivation; SD = sleep deprivation; DA = divided attention, SA = selective attention; MFG = middle frontal gyrus; STG = superior temporal gyrus; BA = Brodmann's area; MNI = Montreal Neurological Institute. Voxel-level significance $p < 0.005$ (uncorrected).
Figure 5.3A: Three views of areas of significant activation after normal sleep; and B: following sleep deprivation, in response to divided attention compared to selective attention.
5.5 Discussion

The current study examined brain activation associated with selective and divided attention, which are important skills required for the task of driving. This neuroimaging experiment aimed to determine whether sleep deprivation had a differential effect on neural activations during divided attention performance compared to the neural activations observed after normal sleep. Areas of increased neural activation were observed in sleep-deprived participants, when performance on a divided attention task was maintained. This was in addition to the increased activation observed when performing a divided attention task, compared to a selective attention task, after normal sleep. Although some reduced activation was observed in frontal and sensory regions following sleep deprivation, this did not result in a decline in divided attention performance. Better task performance following sleep deprivation was related to increased neural activation, and thus may reflect a compensatory response.

5.5.1 Questionnaire & Behavioural data

A range of sleepiness and mood questionnaires were administered in the current experiment, to determine whether these measures were affected by sleep deprivation. There was no significant difference in the Symptoms Checklist (SCL-90-R) scores between the NSD session and after participants had been awake for 27-hours. This inventory has not been used in sleep deprivation studies previously, and therefore was more of an exploratory measure. The SCL-90-R is designed to reflect psychological symptoms status, and previously has been used as an outcome variable in clinical settings. It is a measure of current, state-level psychological symptoms. The SCL-90 does not appear to be sensitive to acute sleep deprivation effects.

Other mood and sleepiness scores, including the KSS, VAS and POMS, did show a significant decline with sleep loss, as expected. Increased ratings of subjective sleepiness, as measured by the KSS, are consistent with the findings of Experiment 1, and previous studies (Gillberg, 1994). This indicates that the participants in this study were significantly sleepy in the SD session before they underwent the MRI scan, and thus the experimental manipulation was achieved.
Changes in mood during periods of sleep deprivation are often robust and consistent (Pilcher & Huffcutt, 1996). Mood changes associated with sleepiness have previously been measures using the POMS (Dinges et al., 1997; Meney, Waterhouse, Atkinson, Reilly, & Davenne, 1998; Wesensten et al., 2002). As reported in the current study, POMS subscale scores for fatigue, confusion, and total mood disturbance have previously been shown to increase during periods of restricted sleep (Dinges et al., 1997) and sleep deprivation (Meney et al., 1998; Wesensten et al., 2002). The current study also demonstrated a decrease in the Vigor sub-scale. In contrast, other sleep restriction studies have also reported increased rating on the depression and tension subscale of the POMS after sleep restriction to 4.5 hours in bed the previous night (De Valck & Cluydts, 2001; Dinges et al., 1997). The discrepancies between this and previous studies is likely due to the different methods of inducing sleepiness; the current study used a paradigm of total sleep deprivation, whereas these previous reports have used sleep restriction. This is the first study to examine changes in POMS ratings with total sleep loss in a sample of professional drivers.

A number of VAS subscales were rated significantly higher after sleep deprivation. This measure has been used in previous sleep deprivation studies, with similar findings (Dumont et al., 1999; Penetar et al., 1993). This scale has also been correlated performance tasks in previous studies (Gillberg et al., 1994). These measures are clearly more sensitive to sleepiness and sleep loss, and thus appear to be useful measures of mood in the context of sleep deprivation. Mood is often assessed by self-report, which may be overestimated by some people. Thus, measures of behavioural performance can provide more objective estimates of sleepiness levels following sleep deprivation.

The current study demonstrated a small increase in errors of omission following sleep deprivation in each of the three task blocks, however this finding was not statistically significant. Thus, participants were able to maintain their behavioural performance across both sessions, and all task blocks, despite a significant increase in subjective sleepiness during the sleep deprivation session. The effect size for detecting a difference in the divided attention errors of omission data in this experiment was 0.33. In order for an effect size of 0.33 to be significant with an alpha of 0.05% and a power
of 0.8 it is estimated that 41 subjects would be required. Therefore, it is possible that this study lacked adequate power to observe a sleep-deprivation effect. The length of the task used in this study (9 minutes, with a 30 s break in the middle) may have been too short to induce any significant sleep deprivation-related behavioural effect. Vigilance decrements due to sleep deprivation generally occur after an extended or sustained period of behavioural testing (>10 minutes)(Dinges & Powell, 1988; Van Dongen et al., 2003). However, a short task is often beneficial since a loss of interest and boredom-related fatigue, associated with prolonged testing, can result in a decline in arousal and cognitive performance (Wilkinson, 1965). The lack of significant performance changes with sleep deprivation meant we were unable to examine whether there were differential effects on cortical activation in poor performers compared to good performers. Although there was no measurable change in behavioural performance, neural activation following sleep deprivation was altered compared to the rested state, as will be discussed in the following section.

### 5.5.2 Neuroimaging data

An examination of the neural correlates of selective attention by modality revealed that when participants attended to the auditory task alone, regions associated with primary auditory sensory processing (i.e. superior temporal gyrus) were activated, as expected. Some frontal and visual areas were also activated (i.e. inferior frontal gyrus and lingual gyrus), since visual processing is still occurring during the auditory task although attention is not directed to the visual stimuli. During the visual selective attention blocks, significant activations were observed in the temporal lobe, middle frontal gyrus and, at a lower threshold, the right lateral occipital gyrus. Frontal activation has previously been implicated in involuntary shifts of attention between auditory and visual stimuli modalities (Downar et al., 2000; Karayanidis et al., 2003; Shomstein & Yantis, 2004). These activations may be a residual effect of participants switching attention between the different task blocks. The region of the occipital lobe activated in the current study is more lateral than that observed by Loose et al. (2003), who found enhanced primary visual cortex activation, however this is likely to be due to differences in the statistical comparisons used in the two studies. In the current study, random-effects group level modelling was used, whereas Loose et al. (2003) employed more liberal fixed-effects group level modelling; random effects statistics
are generalisable to the population from which they are drawn, whereas fixed effects models are relevant only to that particular sample. Johnson et al. (2006) used a similar statistical comparison as the current study (visual attention vs. auditory attention), and found activations in lateral and inferior occipital regions. The current findings, therefore, provide a more robust observation of regions which are more activated when attention is directed towards one modality compared to the unattended modality, as opposed to simple selective attention per se. It appears that these lateral visual regions are recruited when visual selective attention occurs, with an associated decrease in sensory regions of the unattended modality, as reported previously (Johnson, Strafella, & Zatorre, 2007; Johnson & Zatorre, 2006).

Both auditory and visual selective attention also activated frontal regions. Previous PET (O'Leary et al., 1997) and fMRI studies (Loose et al., 2003) have also reported that auditory selective attention causes activation and regional cerebral blood flow changes which are largely localised in the temporal lobes, whereas visual attention causes widespread activations in frontal and parietal regions. The posterior parietal and superior prefrontal cortices, forming part of the fronto-parietal-cingulate network, is understood to be implicated in involuntary shifts of attention between auditory and visual stimuli modalities (Downar et al., 2000, Karayanidis et al., 2003, Shomstein and Yantis, 2004). These activations therefore may be a residual effect of participants switching attention between the different task blocks.

During divided attention, compared to selective attention, there was a significant increase in behavioural errors, suggesting that divided attention was more difficult. This is in contrast to previous studies (Johnson & Zatorre, 2006; Loose et al., 2003) that have reported accuracy of performance to be equivalent across different task blocks. During divided attention blocks, the current study demonstrated an increased activation of superior frontal regions, as reported previously (Johnson & Zatorre, 2006; Loose et al., 2003). Previous cross-modal divided attention studies have also demonstrated an increase recruitment of dorsolateral prefrontal regions during divided attention, which was hypothesised to assist with maintaining performance during this more demanding task condition (Johnson & Zatorre, 2006; Loose et al., 2003). This activation may also reflect the more difficult nature of the divided attention task blocks, as greater prefrontal activation has previously been observed in individuals
performing executive tasks, relating to increases in task difficulty (Schall et al., 2003). It is difficult to determine in the current study whether prefrontal recruitment is due to the task-switching component of divided attention, or due to the increased difficulty of the divided attention blocks compared to the selective attention blocks.

This is the first study to examine the effects of sleep deprivation on neural activity during a sensory cross-modal divided attention task. We examined changes in neural activation associated with selective and divided attention during sleep deprivation, when attention is usually compromised and baseline neural activity is known to be reduced (Thomas et al., 2000). There was no change in behavioural performance following sleep deprivation in any of the three task conditions. Thus, participants were able to compensate for their sleepiness and maintain their behavioural performance during the nine-minute task across all task conditions, despite a significant increase in subjective sleepiness during the sleep deprivation session. Brain areas which exhibited reduced activation following sleep deprivation included the temporal lobes, cerebellum, and frontal regions. This supports previous studies suggesting that frontal regions of the cortex are more vulnerable to the effects of sleep deprivation (Thomas et al., 1998; Wu et al., 1991). No performance decrements were observed in this study following sleep deprivation, despite the relative reduction in activation of these sensory and motor regions during task performance. It may simply be that the 27-hour period of sleep deprivation, in conjunction with performing a task of relatively short duration during a circadian peak period, did not reduce neural activity enough to result in significant performance decrements. Alternatively, the additional areas of increased neural activation discussed below may represent a compensatory mechanism that enabled maintenance of performance.

In support of the compensatory hypothesis, increased levels of neural activation in parietal and temporal brain regions were demonstrated during divided attention performance following sleep deprivation (compared to activation after normal sleep). Additional activation was observed bilaterally in the precuneus. Precuneus activation has been implicated in attentional processing (Lawrence et al., 2003), attention shifts between foveally-presented visual stimuli (Le et al., 1998), and distinguishing between two different tones (Platel et al., 1997) in non-sleep deprivation individuals. This cortical region is also believed to be a component of the brain’s ‘default-mode’
network, denoting a baseline state of the brain in which the posterior cingulate and precuneus are tonically active, associated with general sensory monitoring (Raichle et al., 2001). When an awake individual engages in an attention-demanding task, activity in these areas is thought to be attenuated (Todd et al., 2005). This may reflect a necessary reduction in resources allocated to general information gathering, thus aiding focused, behaviourally relevant visual attention (Raichle et al., 2001). The increased activation in the precuneus following sleep loss in the current study may reflect an inability of the brain to suppress this activation, thus less efficient processing is occurring following sleep deprivation. This disengagement with the task, in turn, resulted in reduced, although non-significant, behavioural performance after sleep deprivation. Hence, the recruitment of additional areas of the cortex following sleep deprivation may be to the detriment of functional areas normally used in the well-rested state (Chee & Chuah, 2007), however this requires further clarification.

The precuneus also has intimate projections to the temporal lobes - a region which was also further activated following sleep deprivation - which comprise an associative cortical network involved in the integration of auditory, somatosensory and visual information (Cavanna & Trimble, 2006). Previous studies have reported that those participants who demonstrated the best performance during divided attention also recruited more sensory cortex during the task (Johnson & Zatorre, 2006). Recruitment of these regions may therefore assist with maintaining attention, and thus behavioural performance, during sleep deprivation.

The altered activity in the precuneus reported in the current study is slightly superior to that previously demonstrated during performance of two higher-order cognitive tasks following sleep deprivation (Drummond et al., 2001). In contrast to the finding of Drummond et al. (2001), the current study did not report prefrontal activation. This is possibly due to the different tasks employed in these studies; higher cognitive tasks are expected to produce more prefrontal activation, whereas our simple sensory tasks activated more sensory and motor regions following sleep deprivation (temporal and cerebellum). This is not to say that no prefrontal activity occurred following sleep deprivation; rather the difficulty of the task was consistent across sessions and therefore the prefrontal activation was similar. The increase in neural activation in the
precuneus following sleep deprivation may reflect a task-related compensatory response, as increased sleepiness has been associated with increased BOLD response (Drummond et al., 2001) and frontal EEG activity in the frequencies <7 Hz (Cajochen et al., 1999) in other studies. Alternatively, the adaptive cerebral response may relate to cognitive demands rather than increased sleepiness per se, since both Drummond et al. (2001) and the current study did not find significant performance impairment with sleep deprivation. Within the same individual, larger increases in brain activity have previously been related to better performance on tasks, including a divided attention task (Drummond et al., 2001). It appears that when additional regions of the cortex are recruited following sleep deprivation, this may help to maintain task performance. Together, these studies provide support for the “cognitive reserve” theory, which postulates that better cognitive resistance to sleep deprivation is attributed to having more cognitive resources to begin with, or the ability to engage other neural resources when required (Stern, 2002). Thus, individuals who are able to maintain attention and performance when sleep deprived, may do so by recruiting additional areas of the cortex.

Sleepiness may be heritable (Watson et al., 2006), with differences evident in individuals’ susceptibility to sleepiness and the effects of sleep deprivation on their performance (Van Dongen et al., 2004). Studies such as the current one could be used to examine differential neural activation between individuals who are more sleep deprivation-resilient compared to individuals who are more susceptible to the cognitive impairment induced by sleep deprivation. Regions with relatively low activity in poor performers may indicate which areas of the brain are important for task maintenance and efficient processing.

Some limitations of the current study should be noted. First, in relation to the divided attention task, the number of stimuli presented was the same in all blocks, but the number of targets was greater in the divided attention blocks since both visual and auditory targets were employed. Our reason for designing the task this way was to keep the sensory input between different conditions the same. Considering this, we cannot be sure that the increased activation is due to the effects of cross-modal attention, changes in stimulus probability, or whether it reflects an increased motor response frequency and an intrinsic increased neural response to target detection.
However, the regions activated appear to be task specific, and not primarily motor-related brain areas. It would be useful to replicate this study by manipulating the target numbers to keep the probability consistent between task blocks. Second, vigilance decrements due to sleep deprivation generally occur after an extended or sustained period of behavioural testing (>10 minutes) (Dinges and Powell, 1988, Van Dongen, 2003). Most of the participants managed to stay awake in the scanner with little difficulty, especially since it is such a noisy environment, and most drivers were used to experiencing sleep deprivation. There were a few drivers who reported “napping” while the structural scans were occurring and in-between tasks. The experimenter spoke with the drivers throughout the scanning session to ensure they were awake prior to the task starting, and there were very few missed responses during the task, which indicates that drivers were awake throughout the tasks. Task duration in the present experiment may have been too short (9 minutes and 10 seconds) to induce a significant sleep deprivation-related behavioural effect. However, a short task is often beneficial since a loss of interest and boredom-related fatigue, associated with prolonged testing, can result in a decline in arousal and cognitive performance (Wilkinson, 1965). The lack of significant performance changes with sleep deprivation meant we were unable to examine whether there were differential effects on cortical activation in poor performers compared to good performers. Although there was no measurable change in behavioural performance, changes in neural activation following sleep deprivation compared to the rested state were demonstrated. Third, the length of sleep deprivation used in the current study may not have been sufficient to induce behavioural during a relatively short task. Circadian influences can impact on behavioural performance (Gillberg et al., 1996, Jewett et al., 1999), however, the timing of the scan at 10:30h in the current study was used to avoid significant circadian effects on performance. Future studies would benefit from manipulating the task difficulty and duration, and extending the period of sleep deprivation. Finally, due to difficulties in recruitment in the final stages of testing, two non-professional drivers were recruited for this study. These participants had a full drivers licence, and spent an average of 10 hours driving per week.

The pattern of activation found in the current study with sleep deprivation may be explained by neuropsychological studies of visual field functioning following sleep loss. Interestingly, damage to the parietal cortex, when it extends medially to include
the posterior cingulate and precuneus, leads to a condition known as Balint’s syndrome. One of the primary symptoms of Balint’s syndrome is tunnel vision (Hecaen & Ajuriaguerra, 1954). A decrease in behavioural responses to peripheral visual field stimuli may occur following acute sleep loss (Mills et al., 2001, Russo et al., 2002). The reduced activation in the parietal, associated with visual attention, following sleep deprivation, may help to explain the neural basis of this tunnel vision response.

5.6 Conclusion

The ability to divide attention between different sensory inputs is an essential component of the driving task. One possible explanation for the increased accident risk in sleep-deprived drivers is a failure to process all incoming sensory inputs, which may lead to lapses in attentional processing, and cause the driver to fail to respond to potential hazards in the road scene. The findings of Experiment 1 suggest that sleep deprivation reduces neural processing of later cognitive components, which leads to a reduction in reaction times and lapses in attention. The findings of the current experiment indicate that task performance is maintained when increased neural recruitment occurs. Together, these findings suggest that, if neural recruitment fails to occur, (e.g. during a more complex task such as driving, or during longer periods of sleep deprivation) then the subsequent driving performance may be impaired. If a driver fails to respond appropriately to potential hazards in the driving scene, this can potentially lead to an accident.
CHAPTER 6
EXPERIMENT 3

Chapter overview

This chapter presents a pilot study, examining the efficacy of \( d \)-amphetamine as a countermeasure for sleep deprivation. Firstly, this chapter outlines the current epidemiological literature pertaining to drug-related accidents, and provides possible causes of drug- and sleep-related accidents. Secondly, this chapter provides a description of amphetamine-type-stimulants, including the pharmacology, pharmacokinetics and pharmacodynamics of these drugs. A review of the current experimental literature examining the efficacy of amphetamine-type-stimulants in improving performance in sleep-deprived individuals is also provided. The following sections of this chapter reports a pilot study examining the effects of \( d \)-amphetamine and placebo on driving-related performance, both before and after one night of sleep deprivation.

6.1 Introduction

As outlined in Chapter 1, sleep deprivation is a significant issue for professional drivers. One possible explanation for the increased accident risk in this population of drivers is the interaction between sleepiness and drug-use. There is evidence that some professional drivers resort to pharmaceutical means to help them maintain alertness and combat symptoms of sleepiness during times of extended wakefulness (Goldberg & Cone, 1994). Epidemiological reports of fatally-injured truck drivers (Crouch et al., 1993; Drummer et al., 2003; Logan, 1996; Holmgren, Holmgren & Ahlner, 2005), and road-side drug testing data (Couper et al., 2002; Silva et al., 2003), indicate that amphetamine use by truck drivers is a world-wide problem. For instance, a US study of 1,079 tractor-trailer drivers drug-tested reported that 9.5% tested positive to stimulants (Couper et al., 2002). Further, a Brazilian study involved the assessment of 728 urine samples of truck drivers, and reported that 5.6% tested positive to any drug, where the majority of these (85%) contained amphetamine (Silva et al., 2003). In a large Australian study (\( N = 3398 \)), the level of illicit drugs in the blood of fatally injured drivers was reported. Drugs other than alcohol were found in
26.7% of drivers, with amphetamines detected in 4.1% of all drivers. Interestingly, stimulants were much more prevalent in truck drivers, with 23% of the 139 truck drivers testing positive to amphetamine-type-stimulants (Drummer et al., 2003). In an earlier US study, specifically targeting fatally injured truck drivers, 7% of these drivers’ blood specimens tested positive to amphetamine or methamphetamine, with a further 7% containing other amphetamine-type-stimulants (e.g. ephedrine, pseudoephedrine) (Crouch et al., 1993). In the majority (89%) of the cases where psychoactive drugs were detected, it was reported that impairment due to the drug contributed to the fatality. The data from these studies involving fatally injured truck drivers, compared to general incidence data of drug use amongst truck driver population indicates that amphetamine use is over-represented in fatally injured truck drivers (Drummer et al., 2003). It is currently unclear whether these is a causal relationship between amphetamine use and accident risk, and therefore requires further investigation.

Despite the cognitive enhancing properties of amphetamine-type stimulants (Angrist et al., 1987; Caldwell & Caldwell, 1997; Seiden, 1993), it remains unclear why there is an increased accident risk associated with amphetamine use. There are several explanations that may help to understand the paradox in amphetamine-using fatigued drivers. Firstly, there may be a marked increase in sleep propensity and the detrimental neurocognitive effects of sleep loss as the effects of amphetamine-type stimulants dissipate (Hurst et al., 1971; Logan, 1996). Secondly, at high doses, amphetamine-type stimulants may cause negative effects, such as delirium, hallucinations and syncope, impairing a person’s judgement of their ability to drive safely (Logan, 1996). Thirdly, amphetamine-type stimulants may not reverse all the effects of sleep loss (Bakoff, Kelly, & Naitoh, 2001; Bray et al., 2004; Magill et al., 2003; Newhouse et al., 1989) and may in fact exacerbate some of the effects of sleep loss, such as peripheral vision neglect (Mills et al., 2001). Fourthly, amphetamine-type stimulants may enhance risk-taking behaviour (Hurst, 1962; Hurst, Weidner, & Radlow, 1967), which is reported to be associated with an increase in accident risk (Turner & McClure, 2004). Fifthly, binge abuse over a number of days, which may be undertaken by long-haul drivers, can be followed by fatigue and hypersonmolence (Gustavsen, Morland, & Bramness, 2006). Additionally, there is a sleep debt that is accumulated during the stimulant phase which needs to be recovered. For example,
there are reports of high rates of erratic driving amongst amphetamine users, both during the acute intoxication phase and during the rebound fatigue phase (Logan, 1996, 2001). These factors have not been examined experimentally. Finally, there may be detrimental effects on neurocognitive function as a result of long-term stimulant use, which may affect an individual’s ability to drive safely in general, whether they have consumed drugs recently or not (Thompson et al., 2004). The current pilot study aimed to examine the relationship between sleep deprivation and \(d\)-amphetamine administration on the range of driving-related processes assessed in Experiment 1, using a cohort of professional drivers who were past or present amphetamine users. The following sections will provide an overview of amphetamine-type-stimulants, the current literature on the effects of amphetamine in combination with sleep deprivation on driving-related performance, and then describe the methods and results of the current Experiment. This chapter will conclude with a discussion of the findings.

### 6.1.1 Overview of amphetamine-type-stimulants

One commonly reported drug used by transport drivers is \(d\)-amphetamine (trade name: desoxyn), as it is readily available and simple to self-administer. \(d\)-amphetamine (also known as dextroamphetamine sulfate, dextroamphetamine, and Dexadrine™), the dextro isomer of the compound \(d,l\)-amphetamine sulfate, a sympathomimetic amine of the amphetamine group, is a potent central nervous system stimulant (MIMS, 2002). Its primary action is to induce the release of the neurotransmitter dopamine into nerve synapses in certain areas of the brain. The chemical name for \(d\)-amphetamine is (s)-alpha-methylphenethylamine sulphate (MIMS, 2002). \(d\)-amphetamine has a molecular formula of \((C_{19}H_{13}N)2H_2SO_4\) and a molecular weight of 368.5 (MIMS, 2002). The chemical structure of \(d\)-amphetamine is depicted in Figure 6.1.
Clinically, the drug is a prescription-only medication (MIMS, 2002). The primary therapeutic applications of \(d\)-amphetamine are the treatment of narcolepsy, Attention Deficit Hyperactivity Disorder (ADHD) and mild depressive states (Grilly, 2002), with daily oral doses that range from 2.5 mg to 60 mg, administered in divided doses (MIMS, 2003; Fillmore et al., 2005; Grilly, 2002).

There are other common classes of amphetamine-type-stimulants including amphetamine and methamphetamine. Amphetamine (alpha-methyl-phenethylamine), or "speed", is a synthetic stimulant used to suppress the appetite, control weight, and treat disorders including narcolepsy and ADHD. Figure 6.2 depicts the chemical structure of amphetamine. The actions of amphetamine are very similar to \(d\)-amphetamine, increasing norepinephrine and dopamine levels in the synapses. Short-term physiological and psychological effects include decreased appetite, increased stamina and physical energy, involuntary bodily movements, hyperactivity, nausea, increased or irregular heart rate, headaches, increased alertness, euphoria, increased concentration, increased confidence, and nystagmus (rapid eye movements). Fatigue can often follow the dose's period of effectiveness. Amphetamine is highly-psychologically addictive, and, tolerance develops very quickly with chronic use. Amphetamine is considered an FDA Schedule 8 drug in Australia, indicating that it has high abuse potential, and may lead to physiological and psychological dependence. Amphetamine has a similar half life to \(d\)-amphetamine, between 10 and 13 hours.
Methamphetamine, also known as Crystal Meth or Ice, is a synthetic compound similar in structure to amphetamine. The chemical structure of methamphetamine is depicted in Figure 6.3. As in d-amphetamine, the two optical isomers, dextro-methamphetamine and levo-methamphetamine, have different activity on both the peripheral nervous system and CNS. The main difference between d-amphetamine and methamphetamine, is that methamphetamine has a slight modification in the amphetamine molecule, yielding a slightly more potent structure. This in turn gives a stronger feeling of euphoria thus creating a higher potential for addiction. Methamphetamine also produces increased alertness, motivation, and brain activity (short-term), and weight loss.

6.1.1.1 Pharmacology & pharmacokinetics of d-amphetamine

d-amphetamine stimulates both alpha and beta-adrenergic receptors (MIMS, 2003). The effects of d-amphetamine are primarily due to the enhancement of dopaminergic activity in the nucleus accumbens, located in the limbic system. The exact mechanism of action has not been established, however, in animals, d-amphetamine appears to have multiple actions on the catecholamine systems (MIMS, 2003). Firstly, d-amphetamines enhance the release of catecholamines (noradrenalin and dopamine) in the synaptic cleft by increasing their spontaneous leakage from neurons and their
stimulated (action potential-induced) release, thereby increasing receptor activation (Grilly, 2002). Secondly, \textit{d-}amphetamine facilitates the action of dopamine and noradrenaline by blocking re-uptake from the synapse, thereby non-selectively elevating synaptic levels of these neurotransmitters (Grilly, 2002). However, the properties which most contribute to the potential for abuse is the increase in extracellular levels of dopamine. \textit{d-}amphetamine also has a mild, temporary, inhibitory action on the enzyme MAO (Grilly, 2002). This degrades intracellular serotonin levels, thus having a net effect of increased extracellular levels of serotonin. This action has only a minor impact on most of the behavioural effects of amphetamine, but may play a role in hallucinogenic and anorexia aspects of the drug (Grilly, 2002).

Due to its relatively high lipid-solubility, \textit{d-}amphetamine is rapidly absorbed orally, which is the most common route of administration (Grilly, 2002). Oral use of \textit{d-}amphetamine is associated with an approximate one-hour lag time before onset of symptoms, due to its action on gastric emptying and intestinal motility, thus delaying its own absorption (Drummer, 2001). Kinetic studies have demonstrated that levels of \textit{d-}amphetamine in plasma are detectable at one to two hours after oral drug administration, depending on food intake prior to drug administration (Heedes & Ailakis, 1992; Brauer, Ambre & de Wit, 1996; Drummer et al., 2001). Peak plasma levels of \textit{d-}amphetamine are reached between three and four hours post-administration, with absorption generally complete within four to six hours. Plasma levels plateau, and then begin to decline five hours post-administration, but remain detectable up to 24-hours (Brauer, Ambre, & de Wit, 1996).

There appears to be a non-linear effect of dose and blood concentrations of stimulant-like drugs at high doses (Drummer et al., 2002). Oral administration of 0.25 mg/kg \textit{d-}amphetamine, for example, shows maximum cardiovascular effects at one hour post drug-administration, with maximal behavioural effects at two hours (Drummer et al., 2001). In comparison, subjects who have been administered 0.5 mg/kg \textit{d-}amphetamine orally display maximum levels of \textit{d-}amphetamine in plasma of 0.07 mg/l after three to four hours, with maximal subjective and behavioural effects at two to three hours and a decline after four hours, despite stable or rising plasma drug levels (Angrist et al., 1987; MIMS, 2002).
Thirty to 40 percent of \(d\)-amphetamine is metabolised by the liver, with the remainder excreted directly by the kidneys (MIMS, 2003). Generally, the half-life of \(d\)-amphetamine is between four and 30 hours, with an average of 10.25 hours, for doses ranging from 5 mg to 60 mg (Drummer et al., 2001; Drummer et al., 2002; MIMS, 2003). Between 5% and 30% of a therapeutic dose of \(d\)-amphetamine is excreted unchanged in the urine by 24 hours, with a total of about 90% of the dose is excreted in three to four days (MIMS, 2003).

### 6.1.1.2 Pharmacodynamics of \(d\)-amphetamine

When taken therapeutically, \(d\)-amphetamine increases alertness and energy levels, reduces fatigue and appetite, and creates a sense of well-being (MIMS, 2003). However, the primary effect sought by recreational and occupational amphetamine-type-stimulant users, such as transport drivers, is increased arousal and alertness, and diminished fatigue symptoms (Drummer, 2001). Adverse reactions include dry mouth, restlessness, insomnia, tremor, dizziness, heart palpitations and headache (MIMS, 2003). At high therapeutic doses of around 60 mg total dose, symptoms can include shallow rapid breathing, dilated and reactive pupils, fever, chills and sweating, tachycardia, hypertension and coronary vasospasm, as well as restlessness, aggressiveness, confusion, panic attacks and delirium (MIMS, 2003). At acute toxic levels, physiological reactions can include fever, elevated body temperature and increased heart rate and blood pressure, which can lead to liquefaction of muscles leading to hyperkalaemia, intravascular coagulation, convulsions, haemorrhaging in heart and blood vessels, and renal failure (MIMS, 2003). Toxic symptoms are uncommon with doses less than 15 mg total dose.

When the stimulant effect dissipates during the withdrawal phase, there is an associated decrease in mood, with depression, lethargy and exhaustion commonly reported (MIMS, 2003). Abrupt cessation of high doses of \(d\)-amphetamine following prolonged use can result in extreme fatigue and psychological depression, which is a safety concern for users who are driving a motor vehicle. Although it is still
reasonably uncommon, the number of amphetamine-related deaths is on the increase, usually caused by hyperthermia (Drummer, 2001).

### 6.1.2 Overview of the literature

Experiments 1 and 2 demonstrated a negative consequence of sleep deprivation on a number of driving-related processes. These deficits were observed in simple, vigilance-related neurocognitive tasks, and later cognitive processes measured by ERPs. Further, maintenance of divided attention performance during sleep deprivation appears to be associated with an increase in neural activation, as reported in Experiment 2. Although the impact of sleep loss on these processes may account for some heavy vehicle accidents, another explanation is an interaction between sleep loss and amphetamine-type-stimulants, as described in Chapter 1. This section will outline the literature that reports the effectiveness of d-amphetamine, and other amphetamine-type-stimulants on driving-related performance in sleep deprived participants. As there are limited studies on this topic to date, stimulant classes other than d-amphetamine will also be discussed.

Measures of behavioural disposition are one of the most commonly and extensively researched areas with regards to the reversal of the effects of sleep deprivation with d-amphetamine. Low ratings on the visual analogue scale (VAS) discomfort subscale following 48-hours of sleep deprivation improved after a 20 mg dose of d-amphetamine (Newhouse et al., 1989). Similarly, a 20 mg dose of d-amphetamine significantly reduced ratings of fatigue, and increased rating of vigour on the Profile of Mood States (POMS) (Newhouse et al., 1989). This effect appears to be dose dependent, as a 5 mg and 10 mg dose were ineffective on the POMS scores. Similarly, Hartman, et al. (1977) observed increased POMS scores of fatigue and confusion, and decreased scores on vigour after one night of sleep deprivation, however, these ratings remained unchanged after a 10 mg dose of d-amphetamine.

Self-monitoring is an important aspect of making a decision about whether an individual can drive safely, or whether to use a sleep countermeasure, such as d-amphetamine. More importantly, drivers must be aware of when their performance is sub-optimal, or their alertness is declining as the effects of the drug dissipate, and the
amount of sleep debt is rising. As reported in Chapter 3, subjective reports of fatigue and sleepiness are associated with performance decrements (Gillberg et al., 1994; Horne & Reyner, 1996). In general, individuals appear to be generally good at detecting sleepiness, and detecting when their performance is sub-optimal.

Studies investigating the effects of stimulant drugs on inhibitory processes and self-monitoring have produced conflicting results. Drug abuse has been associated with an inability to inhibit inappropriate behaviours and responses, inability to be patient, and insensitivity to negative consequences. Drug use has long been associated with patterns of impulsive behaviour, and impulsive individuals are believed to be predisposed to drug use. Conversely, illicit drugs also have direct effects on decision-making, in turn increasing the likelihood of impulsivity and decreasing inhibitory control (de Wit, Enggasser & Richards, 2002; Ramaekers & Kuypers, 2006; Ramaekers et al., 2006a). Whether d-amphetamine has an effect on introspective ability has not been examined extensively. Baranski and colleagues (1997) found that participants who were sleep-deprived for 64 hours, were exceptionally good at self-monitoring neurocognitive performance following a dose of 20 mg d-amphetamine (Baranski & Pigeau, 1997). Participants who were administered modafinil (a therapeutic stimulant drug, with similar effects to d-amphetamine), however, were overconfident in their assessments of their performance over the period of sleep deprivation (Baranski & Pigeau, 1997). This study indicates that some stimulant drugs may induce very different performance and subjective profiles with sleep deprivation, and further research into these effects is warranted. The current study will examine a single dose of d-amphetamine which has the highest use experimentally, to examine self-ratings of performance, sleepiness symptoms, and whether the driver feels that they would continue to drive in their current state following sleep deprivation, with and without a dose of d-amphetamine.

A limited number of studies have examined the effect of amphetamine-type stimulants on simulated (Brookhuis, de Waard, & Samyn, 2004; Silber et al., 2005) and actual driving performance (Kuypers, Samyn & Ramaekers, 2006; Ramakers et al., 2006c) after normal sleep. Studies examining the effects of acute 3,4 methylenedioxymethamphetamine or MDMA administration on on-road driving (an illicit stimulant, which acts on both serotonin and dopamine) observed a reduce
standard deviation of lateral lane position (Ramekaers et al., 2006c). Similarly, after 0.42 mg/kg d-amphetamine administration, a reduction in speed was observed on a simulated driving task (Silber et al., 2005). In contrast, nocturnal doses of MDMA have been shown to produce impairments in driving-related skills (divided attention and tracking performance) after one night of sleep deprivation (Kuypers, et al., 2007), indicating that sleep loss may interact with the drug-effects and have a negative effect on performance. Currently, there are no studies examining the effects of d-amphetamine following sleep deprivation on the AusEd driving simulator (the simulator used in Experiment 1 of this thesis). However, modafinil has been shown to reduced lateral deviations on the AudEd driving simulator task in partially sleep-deprived subjects (Newcombe et al., 2001). Considering this, it is expected that a dose of d-amphetamine may help to reduce the sleep-deprivation-related increases in lane deviations on the AusEd driving simulator task.

As demonstrated in Experiment 1, and by previous studies (Doran et al., 2001; Koslowsky & Babkoff, 1992), sleep deprivation commonly produces significant deficits in simple, sustained reaction time-type tasks. Low doses of d-amphetamine improve reaction time and vigilance during extended periods of sleep deprivation (Babkoff & Krueger, 1992; Caldwell et al., 2003; Cochran et al., 1992; Hartmann, Orzack, & Branconnier, 1977; Logan, 2002; Magill et al., 2003; Newhouse et al., 1989; Wiegmann et al., 1996) and circadian rhythm disruption (Hart et al., 2003). However, it remains unclear whether d-amphetamine can restore functioning to pre-sleep deprived levels. The vigilance and reaction time-type tasks which were shown to be affected by sleep deprivation in Experiment 1 will be examined in the current experiment, to determine whether a high dose of d-amphetamine can restore performance on these driving-related tasks.

Experiment 1 of this thesis demonstrated significant changes in later auditory and visual processing with sleep deprivation, as measured by event-related potentials (ERPs). d-amphetamine has been shown to reduce decrements in alertness that are induced by sleep deprivation, as measured by electroencephalography (EEG), when compared to placebo (Hartmann et al., 1977). Specifically, a dose of 20 mg d-amphetamine attenuated low frequency power on the EEG in sleep deprived individuals up to 60 hours of sleep deprivation, indicating that the drug may act via
cortical activation, masking sleep-related processes (Chapotot et al., 2003). However, the effects of $d$-amphetamine on specific neural ERP processes in sleep deprived individuals remains unknown. To replicate Experiment 1, two aspects of visual functioning were also examined in the present study; the two primary visual pathways; parvocellular and magnocellular; and visual processing of the central and peripheral visual field. There is some evidence of behavioural deficits associated with visual field processes following amphetamine-administration. ‘Tunnel vision’ effects have been demonstrated with acute amphetamine administration (Mills et al., 2001). This phenomenon occurs when attentional resources become overwhelmed, resulting in a reduction in the capacity of the individual to gather information from the entire visual field efficiently. Improvements occur at the focus of attention, due to attention restriction to the focal point, with associated functional decrements in the peripheral regions of focus (Easterbrook, 1959). Consistent with this, behaviourally, tunnel vision has been observed in subjects following doses of 10 mg $d$-amphetamine (Mills et al., 2001; Hurst et al., 1967). This effect has not been examined using the more sensitive ERPs, or when amphetamine has been combined with sleep deprivation. Experiment 1 demonstrated a non-significant trend for an attenuation of the amplitude of the magnocellular response following sleep loss. The current study will examine the parvocellular and magnocellular visual pathways under the different sleep and drug conditions to determine whether this effect is restored to pre-sleep deprived levels with $d$-amphetamine. These experiments will provide more evidence as to the early sensory visual effects; measures not previously examined in this setting. Sleep deprivation attenuates later visual processes in the present thesis and in previous studies (Gosselin et al., 2005; Raz et al., 2001). This suggests an overall reduction in attention and cortical responsiveness following sleep loss. Stimulant drugs, administered to rested participants, appear to have little effect on mid-to-late latency of ERPs, including the P300, during task performance. Whether $d$-amphetamine can restore the effects on the visual P300 component in sleep-deprived participants is yet to be elucidated.

Sleep deprivation also had a negative influence on auditory processing in Experiment 1; reflected as a deficit in behavioural responses and an associated attenuation of the P300 response. Later cognitive processes, examined using an auditory odd-ball paradigm to elicit a P300 response, are believed to reflect selective attention and later
active selection and rejection of information. Since studies suggest that amphetamine improves recognition of the relevant stimulus, and decreases attention to irrelevant stimuli (McKetin et al., 1999), it could be hypothesised that \( d \)-amphetamine may have a positive effect on the attenuation of the P300 amplitude following sleep deprivation. The effect of \( d \)-amphetamine administration in sleep-deprived individuals remains unknown for many aspects of ERP, and may provide an indication of where along the information processing chain deficits in driving-related performance are occurring.

Controlled laboratory studies on the influence of amphetamines on driving behaviour are limited and inconsistent. Although stimulants improve some aspects of neurocognitive function relevant to driving (Cami et al., 2000; de Wit et al., 2002; Fleming, Bigelow, Weinberger, & Goldberg, 1995; Halliday et al., 1994; Wachtel & De Wit, 1999), they may in fact have detrimental effects on other functions that are important for driving (Hurst, 1962; Logan, 1996; Mills et al., 2001; Ward et al., 1997). Risk-taking behaviour may increase (Hurst, 1962) and ‘tunnel vision’ may occur, even at low doses (Mills et al., 2001; Hurst et al., 1967). These laboratory studies have used recommended therapeutic doses of amphetamines (Hurst et al., 1967), which are considered low compared to those consumed recreationally. The higher drug doses consumed by recreational users may result in more profound behavioural and electrophysiological abnormalities. Thus, the combined effect of \( d \)-amphetamine and sleep deprivation on these functions has not been well studied.

6.2 Aims

Experiment 3 was largely exploratory in nature, due to the lack of previous literature justifying its hypotheses and the differences between the subjects recruited in this Experiment compared to the drug-naïve participants recruited from Experiments 1 and 2. This study aimed to examine each of these driving-related domains outlined in Chapter 2, in three stages. Firstly, this study aimed to examine the effect of sleep deprivation alone on driving-related measures in a population of professional drivers, in order to determine if there is a different effect of sleep loss on individuals who are past or current drug-users. Secondly, this study aimed to examine the effects of \( d \)-amphetamine compared to placebo, with no sleep deprivation, to determine whether \( d \)-amphetamine improves performance in the rested state. Finally, the effects of \( d \)-
amphetamine compared to placebo when participants were sleep deprived was examined, to determine whether \(d\)-amphetamine restores performance to pre-sleep deprived levels.

6.3 Methods

6.3.1 Participants

6.3.1.1 Selection criteria

A sample of professional drivers who are current or past amphetamine-type stimulant users was recruited for this study. Recruitment of past or current users was primarily for ethical reasons, as it was not possible to administer amphetamines to drug-naïve participants with approval from appropriate ethics bodies. Although previous studies have used drug naïve subjects in such studies, there are also advantages of using previous users. Firstly, drug users potentially have different brain structures due to long-term use, which may result in different behaviours, neurophysiological profiles, or neural processing (Daumann et al., 2004; McKetin et al., 1999), and so results from drug-naïve participants may not be representative of users. Secondly, drug-naïve participants are not familiar with the subjective effects of the drug, and therefore may demonstrate some performance and neurophysiological differences due to the novelty of the sensations experienced, above and beyond the direct effect of the drug on the brain. Thus, the current study used a sample of current/past users, who may have different responses to both acute amphetamine administration, and sleep deprivation, compared to drug naive individuals. However, a limitation of using drug-users is the likelihood that they are poly-drug users. This is somewhat overcome by using extensive drug history and drug use questionnaires in the current study, and reporting the previous drug use, type, dose and length of use of the participants.

This group of drivers was recruited through advertising in a local newspaper, trucking magazines, the Transport Workers Union newsletter and through advertising on trucking radio stations. Inclusion criteria for participation was; a current heavy vehicle drivers licence, used amphetamine-type-stimulants at least weekly for at least six months, able to have at least three days free from amphetamine-type stimulants per week (as drivers were required to refrain from any drug use for three days before the start of each session in order for the drugs to be sufficiently removed from their
system when the study started), aged between 18 and 65, and English as a first language. Interested drivers were given a brief explanation of the study requirements and protocol, and were sent a more detailed information sheet. Drivers who agreed to participate were booked in for a medical examination.

### 6.3.1.2 Medical examination

All interested drivers attended a medical examination. The screening questionnaires used in this session are described in detail Chapter 4, Section 4.3.1.2. These included a Medical Questionnaire (Appendix C), a Demographic Questionnaire (Appendix D), a Drug Use History Questionnaire (Appendix E), the Drug Abuse Screening Test (DAST-20; Skinner, 1982), the Epworth Sleepiness Scale (ESS; Johns, 1991), and the Multiple Apnoea Prediction Scale (MAPS; Maislin et al., 1995).

The practitioner interviewed the participant on their medical and drug history, physical and mental health, any medical procedures or implants, smoking history, and obtained other physiological measures (i.e. weight, height, blood pressure). Drivers were excluded if they had a medical contraindication for sleep deprivation protocol, including a history of cardiovascular disease, hypertension, epilepsy, diabetes, psychiatric illness or any other medical condition which who be exacerbated by sleep deprivation; a sleep disorder or sleep apnoea (as assessed by the MAPS and the ESS); pregnancy; participants who smoked more than ten cigarettes per day, or could not tolerate having no cigarettes in a 12-hour period, (drivers were asked to avoid smoking during the sleep deprivation session due to the possible stimulating effect); high-level caffeine users, defined as five or more caffeinated beverages per day (Lenne et al., 1998), as drivers were asked to refrain from drinking caffeinated beverages (cola, black tea, coffee, red bull) for 6 hours before each session until the conclusion of each session, participants who could not refrain from drug use for three days prior to the study session, and participants who had a visual impairment that does not correct with glasses. Based on this examination, the physician made a decision about whether the driver was fit to participate, and if they were deemed unfit, they were excluded from the sample.
6.3.1.3 Sample characteristics

Eleven drivers were recruited for the study. Three drivers withdrew prior to completing all four session, because of work commitments. The final sample consisted of eight professional transport drivers (one female). Demographics of the participants are displayed in Table 6.1. All participants reported normal hearing, normal or corrected-to-normal vision, and did not report any significant daytime sleepiness according to the ESS (Johns, 1993).

<table>
<thead>
<tr>
<th>Table 6.1: Demographics of the participants</th>
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<tr>
<td>Minimum</td>
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<td>Age</td>
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<tr>
<td>Body Mass Index</td>
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<td>No. of hours driving per week</td>
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<td>Multiple apnoea prediction scale</td>
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<td>Epworth Sleepiness Scale</td>
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</table>

Data from sleep diaries indicated that, on average, participants reported sleeping 7.67 hours on the night prior to the no sleep deprivation session, and 5.60 hours on the night prior to the sleep deprivation session. There was no significant difference between the two sessions on the average hours of sleep obtained (p = 0.18). There was a large range of hours spent driving for work per week in the sample (range = 40 to 90 hours per week), with an average of 63 hours. On average, participants drank 3.6 caffeinated beverages per day (range one to eight) and seven participants reported being smokers, averaging 11 cigarettes per day (range 2 – 25). The majority of participants reported drinking alcohol socially (i.e. less than 5 alcoholic beverages per week; 80%).

Drug use of the participants is summarised in Table 6.2. On average, participants consumed amphetamine, ecstasy, and cocaine less than once a month during the preceding year, while marijuana was on average consumed once a fortnight over the preceding year (approximately 27 times). During the period when participants consumed drugs most frequently in their lifetime, amphetamine was on average consumed less than once a month, whereas ecstasy was consumed one to two times per month over the year (approximately 20 times). During the period when
participants consumed marijuana most frequently, participants on average reported to have used marijuana approximately twice a week in that year (approximately 100 times).

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current amphetamine use (times per year)</td>
<td>1</td>
<td>365</td>
</tr>
<tr>
<td>Time when used most</td>
<td>12</td>
<td>365</td>
</tr>
<tr>
<td>Years used amphetamine</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Current cannabis use (times per year)</td>
<td>0</td>
<td>365</td>
</tr>
<tr>
<td>Time when used cannabis most</td>
<td>1</td>
<td>365</td>
</tr>
<tr>
<td>Years used cannabis</td>
<td>0.4</td>
<td>35</td>
</tr>
<tr>
<td>Current ecstasy use</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Time when used ecstasy most</td>
<td>1</td>
<td>365</td>
</tr>
<tr>
<td>Years used</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Current cocaine use*</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Time when used cocaine most</td>
<td>1</td>
<td>52</td>
</tr>
</tbody>
</table>

* three of the four drivers who reported using cocaine, only used it once.

### 6.3.2 Experimental Design

A repeated-measures, counter-balanced, double-blind, placebo-controlled design was employed. Participants completed four experimental sessions: 1) no sleep deprivation with placebo (NSD + P); 2) 27-hours sleep deprivation with placebo (SD + P); 3) no sleep deprivation with an oral dose of \( d \)-amphetamine (0.42mg/kg) (NSD + A); and 4) 27-hours sleep deprivation with an oral dose of \( d \)-amphetamine (0.042mg/kg) (SD + A). Each session was separated by at least a one week wash-out period, to allow for the regulation of the participants sleep patterns following the sleep deprivation session, and to reduce residual effects of the drug. Due to the time constraint and work schedules, most of the drivers completed a session once every few weeks. The participants in Experiment 3 undertook an identical protocol as Experiment 1, in order to compare across subject groups. Participants in this Experiment underwent urine and blood samples and capsule administration, which was administered in a double-blind fashion. This experiment was divided into three sections; simulated driving, driving-related cognitive assessment, and electrophysiological (ERP) assessment.
6.3.3 Procedure

Prior to conducting the study, ethics approval was obtained from the Swinburne University Human Research Ethics Committee and the Austin Health Human Research Ethics Committee. After agreeing to participate, drivers attended Austin Health for an initial screening session and medical examination to assess their fitness for the study by a physician. Individuals who passed the medical examination and selection criteria were recruited as participants. Participants were provided with an information sheet outlining details of the research study, and when the participant had all questions answered and were satisfied with the requirements of the study, they gave written informed consent (see Appendix M and N for Participant Information Sheet and Consent Form). Participants were informed that they were free to withdraw from the study at any time.

Participants attended four experimental sessions in a counterbalanced order, alternating the no sleep deprivation and sleep deprivation sessions (See Appendix F for subject counterbalancing). The four experimental sessions involved the following conditions:

- oral dose of placebo after waking, no sleep deprivation (NSD + P).
- oral dose of d-amphetamine after waking, no sleep deprivation (NSD + A).
- 27-hours sleep deprivation with oral placebo after 22 hours (SD + P).
- 27-hours sleep deprivation with oral d-amphetamine after 22 hours (SD + A).

The timeline for the sleep deprivation and no sleep deprivation sessions are shown in Tables 6.3 and 6.4 respectively. These sessions were identical to those carried out in Experiment 1 (see Chapter 4, Section 4.3.3 for details). Briefly, for the sleep deprivation (SD) sessions, participants were asked to wake at 07:00h on the morning of their session, attended the sleep laboratory at 22:00h following a normal eight-hour day driving shift, and stayed awake all that night until the following morning, monitored by the laboratory staff. The following morning at 07:00h, participants were taken by taxi to Swinburne University where the testing part of the study was carried out. Participants provided a urine sample and completed the SCL-90-R questionnaire. Participants were then given a capsule which contained either placebo or d-amphetamine, and a blood sample was taken 120 minutes later. Participants then
completed the simulated driving task and questionnaires, the neurocognitive tasks, and ERP tasks. A second blood sample was obtained approximately five hours following capsule administration at the end of the session. Participants were provided with a taxi voucher for transport home. The NSD sessions were identical to the SD sessions, differing only in that drivers attended the Brain Science Institute, Swinburne University by taxi at 09:30h after a normal day shift followed by a normal nights’ sleep, instead of 24-hours sleep deprivation. Where appropriate, alternate forms of the EEG and neurocognitive tasks were presented to each participant.

Table 6.3: Sleep Deprivation Sessions timeline

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>07:00</td>
<td>Wake, complete SCL-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Normal day shift</strong></td>
</tr>
<tr>
<td></td>
<td>22:00</td>
<td>Attended the Sleep Laboratory</td>
</tr>
<tr>
<td>2</td>
<td>06:30</td>
<td>Taxi to Swinburne University</td>
</tr>
<tr>
<td></td>
<td>07:00</td>
<td>Urine sample, SCL-90</td>
</tr>
<tr>
<td></td>
<td>08:00</td>
<td>Breakfast</td>
</tr>
<tr>
<td></td>
<td>09:15</td>
<td>Administer placebo/ d-amphetamine capsules</td>
</tr>
<tr>
<td></td>
<td>11:15</td>
<td>Blood sample 1</td>
</tr>
<tr>
<td></td>
<td>11:30</td>
<td>Neurocognitive test battery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Driving Simulation/ Questionnaires</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ERP tasks</td>
</tr>
<tr>
<td></td>
<td>14:15</td>
<td>Blood sample 2</td>
</tr>
<tr>
<td></td>
<td>15:00</td>
<td>End of session (Taxi home)</td>
</tr>
</tbody>
</table>
6.3.3.1 Drug

d-amphetamine capsules were prepared by the pharmacy at Austin Health, Melbourne. Gelatinous capsules were filled with 0.42mg/kg dose of d-amphetamine and lactose, with placebo capsule containing only lactose. This dosage was administered in 5mg capsules, and rounded to the nearest 5mg. The dose of d-amphetamine was implemented by a dose by weight equation, as used by Shappell et al. (1996) and Shenberger et al. (1998). The equation was 0.42mg/kg, where 0.42mg of dexamphetamine was administered for every 1kg the participant weighs. The dosage of 0.42mg/kg was chosen as it is detectable in blood samples, while still being at the lower end of the range of recreational drug doses. This level is also lower than that detected in many drivers involved in fatal accidents (Logan, 2001). This is one of the highest, ethically administered doses in human subjects in current research studies. Kinetic studies of d-amphetamine have found that doses of 30 mg per 70 kg body weight produce levels of around 100 ng/ml in blood (Silber et al., 2005). The dose used in the current experiment is the same as Silber, et al., (2005), and therefore will produce blood levels in the order of 100 ng/ml. In comparison, studies of drivers suspected of driving under the influence of drugs have amphetamine blood concentrations between 270 ng/ml and 530 ng/ml, which correspond to an intake of 70 mg to 150 mg amphetamine (Gustavsen et al., 2006). Other studies have reported median blood concentration of amphetamine in drivers apprehended for driving under
the influence of drugs of 54 ng/ml and 70 ng/ml, with some amphetamine levels reaching 500 ng/ml to 1700 ng/ml (Jones & Holmgren, 2005; Augsburger, 2005). Although the dose used in the current Experiment is at the lower end of the levels found with recreational drug use, it will provide some indication of the driving-related performance changes associated with an acute dose of \( d \)-amphetamine.

6.3.3.2 Blood and urine samples

One urine and two blood samples were taken from each participant during each session. A urine sample was taken at the start of each session as a screening tool to confirm that no substances were present prior to the session. As \( d \)-amphetamine has a peak blood concentration between two and four hours (Angrist et al., 1987; Brauer et al., 1996), the first blood sample was obtained 120 minutes after administration of the capsules, and the second sample was obtained at the conclusion of the session (approximately 300 minutes after administration of the capsules). Blood and urine sample collection and analysis were performed as described in Chapter 4, Section 4.3.3.1. Blood samples were analysed for the seven major drug classes and amphetamine levels using the GC/MS method (Moeller & Kraemer, 2002). This method has been documented to be the most accurate technique for testing specific drug levels in blood. Specific levels of \( d \)-amphetamine were reported in \( \mu \)g/ml.

Recent drug use was detected in the urine of seven of the eight drivers. The drugs included methamphetamine, pseudoephedrine, morphine, codeine and low-levels of THC metabolite. The levels of these drugs were very low, and were representative of drug use days prior to the session. Considering this, it was unlikely that the level of drugs in these participants would not greatly affect performance during the experimental session.

6.3.4 Materials

6.3.4.1 Questionnaires

The questionnaires used in the current experiment were the same as those used in Experiment 1. These included the Symptoms Checklist 90 Revised (SCL-90-R; Derogatis et al., 1976), Performance questionnaire (Appendix I), the Karolinska
Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990), the Sleepiness Symptoms Questionnaire (SSQ; Appendix H), Stop driving questionnaire (Appendix J), and the Visual Analogue Rating Scale (VAS; Bond & Lader, 1974). Refer to Chapter 4, Section 4.3.4.1 for details of the questionnaires.

### 6.3.4.2 Aus Ed™ driving simulator (Woolcock Institute)

The driving simulator task used in the study was the same as described for Experiment 1. Refer to Chapter 4, Section 4.3.4.2 for full description of the AusEd simulated driving task.

### 6.3.4.3 Neurocognitive tasks related to driving

The current experiment used a small battery of tasks that were used in Experiment 1. These included the Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985), Simple reaction time (RT), Complex RT and Digit Vigilance Tasks. Refer to Chapter 4, Section 4.3.4.3 for full description of the tasks.

### 6.3.4.4 Event-related potential (ERP) analysis

ERPs were recorded while participants perform computerised visual and auditory tasks. A sub-set of the ERP tasks used in Experiment 1 were administered in the current experiment. These included the Pattern Reversal (PR) and Tunnel Vision (TV) visual tasks, and the auditory oddball auditory task. For each of the visual and auditory tasks, four alternate forms, (one for each of the four sessions), were created and employed such that the subject did not perform the same version of the task twice. The order of administration of the auditory and visual sets of tasks, as well as the alternate forms, were counterbalanced and randomly assigned. Only those tasks that were affected by sleep deprivation in Experiment 1 will be presented in the current experiment. Refer to Chapter 4, Section 4.3.4.4 for full description of the tasks.

### 6.3.5 Data acquisition

EEG data were collected using tin electrodes located at 30 scalp sites plus one ocular site (below the left eye), referenced to the left mastoid, according to the International 10/20 system. The ground electrode site was located between FPz and Fz. All data
were EOG corrected (Croft & Barry, 2000) and re-referenced to common average (unless otherwise stated). Non-ocular artefacts were identified manually, and remaining segments removed if the recorded signal at any EEG electrode exceeded ±200µV. All data were continuously sampled at 500 Hz, with a 0.05 Hz to 100 Hz band pass. Impedances were below 5 kOhm at the start of each session.

6.3.6 ERP Data analysis

Data were analysed using Neuroscan Edit 4.2 software (Neurosoft Inc., 1998). All data were EOG corrected (Croft & Barry, 2000) and re-referenced to common average. Non-ocular artefacts were identified manually, and remaining segments removed if the recorded signal at any EEG electrode exceeded ±200µV.

6.3.6.1 Pattern Reversal task

Data were low pass filtered at 30 Hz (zero-phase shift, 12 dB slope), segmented (-100 ms to +460 ms post stimulus), and baseline corrected using the pre-stimulus interval. Trials were averaged in the time domain, separately for the magnocellular and parvocellular stimuli for each session. The early P100 and N100 components were analysed at Oz only, as this midline occipital site is where these electrophysiological components of interest display the greatest signal-to-noise ratio (Mangun & Hillyard, 1991). To determine each individual magnocellular and parvocellular amplitude, the four sessions were averaged, and the most positive going peak within the window defined by the grand mean peak latency ± 30 ms was selected. Secondly, for each individual waveform for each subject, the P100 peaks were classified as the individual grand mean peak latency ± 15 ms. This procedure was repeated for the N100 peaks. The peak-to-peak amplitude for the P100 and N100 was used as it is less susceptible to noise. Overall, there were 180 trials for each of the PR ERPs.

6.3.6.2 Tunnel Vision Task

Data were low pass filtered at 30Hz (zero-phase shift, 12dB slope), segmented (−200 ms to +800 ms post-stimulus), and baseline corrected using the pre-stimulus interval. Correct trials were averaged separately for the target (triangle) and non-target (square) stimuli for the TV task.
The early sensory P100 and N100 components, attentional N100 and later P300 components were assessed. The electrodes used were Oz for the P100 and N100 peak-to-peak amplitudes of non-target responses, Fz for the N100 attentional peak-to-peak amplitudes (Hillyard & Anllo-Vento, 1998), and Pz for the P300 peak-to-peak amplitudes (Tsai et al., 2005). These midline sites were chosen as they are where the specific electrophysiological components are generally most prevalent and display the greatest signal-to-noise ratio. Amplitudes and latencies for the TV task responses were detected by proprietary software routines and based on previously employed latency windows. These were the most positive peak in the window from 80ms to 140 ms for the P100 (Han et al., 2000), the most negative peak in the window from 120 ms and 180 ms for the N100 (Krull et al., 1993), the most negative peak between 140 ms and 200 ms for the attentional N100 (Hillyard & Anllo-Vento, 1998), and the most positive peak between 320 ms and 600 ms for the P300 (Han et al., 2000; Polich & Bondurant, 1997). The EEG epochs of the trials with omitted responses were not included in the stimulus-locked ERP. Reaction times (RT) were recorded as the time between target onset and the first correct key press. Trials with RTs shorter than 200 ms and longer than the next stimulus onset were excluded from the analyses. Errors of omission were calculated as the percentage of correct responses to targets.

6.3.6.3 Auditory Oddball task

Data were low pass filtered at 30 Hz (zero-phase shift, 24dB slope) and segmented (–200 ms to +800 ms post-stimulus). Trials were averaged in the time domain for each session separately. As the N1/P2 complex has previously been reported to be elicited maximally from central sites (Barry, Kirkaikul, & Hodder, 2000), the Cz electrode was used for this analysis. The N1/P2 complex was calculated for the non-target trials. The N100 component was defined as the largest negative peak occurring within the latency window of 80 ms to 140 ms, and the P200 component was defined as the largest positive peak within the window of 140 ms to 250 ms (Polich & Bondurant, 1997). Peak amplitude was measured relative to the previous peak, and peak latency was measured from the time of stimulus onset. P300 is maximal over parietal scalp regions (Polich & Kok, 1995), as so the Pz electrode was used for analysis. Only target trials that received a correct response were included in the P300 averages. The
difference between the P300 waveforms elicited in each session was quantified by calculating the integral of the area under the curve of each, over the interval from 250 ms to 600 ms (Croft et al., 2003). Reaction times were measured as the time between the onset of the target tone and the first button press. Valid behavioural responses were classified as those within the response window of 100 ms to 900 ms. Response accuracy, error rate, and omission rate were calculated as percentage correct, erroneous, and omitted responses respectively.

6.3.7 Statistical analysis

Due to the low subject numbers, a conservative approach was taken with all analyses. The aim of this study was to determine whether the effects of sleep deprivation can be reversed with a dose of \(d\)-amphetamine. Therefore, the three primary contrasts of interest, used for all tasks were:

1) the effects of sleep deprivation (NSD + P vs SD + P);

2) whether a dose of \(d\)-amphetamine when sleep deprived improves performance compared to placebo (SD + A vs SD + P), and

3) whether a dose of \(d\)-amphetamine when sleep deprived restores performance compared to pre-sleep deprived levels (SD + A vs NSD + P).

6.3.7.1 Behavioural dispositional measures, simulated driving task and neurocognitive tasks

Mood, as measured by the SCL-90-R, and sleep recorded for the week and night prior to each session was compared between sessions using Wilcoxon Signed Ranks tests. In order to determine whether there was a difference in subjective measures, simulated driving performance, and neurocognitive performance for the three comparisons of interest, Signed Ranks tests were calculated. The dependent variables were: responses on each questionnaire, lateral lane position, speed variation, median braking reaction time and crashes on the simulated driving task; median reaction time, lapses, fastest 10% of RTs, and slowest 10% of RTs on the Psychomotor Vigilance Task; Simple and Choice mean reaction time; and mean reaction time and number of
errors on the Digit Vigilance task. For the Stop Driving questionnaire, chi-squared statistics were performed to determine whether there was a difference in the proportion of drivers who stated that they would continue to drive for each of the contrasts of interest.

6.3.7.2 ERP data

6.3.7.2.1 Pattern Reversal task

In order to determine whether there was a difference in the magnocellular and parvocellular visual responses for the three contrasts of interest, Wilcoxon Signed Ranks tests were conducted on the amplitude of early visual processing (P100 and N100 separately) in the magnocellular and parvocellular visual pathway. Further, to determine whether there was any effect on the speed of processing of the above early sensory processes, parallel analyses were performed using latency instead of amplitude as the dependent variable.

6.3.7.2.2 Tunnel Vision task

Due to the complex analyses required for this task, a general linear model approach was applied to the behavioural data. To determine the whether there were differences in behavioural responses to peripheral and foveal stimuli following sleep deprivation and d-amphetamine, a three-way (Session: SD, NSD; Drug: Placebo, d-amphetamine; Field: foveal, peripheral) repeated measures analysis of variances (ANOVA) were performed, where the dependent variables were 1/ reaction time to correct targets, 2/ the number of errors of omission, and 3/ the percentage of errors of commission.

In order to determine whether there was difference sleep in the early P100 visual processing response for the three contrasts of interest, Wilcoxon Signed Ranks tests were conducted on, with peak-to-peak amplitudes as the dependent variables. These analyses were repeated for the early N100 peak-to-peak amplitudes at Oz, N100 attentional peak-to-peak amplitudes at Fz and the P300 peak-to-peak amplitudes and Pz. Further, to determine whether there was any effect of sleep deprivation and d-amphetamine on the speed of processing of the above early sensory, attentional and later cognitive processes, parallel analyses were performed using latency instead of
amplitude as the dependent variable. In order to determine the effect of sleep deprivation and \(d\)-amphetamine on behavioural responses, parallel analyses were conducted using reaction time to correct targets, and number of errors of omission as the dependent variables.

6.3.7.2.3 Auditory Oddball Task

To determine whether there was a difference in the N1 and P2 amplitudes at Cz for the three contrasts of interest, Wilcoxon Signed Ranks tests were used on the peak-to-peak amplitude data. To determine whether there was any effect on the speed of processing of the N1 or P2 complexes, parallel analyses were performed using latency instead of amplitude as the dependent variable. As the P300 component has previously been found to be maximal over parietal regions, Pz was used for subsequent analyses. To determine whether there was a difference in the area under the curve of the P300 component as a function of sleep deprivation, or \(d\)-amphetamine, a directional t-test was performed using the same comparisons as above for the P300 response. To determine whether there was a difference in behavioural measures between conditions, the above analyses were repeated for errors of omissions and percentage of correct responses.

6.4 Results

6.4.1 Level of \(d\)-amphetamine in blood

In the NSD +A session the mean level of \(d\)-amphetamine detected in blood at 120 minutes after drug administration was 65.85ng/ml (Std. Dev. = 14.36) and at 240 minutes after administration was 65.36ng/ml (Std. Dev. = 12.32). In the SD + A session, mean level of \(d\)-amphetamine detected in blood at 120 minutes after drug administration was 65.86ng/ml (Std. Dev = 28.99) and after 240 minutes was 68.71ng/ml (Std. Dev = 11.10). There was no significant difference in drug levels between sessions (Wilcoxon; p > 0.05).

6.4.2 Measures of behavioural disposition

One subjects’ data was missing for the SSQ in the SD + A session, therefore only seven subjects were used in the final analysis. The scores for the questionnaire data
Scores on the Karolinska Sleepiness Scale (KSS) were significantly higher following sleep deprivation with placebo (SD + P), compared to after normal sleep with placebo (NSD + P) ($\text{Wilcoxon} = -2.55, p<0.05$). A dose of $d$-amphetamine following sleep deprivation (SD + A) significantly improved ratings on the KSS compared to when participants were sleep deprived with placebo (SD + P) ($\text{Wilcoxon} = -2.24, p<0.05$). There was no difference in KSS ratings following sleep deprivation with a dose of $d$-amphetamine (SD + A) compared to after normal sleep with placebo (NSD + P) ($p = 0.53$).

Subjective ratings of mood, as measured by the visual analogue scale (VAS) total mood score, were significantly higher in the SD + P session compared to the NSD + P session ($\text{Wilcoxon} = -2.37, p<0.05$), indicating a worse mood. Specifically, the symptoms alert ($\text{Wilcoxon} = -2.38, p<0.05$), strong ($\text{Wilcoxon} = -2.26, p<0.05$), clear-headed ($\text{Wilcoxon} = -2.54, p<0.05$), energetic ($\text{Wilcoxon} = -2.22, p<0.05$), quick-witted ($\text{Wilcoxon} = -1.98, p<0.05$), proficient ($\text{Wilcoxon} = -2.06, p<0.05$) and sociable ($\text{Wilcoxon} = -2.23, p<0.05$) were significantly higher in the NSD + P session compared to the SD + P session. Mood scores significantly improved in the SD + A session compared to the SD + P session ($\text{Wilcoxon} = -2.10, p <0.05$). Ratings of drowsiness ($\text{Wilcoxon} = -2.21, p<0.05$), muzzy ($\text{Wilcoxon} = -2.38, p<0.05$), lethargy ($\text{Wilcoxon} = -2.11, p<0.05$), and mental slowness ($\text{Wilcoxon} = -2.11, p<0.05$) improved in the SD + A session compared to the SD + P session. There was no significant difference in total mood score between the SD + A session and the NSD + P session ($p = 0.33$). Ratings of lethargy were significantly lower in the SD + A session and the NSD + P session ($\text{Wilcoxon} = -2.13, p<0.05$).
Table 6.5: Means and standard deviations (Std. Dev.) of the questionnaires data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NSD + A (Mean ± Std. Dev.)</th>
<th>NSD + P (Mean ± Std. Dev.)</th>
<th>SD + A (Mean ± Std. Dev.)</th>
<th>SD + P (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAMS (total)</td>
<td>8</td>
<td>31.00 ± 10.93</td>
<td>54.63 ± 11.49</td>
<td>46.38 ± 17.32</td>
<td>79.38 ± 23.86</td>
</tr>
<tr>
<td>Alert - Drowsy</td>
<td>8</td>
<td>1.13 ± 0.35</td>
<td>3.63 ± 1.92</td>
<td>2.63 ± 2.67</td>
<td>6.25 ± 2.05</td>
</tr>
<tr>
<td>Calm - Excited</td>
<td>8</td>
<td>3.25 ± 2.96</td>
<td>2.63 ± 1.77</td>
<td>2.63 ± 2.00</td>
<td>2.13 ± 1.46</td>
</tr>
<tr>
<td>Strong - Feeble</td>
<td>8</td>
<td>1.50 ± 0.53</td>
<td>3.00 ± 1.07</td>
<td>2.75 ± 1.83</td>
<td>5.00 ± 2.51</td>
</tr>
<tr>
<td>Clear-headed - Muzzy</td>
<td>8</td>
<td>2.13 ± 0.83</td>
<td>4.38 ± 2.26</td>
<td>3.38 ± 2.50</td>
<td>7.13 ± 2.42</td>
</tr>
<tr>
<td>Well-coordinated - Clumsy</td>
<td>8</td>
<td>2.00 ± 0.82</td>
<td>4.43 ± 1.40</td>
<td>3.57 ± 2.70</td>
<td>6.00 ± 1.73</td>
</tr>
<tr>
<td>Energetic - Lethargic</td>
<td>8</td>
<td>1.63 ± 0.52</td>
<td>5.13 ± 1.64</td>
<td>3.50 ± 2.51</td>
<td>7.00 ± 2.00</td>
</tr>
<tr>
<td>Contented - Discontented</td>
<td>8</td>
<td>1.63 ± 0.74</td>
<td>3.13 ± 1.73</td>
<td>2.50 ± 1.60</td>
<td>3.75 ± 2.92</td>
</tr>
<tr>
<td>Tranquil - Troubled</td>
<td>8</td>
<td>2.63 ± 2.07</td>
<td>3.50 ± 1.93</td>
<td>3.38 ± 1.60</td>
<td>4.38 ± 1.92</td>
</tr>
<tr>
<td>Mentally slow - Quick-witted</td>
<td>8</td>
<td>2.38 ± 1.06</td>
<td>5.13 ± 2.00</td>
<td>4.00 ± 2.20</td>
<td>6.88 ± 1.73</td>
</tr>
<tr>
<td>Relaxed - Tense</td>
<td>8</td>
<td>3.75 ± 2.31</td>
<td>3.00 ± 0.93</td>
<td>3.75 ± 2.31</td>
<td>4.25 ± 2.12</td>
</tr>
<tr>
<td>Attentive - Dreamy</td>
<td>8</td>
<td>1.50 ± 0.76</td>
<td>4.00 ± 1.60</td>
<td>2.50 ± 1.20</td>
<td>4.88 ± 2.95</td>
</tr>
<tr>
<td>Proficient - Incompetent</td>
<td>8</td>
<td>2.25 ± 1.39</td>
<td>3.88 ± 1.46</td>
<td>3.50 ± 1.69</td>
<td>6.00 ± 2.00</td>
</tr>
<tr>
<td>Happy - Sad</td>
<td>8</td>
<td>1.25 ± 0.46</td>
<td>2.00 ± 2.14</td>
<td>1.88 ± 0.83</td>
<td>3.38 ± 1.85</td>
</tr>
<tr>
<td>Amicable - Antagonistic</td>
<td>8</td>
<td>1.75 ± 1.16</td>
<td>2.38 ± 1.06</td>
<td>2.38 ± 1.06</td>
<td>3.88 ± 2.36</td>
</tr>
<tr>
<td>Interested - Bored</td>
<td>8</td>
<td>1.13 ± 0.35</td>
<td>2.25 ± 1.58</td>
<td>2.13 ± 1.36</td>
<td>4.13 ± 3.04</td>
</tr>
<tr>
<td>Sociable - Withdrawn</td>
<td>8</td>
<td>1.38 ± 1.06</td>
<td>2.13 ± 1.55</td>
<td>2.38 ± 1.77</td>
<td>4.38 ± 2.72</td>
</tr>
<tr>
<td>KSS</td>
<td>8</td>
<td>3.00 ± 2.00</td>
<td>4.25 ± 1.91</td>
<td>3.25 ± 2.43</td>
<td>7.50 ± 1.31</td>
</tr>
<tr>
<td>Performance</td>
<td>8</td>
<td>5.00 ± 2.45</td>
<td>3.88 ± 0.64</td>
<td>4.50 ± 2.45</td>
<td>2.00 ± 0.76</td>
</tr>
<tr>
<td>Sleepiness Symptoms (total)</td>
<td>7</td>
<td>15.00 ± 3.83</td>
<td>18.86 ± 5.61</td>
<td>16.14 ± 6.39</td>
<td>22.25 ± 9.05</td>
</tr>
<tr>
<td>Struggling to keep eyes open</td>
<td>7</td>
<td>1.38 ± 1.06</td>
<td>1.88 ± 0.99</td>
<td>1.57 ± 1.51</td>
<td>3.13 ± 1.89</td>
</tr>
<tr>
<td>Vision becoming blurred</td>
<td>7</td>
<td>1.13 ± 0.35</td>
<td>1.50 ± 0.93</td>
<td>1.43 ± 0.79</td>
<td>2.38 ± 1.60</td>
</tr>
<tr>
<td>Nodding off to sleep</td>
<td>7</td>
<td>1.00 ± 0.00</td>
<td>1.38 ± 0.52</td>
<td>1.29 ± 0.76</td>
<td>2.25 ± 1.39</td>
</tr>
<tr>
<td>Difficulty keeping to the middle of the road</td>
<td>7</td>
<td>2.88 ± 1.46</td>
<td>3.13 ± 0.99</td>
<td>3.57 ± 1.90</td>
<td>4.00 ± 1.20</td>
</tr>
<tr>
<td>Difficulty maintaining correct speed</td>
<td>7</td>
<td>3.00 ± 1.41</td>
<td>2.88 ± 0.64</td>
<td>3.43 ± 1.90</td>
<td>4.00 ± 0.76</td>
</tr>
<tr>
<td>Mind wandering to other things</td>
<td>7</td>
<td>2.13 ± 1.13</td>
<td>3.00 ± 1.60</td>
<td>1.43 ± 0.53</td>
<td>3.25 ± 1.75</td>
</tr>
<tr>
<td>Reactions slow</td>
<td>7</td>
<td>2.00 ± 0.93</td>
<td>3.00 ± 1.93</td>
<td>2.14 ± 0.90</td>
<td>3.88 ± 1.25</td>
</tr>
<tr>
<td>Head dropping down</td>
<td>7</td>
<td>1.00 ± 0.00</td>
<td>1.25 ± 0.46</td>
<td>1.00 ± 0.00</td>
<td>2.38 ± 1.41</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo.
Sleepiness symptoms ratings were significantly higher in the SD + P session compared to the NSD + P session \( (\text{Wilcoxon} = -2.53, p<0.05) \). There was a trend for sleepiness symptoms ratings to improve in the SD + A session compared to the SD + P session \( (p = 0.08) \). There was no difference in symptoms ratings between the SD + A session and the NSD + P session \( (p = 0.29) \). Specifically, the symptoms “struggling to keep eyes open” \( (\text{Wilcoxon} = -2.06, p<0.05) \), “nodding to sleep” \( (\text{Wilcoxon} = -2.12, p<0.05) \), “Difficulty maintaining correct speed” \( (\text{Wilcoxon} = -2.46, p<0.05) \) and “head dropping down” \( (\text{Wilcoxon} = -2.06, p<0.05) \) were rated significantly more frequently in the SD + P session compared to the NSD + P session. Symptoms “mind wandering” \( (\text{Wilcoxon} = -2.03, p<0.05) \), “reactions slow” \( (\text{Wilcoxon} = -2.41, p<0.05) \), and “head dropping down” \( (\text{Wilcoxon} = -2.06, p<0.05) \) were significantly lower in the SD + A session compared to the SD + P session.

Participants rated their performance significantly lower in the SD + P session compared to in the NSD + P session \( (\text{Wilcoxon} = -2.57, p<0.05) \). Performance ratings were significantly improved in the SD + A session compared to the SD + P session \( (\text{Wilcoxon} = -2.03, p<0.05) \). There was no difference in performance ratings between the SD + A session and the NSD + P session \( (p = 0.60) \).

Results from the Stop driving questionnaire are displayed in Table 6.6. There was no significant difference in the proportion of drivers who stated that they would continue to drive between the NSD + P session and the SD + P session \( (\chi^2 = 0.69, p = 0.41) \), or between the SD + P session and the SD + A session \( (\chi^2 = 0.69, p = 0.41) \).

<table>
<thead>
<tr>
<th></th>
<th>NSD + P</th>
<th>SD + P</th>
<th>SD + A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short drive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue to drive</td>
<td>87.5%</td>
<td>37.5%</td>
<td>75.0%</td>
</tr>
<tr>
<td><strong>Long drive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue to drive</td>
<td>87.5%</td>
<td>37.5%</td>
<td>87.5%</td>
</tr>
</tbody>
</table>

NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo.

Table 6.6: Percentage of drivers who stated they would continue to drive on a short city drive and long country drive, in each session
6.3.4 Simulated Driving Task

Two participants’ driving simulator speed and lane position data in the sleep deprivation session could not be analysed due to technical problems. There was one outlier for the crashes data, therefore only seven subjects were included in the crashes analysis. Mean data from the Simulated Driving Task variables are displayed in Table 6.7.

<table>
<thead>
<tr>
<th></th>
<th>NSD + A (Mean ± Std. Dev)</th>
<th>NSD + P (Mean ± Std. Dev)</th>
<th>SD + A (Mean ± Std. Dev)</th>
<th>SD + P (Mean ± Std. Dev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral lane position (cms)</td>
<td>34.44 ± 9.34</td>
<td>40.09 ± 9.37</td>
<td>39.58 ± 14.94</td>
<td>42.55 ± 9.79</td>
</tr>
<tr>
<td>Speed Variation (km/h)</td>
<td>1.74 ± 1.18</td>
<td>2.32 ± 1.40</td>
<td>2.20 ± 1.35</td>
<td>2.30 ± 1.01</td>
</tr>
<tr>
<td>Mean braking RT (ms)</td>
<td>945.33 ± 408.56</td>
<td>1055.45 ± 476.15</td>
<td>904.11 ± 573.45</td>
<td>955.99 ± 412.40</td>
</tr>
<tr>
<td>Crashes</td>
<td>0.14 ± 0.38</td>
<td>0.29 ± 0.49</td>
<td>0.00 ± 0.00</td>
<td>0.14 ± 0.38</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo.

There was no difference in lateral lane deviations between the NSD + P session and the SD + P session (p = 0.24), between the SD + A session and the SD + P session (p = 0.60), or between the SD + A session and the NSD + P session (p = 0.87). For speed variations, there was no significant difference between the NSD + P session and the SD + P session (p = 0.87), between the SD + P session and the SD + A session (p = 0.92), nor was there a difference between the SD + A session and the NSD + P session (p = 0.50). There was a trend towards a faster mean braking reaction time (RT) in the SD + P session compared to the NSD + P session (p = 0.05). There was no difference in braking RT in the SD + A session and the SD + P session (p = 0.13), nor was performance different between the SD + A session and the NSD + P session (p = 0.50). There was no difference in the number of crash events between the NSD + P session and the SD + P session (p = 0.13). The number of crashes did not differ between the SD + A session and the SD + P session (p = 0.32), nor did crashes differ between the SD + A session and the NSD + P session (p = 0.32).
6.3.5 Neurocognitive tasks related to driving

One participant’s PVT data was excluded, as this task was not completed because the equipment was not available for both sessions, leaving seven participants in total for the PVT analysis. Mean data from the neurocognitive tasks variables are displayed in Table 6.8.

Table 6.8: Means and Standard deviations (Std. Dev.) of the neurocognitive task variables in each session

<table>
<thead>
<tr>
<th></th>
<th>NSD + A (Mean ± Std. Dev.)</th>
<th>NSD + P (Mean ± Std. Dev.)</th>
<th>SD + A (Mean ± Std. Dev.)</th>
<th>SD + P (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVT Median RT (ms)</td>
<td>219.36 ± 33.77</td>
<td>218.14 ± 22.25</td>
<td>231.64 ± 33.17</td>
<td>230.57 ± 24.32</td>
</tr>
<tr>
<td>PVT Lapses</td>
<td>2.14 ± 2.12</td>
<td>1.57 ± 0.98</td>
<td>2.71 ± 5.09</td>
<td>3.14 ± 2.34</td>
</tr>
<tr>
<td>PVT Fastest 10% RT (ms)</td>
<td>177.14 ± 18.39</td>
<td>173.91 ± 11.93</td>
<td>184.03 ± 18.96</td>
<td>185.04 ± 17.69</td>
</tr>
<tr>
<td>PVT Slowest 10% RT (ms)</td>
<td>2.82 ± 0.68</td>
<td>2.84 ± 0.36</td>
<td>2.82 ± 0.73</td>
<td>2.12 ± 0.83</td>
</tr>
<tr>
<td>Mean Simple RT (ms)</td>
<td>236.84 ± 22.76</td>
<td>246.06 ± 26.44</td>
<td>234.97 ± 25.97</td>
<td>252.24 ± 23.63</td>
</tr>
<tr>
<td>Mean Choice RT (ms)</td>
<td>401.32 ± 47.21</td>
<td>415.64 ± 37.44</td>
<td>398.32 ± 42.61</td>
<td>424.73 ± 42.71</td>
</tr>
<tr>
<td>Digit Vigilance RT (ms)</td>
<td>405.82 ± 30.82</td>
<td>422.36 ± 20.67</td>
<td>385.51 ± 43.02</td>
<td>448.92 ± 30.05</td>
</tr>
<tr>
<td>Digit Vigilance False Alarms</td>
<td>2.25 ± 2.49</td>
<td>1.75 ± 2.25</td>
<td>0.88 ± 0.99</td>
<td>1.75 ± 1.83</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo.

Of the PVT measures, there was a trend towards a slower median RT in the SD + P session compared to the NSD + P session (Wilcoxon = -1.86, p = 0.06). There was no significant difference between the SD + A session and the SD + P session (p = 0.61), however there was a trend towards an increase in median RT in the SD + A session compared to the NSD + P session (p = 0.12). There was a trend toward a higher number of lapses in the SD + P session compared to the NSD + P session (p = 0.10). There was no significant difference in the number of lapses between the SD + A session and the SD + P session (p = 0.24), nor did the number of lapses improve differ between the SD + A session and the NSD + P session (p = 0.89). There was a significant increase in the slowest 10% of RTs in the SD + P session compared to the NSD + P session (Wilcoxon = -2.03, p<0.05). Slowest 10% of RTs did not differ between the SD + A session and the SD + P session (p = 0.09), nor was there a
significant difference between the SD + A session and the NSD + P session (p = 0.92). There was also a significant increase in the fastest 10% of RTs in the SD + P session compared to the NSD + P session (Wilcoxon = -2.20, p<0.05). Fastest 10% of RTs did not differ between the SD + A session and the SD + P session (p = 0.50), however performance on this measure was significantly worse in the SD + A session than in the NSD + P session (Wilcoxon = -2.20, p<0.05).

There was no significant difference in mean Simple RT in the SD + P session compared to the NSD + P session (p = 0.40), between the SD + A session and the SD + P session (p = 0.21), nor was there a difference between the SD + A session and the NSD + P session (p = 0.78). Mean Choice RT did not differ between the NSD + P session and the SD + P session (p = 0.64), between the SD + A session and the SD + P session (p = 0.21), nor was there a significant difference between the SD + A session and the NSD + P session (p = 0.21). Digit vigilance RT was significantly faster in the NSD + P session compared to the SD + P session (Wilcoxon = -2.10, p<0.05). Digit Vigilance RT was significantly faster in the SD + A session compared to the SD + P session (Wilcoxon = -2.52, p<0.05), and there was a trend for Digit Vigilance RT to be faster in the SD + A session and the NSD + P session (Wilcoxon = -1.96, p=0.05). There was no difference in the number of false alarms on the Digit Vigilance task between the NSD + P session and the SD + P session (p = 0.89), between the SD + A session and the SD + P session (p = 0.75), nor between the SD + A session and the NSD + P session (p = 0.26).

6.4.5 Visual & Auditory ERPs

The data from one subject’s session was not saved, therefore there are seven subjects in the final analysis for all ERP results.

6.4.5.1 Pattern Reversal Task

Means and standard deviations for the early sensory peak-to-peak amplitudes and latencies, for magnocellular and parvocellular evoked responses in each session, are shown in Table 6.9. Grand averages of the parvocellular and magnocellular pathways, for all sessions, are shown in Figure 6.4 and 6.5 respectively.
There was no difference in the parvocellular P100 amplitude (p = 1.00) or latency (p = 0.24), or on the N100 amplitude (p = 0.74) or latency (p = 0.46) between the NSD + P session and the SD + P session. There was also no difference in parvocellular P100 amplitude (p = 0.24) or latency (p = 0.18), or on the N100 amplitude (p = 0.87) or latency (p = 0.61) between the SD + P session and the SD + A session. Finally, there was no significant difference in the parvocellular P100 amplitude (p = 0.40) or latency (p = 0.24), or on the N100 amplitude (p = 0.87) or latency (p = 0.34) between the NSD + P session and the SD + A session.

Figure 6.4: Grand Averaged ERPs for Parvocellular Visual Pathway for each session.
Table 6.9: Means and Standard deviations (Std. Dev.) of the peak-to-peak amplitudes and latencies for the magnocellular and parvocellular pathway responses in the Pattern Reversal (PR) task the four experimental sessions

<table>
<thead>
<tr>
<th></th>
<th>Magnocellular</th>
<th>Parvocellular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amplitude (uV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD + A (Mean ± Std. Dev.)</td>
<td>1.56 ± 1.18</td>
<td>3.58 ± 1.96</td>
</tr>
<tr>
<td>NSD + P (Mean ± Std. Dev.)</td>
<td>1.38 ± 1.35</td>
<td>3.01 ± 2.52</td>
</tr>
<tr>
<td>SD + A (Mean ± Std. Dev.)</td>
<td>1.34 ± 0.98</td>
<td>3.66 ± 2.52</td>
</tr>
<tr>
<td>SD + P (Mean ± Std. Dev.)</td>
<td>1.63 ± 1.94</td>
<td>2.66 ± 1.98</td>
</tr>
<tr>
<td>NSD + A (Mean ± Std. Dev.)</td>
<td>121.00 ± 8.79</td>
<td>113.14 ± 10.84</td>
</tr>
<tr>
<td>NSD + P (Mean ± Std. Dev.)</td>
<td>125.42 ± 12.59</td>
<td>113.29 ± 12.42</td>
</tr>
<tr>
<td>SD + A (Mean ± Std. Dev.)</td>
<td>117.71 ± 9.72</td>
<td>111.57 ± 10.64</td>
</tr>
<tr>
<td>SD + P (Mean ± Std. Dev.)</td>
<td>121.42 ± 11.12</td>
<td>117.29 ± 9.55</td>
</tr>
<tr>
<td><strong>Latency (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSD + A (Mean ± Std. Dev.)</td>
<td>190.86 ± 19.27</td>
<td>155.71 ± 16.96</td>
</tr>
<tr>
<td>NSD + P (Mean ± Std. Dev.)</td>
<td>195.00 ± 17.87</td>
<td>161.57 ± 22.15</td>
</tr>
<tr>
<td>SD + A (Mean ± Std. Dev.)</td>
<td>196.57 ± 18.79</td>
<td>159.57 ± 19.34</td>
</tr>
<tr>
<td>SD + P (Mean ± Std. Dev.)</td>
<td>197.57 ± 21.53</td>
<td>158.71 ± 15.53</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo
Similarly, there was no difference in the magnocellular P100 amplitude ($p = 0.87$) or latency ($p = 0.14$), or on the N100 amplitude ($p = 0.50$) or latency ($p = 0.50$) between the NSD + P session and the SD + P session. There was also no difference in magnocellular P100 amplitude ($p = 0.24$) or latency ($p = 0.18$), or on the N100 amplitude ($p = 0.87$) or latency ($p = 0.61$) between the SD + P session and the SD + A session. Finally, there was no significant difference in the magnocellular P100 amplitude ($p = 0.24$) or latency ($p = 0.14$), or on the N100 amplitude ($p = 0.40$) or latency ($p = 0.61$) between the NSD + P session and the SD + A session.

Figure 6.5: Grand Averaged ERPs for the Magnocellular Visual Pathway for each session.
6.4.5.2 Tunnel vision task

One participant’s data for the P100 and N100 peaks was excluded, as the data could not be identified for the NSD + placebo session, and one participants’ data for the P300 peaks was excluded, as the data could not be identified for any of the sessions, leaving six subjects for these analyses.

The means and standard deviations of the behavioural data are displayed in Table 6.10. No overall effect on mean reaction time was found for session ($F(1,6) = 0.38, p = 0.80$), or drug ($F(1,6) = 2.32, p = 0.18$), however there was a trend towards a visual field position effect ($F(1,6) = 4.48, p= 0.08, \text{eta}^2= 0.43$), with slower reaction times to peripheral stimuli. There was a significant effect of visual field for errors of omission ($F(1,6) = 9.35, p<0.05$), with more errors to peripheral stimuli. There was also a trend towards an effect of session ($F(1,6) = 5.79; p = 0.053$), with more errors of omission in the SD session. No significant effect of drug was found for errors of omission ($p = 1.00$). No effect of errors of commission was found for visual field position ($p = 0.90$), session ($p = 0.34$), or drug ($p = 0.36$).
Table 6.10: Means and standard deviations (Std. Dev.) for reaction time to targets, and errors of omission and commission in the foveal and peripheral visual field separately, in the four experimental sessions

<table>
<thead>
<tr>
<th></th>
<th>NSD + A (Mean ± Std. Dev.)</th>
<th>NSD + P (Mean ± Std. Dev.)</th>
<th>SD + A (Mean ± Std. Dev.)</th>
<th>SD + P (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Foveal peripheral</td>
<td>foveal peripheral</td>
<td>foveal peripheral</td>
<td>foveal peripheral</td>
</tr>
<tr>
<td>Mean reaction time</td>
<td>418.19 ± 42.99</td>
<td>418.90 ± 27.89</td>
<td>419.94 ± 23.85</td>
<td>444.13 ± 37.82</td>
</tr>
<tr>
<td></td>
<td>410.97 ± 49.77</td>
<td>438.31 ± 45.13</td>
<td>418.33 ± 54.88</td>
<td>442.40 ± 30.74</td>
</tr>
<tr>
<td>Errors of omission</td>
<td>0.29 ± 0.49</td>
<td>1.57 ± 1.40</td>
<td>0.43 ± 0.53</td>
<td>1.71 ± 1.70</td>
</tr>
<tr>
<td></td>
<td>1.86 ± 2.34</td>
<td>1.71 ± 1.50</td>
<td>2.86 ± 2.34</td>
<td></td>
</tr>
<tr>
<td>False alarms</td>
<td>18.29 ± 3.25</td>
<td>16.43 ± 7.18</td>
<td>16.43 ± 4.24</td>
<td>16.43 ± 3.78</td>
</tr>
<tr>
<td></td>
<td>16.43 ± 3.55</td>
<td>31.57 ± 39.48</td>
<td></td>
<td>32.43 ± 39.12</td>
</tr>
<tr>
<td>% correct</td>
<td>98.23 ± 3.03</td>
<td>92.13 ± 5.82</td>
<td>97.34 ± 3.31</td>
<td>89.26 ± 10.61</td>
</tr>
<tr>
<td></td>
<td>97.34 ± 3.31</td>
<td>89.30 ± 9.35</td>
<td></td>
<td>82.16 ± 14.62</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo.
Table 6.11: Means and Standard deviations (Std. Dev.) of the Tunnel vision (TV) tasks peak-to-peak amplitudes and latencies for the foveal and peripheral evoked responses, in the four experimental sessions

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (uV)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSD + A (Mean ± Std. Dev.)</td>
<td>NSD + P (Mean ± Std. Dev.)</td>
</tr>
<tr>
<td>P100 (Oz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal</td>
<td>2.17 ± 3.81</td>
<td>1.71 ± 2.02</td>
</tr>
<tr>
<td>Peripheral</td>
<td>1.30 ± 0.53</td>
<td>1.81 ± 1.21</td>
</tr>
<tr>
<td>N100 (Oz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal</td>
<td>1.52 ± 1.48</td>
<td>1.58 ± 1.14</td>
</tr>
<tr>
<td>Peripheral</td>
<td>0.94 ± 0.56</td>
<td>0.97 ± 0.95</td>
</tr>
<tr>
<td>N100 (Fz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal</td>
<td>2.23 ± 3.80</td>
<td>1.27 ± 1.31</td>
</tr>
<tr>
<td>Peripheral</td>
<td>5.45 ± 8.48</td>
<td>1.49 ± 1.22</td>
</tr>
<tr>
<td>P300 (Cz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal</td>
<td>4.43 ± 2.06</td>
<td>2.95 ± 2.15</td>
</tr>
<tr>
<td>Peripheral</td>
<td>3.20 ± 1.48</td>
<td>3.39 ± 2.41</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo
Grand averages of the foveal and peripheral early visual ERPs in the four conditions are shown in Figure 6.6. Means and standard deviations for the P100 and N100 sensory amplitudes, N100 attentional amplitudes and P300 amplitudes, for foveal and peripheral evoked responses in each session are shown in Table 6.11.

There was no difference in the P100 amplitude (p = 0.40) or latency (p = 0.61) to foveal stimuli, or the P100 latency (p = 1.00) of response to peripheral stimuli between the NSD + P session and the SD + P session. There was, however, a significant attenuation of the amplitude of response to peripheral stimuli in the SD + P session compared to the NSD + P session (Wilcoxon = -2.03; p < 0.05). There was also no difference in P100 amplitude (p = 0.87) or latency (p = 0.67) to foveal stimuli, or the P100 amplitude (p = 0.06) or latency (p = 0.75) of response to peripheral stimuli between the SD + P session and the SD + A session. Finally, there was no significant difference in the P100 amplitude (p = 0.87) or latency (p = 0.67) of response to foveal stimuli, or the P100 amplitude (p = 0.06) or latency (p = 0.75) of response to peripheral stimuli between the SD + A session and the NSD + P session. There were no significant differences in the N100 amplitudes and latencies for foveal or peripheral responses for any of the contrasts (p > 0.05).
Figure 6.6: Grand Averaged Early Visual Processing ERPs at Oz in response to Foveal and Peripheral Visual Field Stimuli in each session
Grand averages of the foveal and peripheral attentional components in each session are shown in Figure 6.7. There was no difference in the N100 amplitude (p = 0.87) or latency (p = 0.74) to foveal stimuli, or the N100 amplitude (p = 0.61) or latency (p = 0.93) of response to peripheral stimuli between the NSD + P session and the SD + P session. There was also no difference in N100 amplitude (p = 1.00) or latency (p = 1.00) to foveal stimuli, or the N100 amplitude (p = 0.24) or latency (p = 0.87) of response to peripheral stimuli between the SD + P session and the SD + A session. Finally, there was no significant difference in the N100 amplitude (p = 0.73) or latency (p = 0.12) of response to foveal stimuli, or the N100 amplitude (p = 0.50) or latency (p = 0.31) of response to peripheral stimuli between the SD + A session and the NSD + P session.

![Figure 6.7: Grand Averaged attentional N100 ERPs at Fz in response to Foveal and Peripheral Visual Field Stimuli in each session](image)
Grand averages of the foveal and peripheral P300 responses in all sessions are shown in Figure 6.8. There was no significant difference in the P300 amplitude (p = 0.60) or latency (p = 0.92) of response to foveal stimuli, or amplitude (p = 0.35) or latency (p = 0.92) of response to peripheral stimuli between the NSD + P session and the SD + P session. There was no significant difference in P300 amplitude (p = 0.75) or latency (p = 0.17) of response to foveal stimuli, or on the P300 amplitude (p = 0.75) or latency (p = 0.25) of response to peripheral stimuli between the SD + P session and the SD + A session. The P300 amplitude (p = 0.46) or latency (p = 0.17) of response to foveal stimuli, and P300 amplitude (p = 0.46) or latency (p = 0.25) of response to peripheral stimuli did not differ between the SD + A session and the NSD + P session.

Figure 6.8: Grand Averaged P300 ERPs to target stimuli presented in the Foveal and Peripheral Visual Field Stimuli in each session.
6.4.5.3 Auditory Oddball Task

One subject was excluded as the task did not run properly during the SD + A session, leaving six subjects for the N1-P2, P300 and behavioural data analyses. Behavioural data, amplitude and latencies for the N1 and P2 complexes, and P300 area under the curve (AUC) results are displayed in Table 6.12.

There was no significant difference between the NSD + P session and the SD + P session on errors of omission (p = 0.61), nor was there a difference between the SD + A session compared to the SD + P session (p = 0.46). The number of errors of omission was significantly lower in the SD + A session compared to the NSD + P session (Wilcoxon = -2.02, p<0.05). There was no significant difference between the NSD + P session and the SD + P session on percentage of correct responses (p = 0.61), however, there was a trend towards an improvement in the percentage of correct responses in the SD + A session compared to the SD + P session (Wilcoxon = -1.81, p = 0.07). Percentage of correct responses was significantly improved in the SD + A session compared to the NSD + P session (Wilcoxon = -2.02, p<0.05). There was no significant effects for reaction times and false alarms for any of the contrasts of interest (p>0.05).
Table 6.12: Means and Standard deviations (Std. Dev.) of the behavioural and electrophysiological responses for the Auditory Oddball Task

<table>
<thead>
<tr>
<th>Response</th>
<th>NSD + A (Mean ± Std. Dev.)</th>
<th>NSD + P (Mean ± Std. Dev.)</th>
<th>SD + A (Mean ± Std. Dev.)</th>
<th>SD + P (Mean ± Std. Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors of omission</td>
<td>7 2.71 ± 5.47</td>
<td>7 4.57 ± 4.35</td>
<td>6 0.67 ± 1.21</td>
<td>7 6.43 ± 5.09</td>
</tr>
<tr>
<td>False alarms / errors of commission</td>
<td>7 4.86 ± 8.17</td>
<td>7 2.71 ± 4.11</td>
<td>6 4.83 ± 6.37</td>
<td>7 3.43 ± 6.50</td>
</tr>
<tr>
<td>% correct responses</td>
<td>792.33 ± 15.66</td>
<td>787.31 ± 12.11</td>
<td>6 98.20 ± 3.27</td>
<td>7 82.37 ± 14.12</td>
</tr>
<tr>
<td>Mean Reaction Time (ms)</td>
<td>7433.96 ± 35.64</td>
<td>7432.33 ± 1.58</td>
<td>6409.97 ± 16.67</td>
<td>7 449.14 ± 52.63</td>
</tr>
<tr>
<td>P300 AUC</td>
<td>7 2.98 ± 3.61</td>
<td>7 2.69 ± 4.32</td>
<td>6 0.66 ± 0.72</td>
<td>7 3.08 ± 2.57</td>
</tr>
<tr>
<td>N1 peak to peak amplitude (µV)</td>
<td>7 4.28 ± 3.59</td>
<td>7 2.85 ± 2.62</td>
<td>6 1.29 ± 1.26</td>
<td>7 3.69 ± 3.00</td>
</tr>
<tr>
<td>N1 latency (ms)</td>
<td>7 92.57 ± 10.88</td>
<td>7 89.00 ± 8.23</td>
<td>6 90.33 ± 10.98</td>
<td>7 94.57 ± 6.00</td>
</tr>
<tr>
<td>P2 peak to peak amplitude (µV)</td>
<td>7 2.18 ± 2.99</td>
<td>7 1.94 ± 1.95</td>
<td>6 0.84 ± 0.94</td>
<td>7 2.40 ± 2.26</td>
</tr>
<tr>
<td>P2 latency (ms)</td>
<td>7 204.57 ± 30.21</td>
<td>7 203.71 ± 19.81</td>
<td>6 193.83 ± 28.51</td>
<td>7 207.43 ± 18.94</td>
</tr>
</tbody>
</table>

NSD + A = no sleep deprivation with d-amphetamine, NSD + P = no sleep deprivation with placebo, SD + A = sleep deprivation with d-amphetamine, SD + P = sleep deprivation with placebo
Figure 6.9 depicts the N1P2 ERP response to the auditory oddball task at Cz. There was no significant difference between the NSD + P session and the SD + P session on the N1 amplitude (p = 0.31), however there was a trend for latency, with a longer latency in the SD + P session (Wilcoxon = -1.78, p = 0.08). There was no difference between the SD + A session and the SD + P session on N1 amplitude (p=0.50), or latency (p = 0.46), nor was N1 amplitude (p = 0.46) or latency (p = 0.60) different between the SD + A session and the NSD + P session. Similarly, there was significant difference between the NSD + P session and the SD + P session on P2 amplitude (p = 0.61), however there was a trend for latency, with a longer latency in the SD + P session (Wilcoxon = -1.69, p = 0.09). There was no significant difference between the SD + P session and the SD + A session on P2 amplitude (p = 0.18), however latency was significantly shorter in the SD + A session (Wilcoxon = -1.99, p < 0.05). There was no difference in P2 amplitude (p = 0.24) or latency (p = 0.25) between the SD + A session and the NSD + P session.

Figure 6.9: Grand Averaged ERPs for N1P2 complex of the TTI response at the Cz scalp site in the NSD + d-amphetamine (blue), NSD + placebo (green) SD + placebo (black), and SD + d-amphetamine (red) sessions separately.
Figure 6.10 depicts the grand averaged ERPs for P300 complex of the Auditory Oddball response at the Pz scalp site. For the P300 AUC, there was no significant difference between the NSD + P session and the SD + P session (p = 0.92). There was a significant difference in the P300 AUC between the SD + A session and the SD + P session, with a significantly reduced P300 with d-amphetamine compared to placebo, when drivers were sleep deprived (Wilcoxon = -1.75, p = 0.08). There was no difference in the P300 AUC between the NSD + P session and the SD + A session (p = 0.50).
6.7 Discussion

The current pilot study examined the influence of \textit{d}-amphetamine on a range of driving-related processes in sleep-deprived subjects. This study was conducted on a sample of professional drivers who were past or current amphetamine users. Participants were administered placebo on one occasion, and \textit{d}-amphetamine on another occasion; once after normal sleep and once following 24-hours of sleep deprivation.

In terms of drug levels detected in blood after the administration of \textit{d}-amphetamine administration, the current study found that the level of amphetamine in plasma, at two hours post-ingestion was approximately 65 ng/ml in both sessions, and did not change across the testing period. The dose of \textit{d}-amphetamine administered in this study is considered quite low compared to that used occupationally by truck drivers. However, in relation to road-side drug test results, the plasma levels reached in this study is comparable. In a Norwegian study of 878 drivers suspected of driving under the influence of drugs, a positive relationship between blood levels of amphetamine and impairment was found, as assessed by a clinical test of impairment (CTI) by a police physician (Gustavsen et al., 2006), with the mean amphetamine levels in blood of drivers of 52 ng/ml (range 4 ng/ml to 370 ng/ml). At this level, only 73\% of the drivers were considered impaired using the CTI. In the groups with amphetamine blood concentrations between 270 ng/ml and 530 ng/ml (corresponding to an intake of 70 mg to 150 mg amphetamine) or above, nearly 80\% of the drivers were considered impaired. Similar amphetamine levels have been detected in drivers apprehended for driving under the influence of drugs (DUID), with two studies reporting median blood concentration of amphetamine of 54 ng/ml and 70 ng/ml, with some amphetamine levels reaching 500 ng/ml to 1700 ng/ml (Jones & Holmgren, 2005; Augsburger, 2005). Of drugs detected in the specimens of 372 drivers convicted of driving while impaired by a drug, between 2000 and 2005 in Victoria, 9.5\% of these drivers tested positive to amphetamine-type-stimulants. The levels of amphetamine in blood ranged between 20 ng/ml to 900 ng/ml, with a mean amphetamine level of 182 ng/ml. However, the most common level of amphetamine detected was 900 ng/ml. This level indicates recent use of the drug, at a high dose, or may also reflect consistent, repeated doses. These levels are comparable to
amphetamine levels found in fatally injured drivers in Australia, in whom the amphetamine levels range from less than 5 ng/ml (considered trace levels) to between 10 ng/ml and 30 ng/ml (therapeutic level), and some as high as 800 ng/ml.

Experimentally, Silber, et al., (2006) demonstrated that, following an oral dose of 0.42 mg/kg of body weight of d-amphetamine, the mean level of d-amphetamine detected in blood at 120 minutes after drug administration was 83 ng/ml and at 240 minutes after drug administration was 96 ng/ml. To put this in context, therapeutic daily dose of d-amphetamine generally do not exceed 60 mg, with corresponding levels of amphetamine in plasma of approximately 200 ng/ml. Overall, blood levels of 100 ng/ml are considered a therapeutic level, whereas levels greater than 300 ng/ml are considered toxic. The interpretation of these findings is difficult as there is no information regarding time since administration, dosage, or past drug experience in reports relating to intercepted drivers. Therefore, it is difficult to determine whether the impairment is occurring during a time when blood levels where rising, or at a time at the end-of-binge when a person becomes quite fatigued. Further, some past drug use was detected in most of the drivers in the study. The levels and types of drug (some of which were licit drugs e.g. codeine) were not deemed to be high enough to interact with the study manipulations and affect the results. The amphetamine levels reported in the current study are lower than that reported in road fatalities, however, they are within the range detected in drivers apprehended for dangerous driving. Therefore, the findings of the current experiment are very important in providing some indication of the driving-related impairments associated with d-amphetamine blood concentrations found in fatally injured drivers.

6.7.1 Measures of behavioural disposition

A range of subjective sleepiness and mood measures were examined in the current study. Previous studies report that subjective amphetamine effects peak at 1.5 to 2 hours post-administration, and decline within 5 to 6 hours, while amphetamine blood levels tend to remain significantly elevated (Asghar et al., 2003; Brauer et al., 1996). Subjective ratings were assessed in the current study at two hours post drug administration, to capture the height of subjective responses. As expected,
participants rated their sleepiness on the Karolinska Sleepiness Scale (KSS) significantly higher following sleep deprivation. This is the first study to examine the KSS in sleep-deprived individuals following acute d-amphetamine administration. Participants rated their sleepiness lower following d-amphetamine compared to placebo, following sleep deprivation, and interestingly, this sleepiness rating was no different to the rating given after normal sleep. This finding suggests that, after one night of sleep deprivation, 20 mg of d-amphetamine improved subjective sleepiness back to pre-sleep deprived levels. The KSS appears to be sensitive to drug effects, and may be used to detect drug-related changes in subjective alertness following one night of sleep deprivation.

Mood ratings, assessed by the visual analogue scale (VAS), provide a more complete picture of an individuals’ mood state, by examining a range of mood dimensions. VAS scores were found to increase with sleep deprivation, which was mostly driven by an increase in negative mood domains (e.g. drowsy, lethargy and tension). The important finding from the current study was the improvement of mood when d-amphetamine was administered following sleep deprivation, compared to placebo. Increases in mood and arousal levels have been reported previously following d-amphetamine administration, compared to placebo, in well-rested participants, and are associated with plasma amphetamine concentrations (Asghar et al., 2003), and are dose dependent (White, Lott, & de Wit, 2005). For instance, Ashgar et al, (2003) found that amphetamine plasma levels strongly correlated with attention and arousal ratings on the VAS, 30-minutes post drug administration. Higher responses on a VAS included anxiety, energy and speed of thought, and these were significant at 60 minutes to 90 minutes post administration, with amphetamine concentrations of between 19 ng/ml and 31.5 ng/ml (Asghar et al., 2003). The results of the current experiment are consistent with one study which reported a reduction in the fatigue subscale of the POMS following administration of 10 mg and 20 mg of d-amphetamine in subjects who were sleep deprived for 48 hours (Newhouse et al., 1989). Conversely, Hartman et al, (1977) found that increased POMS scores of fatigue and confusion, and decreased scores on the vigour subscale reported after one night of sleep loss, were unaffected by 10 mg d-amphetamine administration (Hartmann et al., 1977). These studies, however, only assessed low doses of amphetamine in healthy individuals who are naive to the subjective and
physiological effects of amphetamine administration. The participants in the current study were past or current amphetamine users, and the dose of \(d\)-amphetamine was likely to be lower than what these drivers would normally consume recreationally/occupationally. Their habitual use may have negated potential detrimental and thus the negative impact on mood.

Consistent with the results of Experiment 1, the detection of sleepiness symptoms increased following sleep deprivation. Participants reported experiencing the symptoms “struggling to keep eyes open”, “nodding off to sleep”, “difficulty maintaining correct speed”, and “head dropping down”. These are relatively late symptoms of sleepiness, that have been associated with performance impairment (Gillberg et al., 1994). This suggests that participants noticed physiological and performance changes during the simulated driving task when sleep-deprived, despite having no change in their performance. There was a trend-level reduction in the frequency of symptoms observed following sleep deprivation when \(d\)-amphetamine was administered compared to placebo, however this did not reach statistical significance. Further, the ratings given after sleep deprivation and \(d\)-amphetamine administration were no different to ratings given after normal sleep and placebo, indicating that \(d\)-amphetamine administration was effective in reducing subjective sleepiness symptoms to levels observed after normal sleep.

The current study also examined whether participants could accurately assess their driving performance under different conditions. Although sleep deprivation did not significantly impact upon driving performance (see Section 6.7.2 for discussion), participants rated their performance significantly worse in the sleep deprivation session, when placebo was administered. Participants may have detected that it was more difficult to maintain attention and drive when sleep-deprived, but they were still able to maintain performance nonetheless. When drivers were sleep-deprived and administered \(d\)-amphetamine, subjective ratings significantly improved, and these ratings were no different to those given after normal sleep (with placebo). This was further examined using the Stop Driving questionnaire. Although not statistically significant, more participants stated that they would stop driving in the sleep deprivation/placebo session, compared to when \(d\)-amphetamine was administered. The findings of this experiment indicate that participants were able to
recognise a change in performance after sleep deprivation, and that they would stop
driving when no $d$-amphetamine was administered. It appears that following $d$-
amphetamine administration during sleep deprivation, participants felt that their
performance was actually better than after sleep deprivation alone, despite having no
change in actual driving performance between the two conditions. This may
therefore reflect an overconfidence of ability, in that participants thought they were
driving better following drug administration, when in actual fact there was no
improvement.

Amphetamines can affect driving skills in a number of ways. These include the direct
effect on alertness and driving performance, as well as impact on judgment, risk-
taking behaviours and decision making, which in turn may have detrimental effects
on driving ability. It is likely that the increase in alertness may be mistaken as an
improvement in actual performance. Drivers consuming high doses of amphetamine
can experience increased self-confidence and this increases risk-taking in traffic
(Logan, 1996). Although the doses used in the current experiment were relatively
low, a similar effect may have occurred. This aspect of judgement and risk-taking
needs further clarification. The relationship between perceptions of sleepiness and
actual performance was not assessed in the current experiment. This may provide
further evidence about whether amphetamine actually improves performance, or
results in an increased confidence and impulsivity reported previously (de Wit et al.,
2002), which may result in an overconfidence of one’s ability to drive safely.

6.7.2 Simulated driving

In contrast to Experiment 1, the current study did not find any effect of sleep
depprivation on driving simulation variables. In fact, braking reaction time was
actually faster under sleep deprived conditions when no drugs were consumed,
compared to placebo. The effect size for detecting a difference in lateral lane position
on the driving simulator between the NSD and SD sessions in this experiment was
0.27. In order for an effect size of 0.27 to be significant with an alpha of 0.05% and a
power of 0.8 it is estimated that 106 subjects would be required. This suggests that
this effect is not likely of physiological significance. The current study did not
observe any statistically significant effects of sleep deprivation and $d$-amphetamine

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administration, compared to placebo, on performance, indicating that \textit{d-}amphetamine administration following sleep deprivation did not improve performance relative to placebo. This is unlikely due to a lack of effect of \textit{d-}amphetamine on simulated driving performance, since previous studies have reported a change in performance with amphetamine-type-stimulants, after normal sleep (Silber et al., 2005) Silber et al. (2005) administrated the same dose as the current study (0.42mg/kg body weight) of \textit{d-}amphetamine, and found a subsequent reduction in overall driving performance, compared to placebo. Errors included decreased signalling adherence and a failure to stop at red traffic lights. Interestingly, drivers under the influence of \textit{d-}amphetamine drove significantly slower compared to placebo. The reduction in speed observed in this study was interpreted as a perceptual narrowing, or a tunnelling of the visual field, which may have caused drivers to be more cautious in order to attend to peripheral information more readily. It is plausible that this may have also occurred in the current study; drivers focusing more on the road and therefore experiencing less lane drifting when \textit{d-}amphetamine was consumed. However, this was not reflected in the speed variation data, which would have been expected to increase as drivers were less able to divide their attention between the road and the speedometer. Due to the lack of previous research in the area, it is difficult to relate these findings to other studies. The effects of peripheral field narrowing on driving following amphetamine administration, and indeed simulated driving performance in general, needs to be clarified.

The effects of sleep deprivation may have overridden the impact of \textit{d-}amphetamine in the current study, especially since the dose of \textit{d-}amphetamine was relatively low. However, it is difficult to interpret this finding, since there is a paucity of research examining the effects of stimulant drugs on simulated driving performance in sleepy individuals, in particular using professional drivers. Newcombe, et al. (2001) reported a reduction in lateral deviations on the AusEd driving simulator in patients with Obstructive Sleep Apnoea (who experience significant daytime sleepiness) who were administered a dose of modafinil. There are some differences in these studies such as the sample population and the type of stimulant administered, however together these studies suggest that this simulated driving task may be used to examine driving performance changes associated with amphetamine-type stimulants. Caldwell and Caldwell (1997) found improvements in performance on a helicopter
simulator after three 10 mg oral doses of \textit{d}-amphetamine when compared to placebo during 40 hours of sleep deprivation (Caldwell & Caldwell, 1997). Although the dosage was similar between this and the current study, the design of these experiments differed significantly; the Caldwell study used split doses across the sleep deprivation period, whereas the current study used one full dose at the conclusion of the sleep deprivation period. Caldwell and Caldwell also tested participants during the circadian nadir (05:00h and 09:00h) which may also have had a negative effect on performance in the placebo condition. Overall, it is difficult to interpret the results of the current study, due to the lack of previous research in this area.

The lack of a significant detrimental effect on driving performance in the current study may have been due to performing the driving simulation during a circadian peak period, or reduced individual driver susceptibility to sleep loss. In the setting that there was no significant deterioration in driving performance, it is less likely that amphetamine administration would be found to improve performance, although a higher dose might still do this. It is likely that the previously reported positive effects of \textit{d}-amphetamine administration during sleep deprivation on performance are due to the influence on alertness and attention, rather than directly improving specific aspects of driving performance \textit{per se}. This assumption was examined further in the current study using neurocognitive measures. These findings will now be discussed.

\textbf{6.7.3 Neurocognitive tasks related to driving}

A number of reaction time tasks were utilized in the current study that were found to be affected by sleep deprivation in Experiment 1. As expected, although not significantly, there was a trend towards a reduction in PVT reaction time performance measures following sleep deprivation, consistent with Experiment 1. In contrast, however, the number of lapses did not increase with sleep deprivation. It is likely that there was not enough power to detect a change in lapse frequency in this study. None of the PVT variables were affected by \textit{d}-amphetamine administration following sleep deprivation. Considering the sensitivity of this measure to sleep loss and sleepiness (Dinges & Powell, 1985), it is surprising that changes in reaction time with \textit{d}-amphetamine were not observed with the PVT, as previously reported in other
psychomotor tasks (Hindmarch, 2004). The PVT is a relatively long (10 minute) and monotonous task, which may have induced some time-on-task fatigue effects over the testing period.

Supporting this postulation, some $d$-amphetamine effects were demonstrated on a shorter reaction time task (Digit Vigilance Task) used in the current study, however, only when performance was impaired by sleep deprivation. Reaction time speed has consistently been found to improve following the administration of low $d$-amphetamine doses, between 5 mg and 0.25 mg/kg (approximately 15 mg) in well-rested participants (Asghar et al., 2003; Fillmore, Kelly, & Martin, 2005; Fleming et al., 1995; Halliday et al., 1994; Rapoport et al., 1980; Servan-Schreiber, Carter, Bruno, & Cohen, 1998; Ward et al., 1997) Consistent with the current experiment, impaired psychomotor and reaction time performance associated with sleep deprivation has been shown to be restored with a dose of oral $d$-amphetamine in previous studies (Newhouse et al., 1989). A 20 mg oral dose of $d$-amphetamine improved performance on a choice RT task after periods of 40.5 hours (Magill et al., 2003) and 60 hours (Newhouse et al., 1989) of sleep deprivation. These studies were not placebo-controlled, nor were any baseline measures assessed, therefore it is difficult to examine the true magnitude of the improvement. Sleep deprivation did not affect performance on any of the other reaction time measures in the current study (Simple and Choice RT), and thus $d$-amphetamine could not improve performance on these tasks when participants were sleep deprived. The length of these tasks (< 4 minutes) may have been too short or insensitive to detect changes related to sleep loss (Dinges et al., 1997).

A significant effect of session was not demonstrated in most of the tasks in this Experiment, in contrast to Experiment 1. The effect size for detecting a difference in the median RT between the NSD and SD sessions in this experiment was 0.54. In order for an effect size of 0.54 to be significant with an alpha of 0.05% and a power of 0.8 it is estimated that 27 subjects would be required. For the lapses data, the effect size was 0.79, which would require only 13 subjects to be significant at with an alpha of 0.05% and a power of 0.8. Therefore, with a substantial effect size and if replicable, only 13 subjects would be required to adequately power this analysis. It therefore appears that the results of this experiment may be due to a real effect,
however this requires further research. The current findings may thus suggest that this sample of drivers were less affected by sleep deprivation compared to those in Experiment 1, and reported previously (Howard et al., 2007). Since the drivers in this study tended to undertake more long-haul work (and hence use amphetamine-type stimulant drugs), it is likely that they often experience driving under sleep-deprived conditions. Given that there is significant inter-individual variation in the tolerance to sleep deprivation, it is possible that these drivers are self-selected to be more tolerant to sleep loss.

These results suggest that the alerting effects on performance of this dose (0.42 mg/kg) of \textit{d}-amphetamine were only effective when participants were experiencing significant sleepiness. However, due to low subject numbers, these findings should be taken with caution. Additionally, it is difficult to compare the finding of this and previous studies, due to the nature of the subjects recruited. Most previous studies use drug-naive subjects, whereas the current study has examined these effects in a cohort of participants who are familiar with the effects of the drug, and also commonly experience sleep deprivation.

6.7.4 Visual & Auditory ERPs

6.7.4.1 Pattern reversal task

In this sample of participants, there were no effects of sleep loss or \textit{d}-amphetamine on the amplitude or latency of the early sensory visual processes of the PR tasks. Previous studies (and as described in Experiment 1), have reported slower processing of the parvocellular visual pathway following sleep deprivation (Jackson et al., 2008). It would be interesting to determine whether \textit{d}-amphetamine is effective in reversing this change in latency of the parvocellular visual pathway. It is likely that with the low subject numbers in this experiment, an effect may not have been detected.
6.7.4.2 Tunnel Vision task

As reported in Experiment 1, evidence of behavioural deficits associated with visual field processes following amphetamine administration was observed in the current experiment. This was manifest as an increase in errors of omission in response to peripheral stimuli, compared to foveal stimuli. There was no effect of session on this response, however, it appeared from the data that there were more errors to peripheral stimuli with sleep deprivation (2.86), and following sleep deprivation when amphetamine was consumed (1.86), with the least number of errors with no sleep deprivation when no amphetamine were consumed (0.43). This has been supported by other reports of a ‘tunnel vision’ effect demonstrated with acute amphetamine administration (Mills et al., 2001). This phenomenon occurs when attentional resources become overwhelmed, resulting in a reduced capacity of the individual to gather information from the visual field efficiently. Improvements occur at the focus of attention, due to a perceptual restriction to the focal point, with a corresponding functional decrement in the peripheral regions of focus (Easterbrook, 1959). This process is also supported by the behavioural data in the current experiment, when amphetamine was consumed after normal sleep. Experimentally, tunnel vision has been observed in subjects following doses of 10mg \textit{d}-amphetamine (Hurst et al., 1967; Mills et al., 2001). This study examined target identification and divided attention responses at three discrete stimulus rings extending outward from the centre of a computer screen (the fixation point). The task assessed ‘tunnelling’ by comparing baseline responses with post-amphetamine dose responses to targets presented at three visual field positions. Performance was improved for tasks where stimuli were presented centrally, however, no change in performance were observed when stimuli were presented in the peripheral positions. Based on these findings, it was concluded that \textit{d}-amphetamine induced ‘tunnel vision’. It can be argued that these results do not reflect ‘tunnel vision’ effects as no significant impairments were noted in the peripheral positions. However, close examination of the data presented in the Mills et al. (2001) paper illustrates notable peripheral decrements in the \textit{d}-amphetamine condition.

For the electrophysiological data, in this sample of participants, there was a reduction in the P100 amplitude in response to peripheral stimuli after sleep deprivation, with
no other effects of sleep loss on the early sensory visual processes. This may indicate that sleep deprivation produced a tunnel vision effect, with a reduction in neural firing to peripheral stimuli. However, this needs to be further examined in a larger sample. Consistent with the findings in Experiment 1, there was no effect of sleep deprivation on the N100 amplitude or the latency of these early visual responses, supporting the hypothesis that sleep deprivation does not impact upon early processing in the visual cortex.

However, in contrast to Experiment 1, no effect of sleep deprivation was found for the P300, and overall, there was little effect on sleep deprivation on the later neural processing and behavioural responses. Further, d-amphetamine administration had no impact on these later responses. This study, therefore, did not find any evidence of a drug-related tunnel vision effect on neural processing, or behavioural responses, as previously suggested. It is likely that this experiment lack statistical power to detect changes in these processes, thus this phenomenon warrants further investigation. Tunnel vision has been reported previously in visual processing to foveal and peripheral stimuli following d-amphetamine administration (Mills et al., 2001). Although this effect was not observed in the current study, the combined effect of sleep loss and d-amphetamine on this tunnel vision response should be examined further in a larger sample.

6.7.4.3 Auditory Oddball Task

The behavioural data from the auditory oddball task revealed that sleep deprivation had no effect on performance, in contrast to Experiment 1. The participants in this study may have been less affected by sleep deprivation and more able to sustain their alertness for the duration of the task, compared with the drivers in Experiment 1. There were, however, significant improvements in the percentage of correct responses and errors of omission, and standard deviations of reaction times when d-amphetamine was administered during sleep deprivation and without sleep deprivation, compared to placebo. Variability in reaction times (as reflected by an increase in standard deviations of reaction times) and errors of omission, which represent lapses in attention leading to missed responses, are cardinal features of
sleep loss. Both of these measures were improved with $d$-amphetamine administration. Previous studies have also reported that $d$-amphetamine reduces the number of errors of omission in continuous vigilance and reaction time tasks after 30-hours of sleep deprivation (Magill et al., 2003). The improvements in this task with $d$-amphetamine despite the lack of impairment following sleep deprivation and in the non-sleep deprived state suggest that $d$-amphetamine can improve baseline performance in this task.

Inspection of the ERP data suggests that these improvements did not occur at the early processing level, since N1 and P2 amplitudes were unaffected by sleep deprivation and $d$-amphetamine. Based on the findings of Experiment One, sleep deprivation was not expected to have an effect on the early auditory processes of this task. However, P2 latency was significantly faster, which may suggest an increase in processing speed following $d$-amphetamine when participants were sleep deprived.

A significant reduction in P300 response was observed following $d$-amphetamine administration when participants were sleep deprived. This may reflect a decrease in an individual’s ability to maintain an attentional trace to irrelevant auditory stimuli following $d$-amphetamine administration. McKetin, et al., (1999) examined the effects of two different doses of $d$-amphetamine (placebo, 10 mg and 20 mg) on reaction times (RT) and P300 response in 12 healthy subjects (McKetin et al., 1999). $d$-amphetamine improved RT performance and hit rate in a dose-related manner, however, it did not affect error rate. A reduction in P300 amplitudes was associated with improved performance, suggesting improved recognition of the target stimulus. Additionally, $d$-amphetamine decreased processing negativity to irrelevant stimuli, with no change to relevant stimuli. Large processing negativity occurring to task irrelevant stimuli suggests that these stimuli are being processed unnecessarily. This measure is believed to reflect selective attention, and later active selection and rejection of information (McKetin et al., 1999). This indicates that amphetamines may improve recognition of the relevant stimulus, and decreases attention to irrelevant stimuli. Due to difficulties in detecting a P300 peak, there were very few participants included in the analysis, therefore these findings should be interpreted with caution.
It appears that in some cases, \( d \)-amphetamine may improve the focusing of attention, as observed by a reduction of the P300 amplitude during the Auditory Oddball task following sleep loss. Thus \( d \)-amphetamine improved the recognition of the target stimulus without processing of unnecessary information. However, this heightened selective attention to one stimulus modality may be to the detriment of other modalities, as was examined in Experiment 2.

6.8 Limitations & Conclusions

The dose of \( d \)-amphetamine was relatively low compared to what would be used “occupationally” by the drivers in the study, due to ethical constraints. It is therefore difficult to make inferences from the results of the present thesis to drug- and sleep-related accidents that occur in the real-world. At this dose, no serious adverse effects on performance were observed. Further, the protocol used in the pilot study was probably different to what would occur in the real-world. The timing of administration of \( d \)-amphetamine occurred following 24-hours of sleep deprivation, whereas drugs would normally be consumed prior to or just after the driver was feeling sleepy. Previous studies have used different protocols during which participants are administered amphetamines in the middle of the sleep deprivation period, rather than at the end. The results of the current study, however, do provide an indication that a single, acute dose of \( d \)-amphetamine, given as a countermeasure for sleep loss, can restore some sleep-related performance impairment in this population and dramatically increases the subjects self reported alertness and perception of their performance.

There are limitations with using chronic past or current drug-users. Long-term drug users are likely to have drug-related neuronal changes which may affect their cognitive performance. Chronic drug effects have also been assessed by other studies, investigating long-term amphetamine use on brain structure and function. The neuropsychological profile of chronic amphetamine users is impaired compared to healthy controls, particularly in memory (Rylander, 1969) and psychomotor performance (Trites et al., 1974). Grey matter deficits have been reported in the cingulate, limbic and paralimbic cortices (Thompson et al., 2004). There is also evidence from functional neuroimaging studies that drug users have differential
neural processing during task performance compared to healthy subjects (Daumann et al., 2004). For ethical reasons, however, current amphetamine users were recruited in the current thesis. One advantage of this is the findings of the study are more representative of drivers who use amphetamines, rather than healthy drivers from the general population.

Recent drug use was detected in the blood samples of some drivers in Experiment 3, despite requests to refrain from drugs for four days prior to each study session. These drugs were not detected in blood. However, due to the low level of drugs in urine and the low number of subjects in this experiment, all drivers were included in the study. This decision was also made because the types of drugs detected (pseudoephedrine, morphine, low-levels of THC metabolite) and the level of drug detected were thought to represent use from a few days prior to the session, and thus would not greatly impact on the drivers’ performance. Often the levels of drugs detected in urine indicated that the drug had been consumed a number of days prior, and the effects on subjective responses and performance would be minimal. A clean cohort of drug users would have been ideal, however this proved to be very difficult, especially since we were testing drivers either side of long haul trips where drug-use would have occurred.

The current experiment examined the effectiveness of d-amphetamine as a countermeasure to the detrimental effects of sleep loss on driving-related performance. There appeared to be a discrepancy between introspective judgements of sleepiness and performance, and actual driving-related processes. For instance, the drivers in this experiment rated their performance better after d-amphetamine compared to placebo following sleep loss, however, no actual improvement in their simulated driving performance was observed. This suggests that although d-amphetamine may improve subjective ratings of alertness and performance, actual performance does not parallel this finding. d-amphetamine therefore, may lead to an individual overestimating their performance and abilities, through an improvement in subjective vigilance and alertness, without any corresponding effect on performance. These changes were only recorded for a few hours post drug-administration. This study was not designed to examine how long these changes are maintained. Due to the lack of statistically significant sleep-related changes in performance, the true
impact of $d$-amphetamine on these driving-related processes was difficult to draw from these results. However, the subjective findings of this study may have implications for how sleepiness can be perceived in different states. It may be less beneficial to promote the use of introspective and performance-related cues of sleepiness (e.g. difficulty maintaining correct speed or struggling to keep eyes open) to drivers who use stimulants to help maintain performance.
CHAPTER 7
LIMITATIONS & FUTURE DIRECTIONS

7.1 Limitations

There are a number of limitations arising from the current thesis which will be addressed in the following section.

The findings of the current thesis are derived from a specific population of subjects - professional drivers. There are a number of inherent issues due to the type of subjects used in the current thesis. Firstly, professional long haul drivers, as outlined in Chapter 2, work under enormous time pressure, and thus it was extremely difficult for many of them to commit to two and four testing sessions over the period of time required. Therefore, due to the difficulties recruiting a specific cohort of professional long haul drivers, we needed to broaden the definition of professional driver to include a range of individuals who drive for a living, including bus drivers, couriers, taxi drivers, movie-set trailer drivers, and heavy vehicle (both local and interstate) drivers.

Secondly, it is difficult to generalise the findings of this study to non-professional drivers. There are likely to be a number of differences between professional and non-professional drivers, such as more driving experience/ hours on the road, professional drivers commonly experience sleepiness and sleep deprivation, and therefore may recognise symptoms of sleepiness than other drivers, such as young or inexperienced drivers. It is also possible that they are self-selected to be less susceptible to sleep loss, if those that are more susceptible leave the industry. Other at-risk populations, such as Obstructive Sleep Apnoea patients, older drivers, or young drivers, should also be examined in this context.

The length of sleep deprivation utilised in the current experiments is relatively short compared to some previous studies. Longer periods of sleep deprivation may have induced additional performance deficits, or increased the effects on the significant changes found. However, a realistic level of sleep loss that would be commonly
experienced by professional drivers was used. The tasks were performed during a circadian peak period. This is likely to have reduced the negative effects on performance (compared to measurement during the circadian nadir), but also provided a cleaner evaluation of pure sleep deprivation effects.

Sleep deprivation cannot be blinded. It is difficult to replicate the motivation and performance that would occur on the road in the laboratory setting. Therefore participants were less likely to be motivated after sleep deprivation in the laboratory than they would be in real-world driving situations. It is also important that participants aim to perform at a high level throughout the testing session. All drivers completed the full 30-minute driving task, and even when crashes occurred, they continued to run the programme to completion. Other neuropsychological tasks were quite short (< 10 minutes) and the experimenter ensured that morale and motivation were kept high and participants were performing the tasks to the best of their ability at all times.

Simulated driving tasks are inherently difficult to translate to real-world conditions. The primary issue is that participants may be less motivated to perform well on a simulator than on the real road, since there is no real adverse personal outcome or consequence of crashing or lane crossing. There is evidence that poorer performance can occur in the laboratory compared to on-road driving (Philip et al., 2005). However, the simulated driving task used did provide an indication of impaired performance, which was further corroborated by a number of driving-related tasks, all of which are likely to give an indication of sleep deprived real-world driving performance.

There are also potential difficulties generalising the findings of the current study to the more complex and variable task of on-road driving. We have assessed a simple reaction time task under very controlled conditions, and these findings cannot be extrapolated across all the other neurocognitive components of the complex, integrated task of driving a motor vehicle nor to the much more variable conditions of the real road environment. These findings do, however, allow insight into the specific effects of sleep deprivation on both the visual behavioural responses, and
smaller electrophysiological brain changes associated with a visual task, which is an important aspect of driving.

For technical reasons and randomisation of the task order, drivers completed the tasks at slightly different times of day. However, the total testing period was selected to remain within the time window between 6am and 2pm, when circadian effects are at their lowest. Thus, there may have been some individual circadian influence on the absolute values, but this would not affect the comparison between the control and experimental situations, since all drivers performed the same task order at the same times each session.

Due to difficulties recruiting participants, there were relatively low subject numbers across the three experiments. Despite this, the changes occurring with sleep deprivation were robust enough to be detected in this number of subjects in Experiment 1. The final three subjects recruited for Experiment 2 were non-professional drivers. It is therefore difficult to generalise the findings of this experiment to the professional driver population. It was particularly difficult to recruit participants for the pilot study, due to confidentiality issues, medical reasons, and the length of time involved. Drivers who use stimulants to maintain wakefulness whilst driving tend to be those who do long haul trips, and therefore found it even more difficult to commit to four sessions. Thus, this study was limited by a lack of statistical power which made the interpretation of the findings difficult.

7.2 Future directions

The current thesis used a range of measures and techniques to examine and determine the deficits underlying sleep-related driving accidents. This study was unique in that a series of measures were employed to examine these effects, providing a more holistic understanding of sleep-related impairment and the processes underlying this impairment. The experiments in this thesis demonstrated significant deficits in overt driving-related behaviours, including simulated driving and driving-related neurocognitive domains. Dispositional measures of sleepiness, mood and performance were also significantly affected by sleep deprivation, which
are important factors in understanding why individuals continue to drive despite feelings of sleepiness. Neural processes, both electrophysiologically and haemodynamically examined, were also affected by sleep loss; specifically, later visual and auditory processes were impaired, and dividing attention between these two modalities also impacted on the brain activations associated with task performance. The findings of the current thesis have thus answered some but consequently also raised a number of questions which could be profitably addressed in future research in this area.

The current thesis has shown that many tasks are not affected by sleep deprivation, but the ‘sustained’ dimension to all such tasks should be examined in more detail. It is difficult to interpret whether the tasks were too short to and/or not sensitive enough to detect sleep-related impairments, or whether specific elements and processes related to the task are actually immune to sleep deprivation.

There is also a body of literature highlighting the issue of individual differences to effects of sleep loss; some individuals are vulnerable to the effects of sleep loss on performance, whereas others are relatively resilient (Van Dongen et al., 2004). This difference in susceptibility between individuals appears to have a genetic basis (Watson et al., 2006). It is therefore likely that some of the participants in this thesis were more susceptible to the effects of sleep deprivation, whereas others were able to cope and sustain their performance during the tasks. Future studies would benefit from examining what factors may lead to an individual being more resilient to the effects of sleep loss on performance, in particular in relation to differences in brain activation related to performance. It is also likely that there are individual differences in individual’s ability to detect sleepiness and symptoms of fatigue when sleep deprived. Research into individuals differences in perception of sleepiness, and its’ relationship to performance, is an area of research which would also have important implications for road safety.

The current thesis aimed to explore driving-related processes in professional drivers. The self-selecting nature of the transport industry indicates that the drivers in this thesis are possibly more resilient to the effects of sleep deprivation than the general population of drivers. Despite this, we did observe a large variability in performance
and subjective sleepiness ratings following sleep deprivation. It would be important to examine these effects in other samples of drivers, such as young or elderly drivers.

This study suggests that drivers recognise specific sleepiness symptoms that are useful markers of sleepiness and performance impairment under conditions of sleep deprivation. Some drivers either fail to recognise when they have become severely sleepy, do not attach enough importance to their sleepiness to stop driving, or purposely ignore severe sleepiness. Education about specific sleepiness symptoms may help people to recognize when they are becoming impaired as a result of sleepiness, and particularly when combined with knowledge of an individual’s sleep deprivation-related impairments, may prove a profitable means of reducing such driving behaviours.

Preliminary results from Experiment 1 indicated that automated measures of slow eye closure were significantly increased with one night of sleep deprivation, and thus may be useful for the detection of drowsiness in drivers. A number of ocular measures have since been employed commercially, and research effort is being made to determine their validity for on-road use. This is a particularly useful and practical outcome of the present thesis, and future research should examine the utility of ocular measures, not only for sleepiness, but also drug-use and sleep disorders, as an in-vehicle safety measure.

The pattern of activation found in the current study with sleep deprivation may be explained by neurocognitive studies of visual field functioning following sleep loss. Interestingly, damage to the parietal cortex, when it extends medially to include the posterior cingulate and precuneus, leads to a condition known as Balint’s syndrome; one of the primary symptoms being tunnel vision (Hecaen & Ajuriaguerra, 1954). Neuroimaging data has demonstrated bilateral parietal region decreases in glucose metabolism following 24 hours of sustained wakefulness, suggesting that if the sleep-deprivation-induced hypometabolism was significant enough, it could in fact produce behavioural manifestations similar to Balint’s syndrome. Currently there has only been one study investigating this hypothesis, and no study to date which has examined this phenomenon using both neuropsychological and neuroimaging techniques in the same subjects. Corresponding to this, a decrease in behavioural
responses to peripheral visual field stimuli may occur following acute sleep loss (Mills et al., 2001; Russo, et al., 2003). The reduced activation in parietal and posterior cingulate regions, associated with visual attention, following sleep deprivation may help to explain the neural basis of this tunnel vision response, and again it would appear important that future research pursues this link in order to better understand the nature of sleep deprivation-related driving impairment.

The current thesis extended the work of previous studies by using a range of tasks and measures that examine different aspect of driving performance. Further, Experiment 3 utilised a sample of current drug-users, which is a novel and unique aspect of the study compared to previous research. This research has implications for understanding the possible mechanisms that may be related to countermeasures, such as caffeine, napping, or stimulant drugs, such as amphetamine or modafinil, and their effectiveness in reversing the changes that occur with sleep deprivation. Currently, there is not enough conclusive data to inform policy with regards to drug-driving. It is difficult to draw firm conclusions as to the effectiveness of amphetamines as a countermeasure to sleep deprivation in this population due to a lack of significant behavioural results in Experiment 3. This null result may be due to a lack of statistical power to detect differences in performance after sleep deprivation in these drivers, and thus warrants further examination in a larger sample of drivers.

It would also be beneficial for future studies to examine the effects of sleep deprivation on a wider visual field, perhaps using a longer, more complex task, and following a longer period of sleep loss. In particular, it would be of great benefit to better understand subjective and objective changes in sleepiness and performance during sleep deprivation, as stimulant countermeasures wear-off and become less effective. Further, there may be differential effects of amphetamine taken in the morning compared to the night (Babkoff & Krueger, 1992). Future studies would benefit from designing a protocol where drug administration occurred during the night, rather than in the morning following sleep loss. This would give an indication of what level of sleep loss is experienced before drivers cannot recognise that they are impaired, or whether the effects of sleep loss override the alerting effect of the drug. It was too difficult in the current study to examine this effect after such a long period of sleep deprivation. More research is needed to better understand the tunnel
vision phenomenon, with regards to its effect following sleep deprivation and drug use. Further, as the influence of sleep deprivation is not uniform across different individuals, it is difficult to make recommendations regarding the time when \(d\)-amphetamine would need to be administered to restore sleep deprivation-related driving impairment. Just as a number of mathematical models of individual differences to sleep loss have been generated, a similar approach to individual effects of amphetamine administration, when sleep deprived, may also be useful.

From a practical viewpoint, the current findings have also highlighted a number of key areas which should be addressed in road safety campaigns. Some of the stronger findings in Experiment 3 indicated that subjective measures of sleepiness and performance were altered by fatigue and drug-use. It appears that amphetamines not only affect cognitive performance, as reported by previous studies, but also impair a driver's judgement of their ability, and increases self-confidence, which in turn may lead to the increased drug-related death toll on the roads. Self-monitoring of performance and ability in drug-users requires further clarification. Advertising may need to be extended to include different messages for different drivers (e.g. recognising symptoms doesn’t work for amphetamine users, so they would need education that amphetamines only improve belief and not actual ability). These findings highlight the importance of future work examining the issue of fatigue and drug-driving on both objective performance outcomes and subjective assessment of driving ability.

The findings of the current thesis support current road safety campaigns, by demonstrating empirically the effects of sleep loss on driving. Recent Australian Traffic Accident Commission’s campaign objectives have been to illustrate the symptoms of fatigue, increase awareness of the risks of being involved in a fatigue related motor vehicle accident, educate the public about the importance of pre-planning trips and resting beforehand as a preventative measure, and provide methods to deal with fatigue once symptoms have begun (e.g. taking a powernap). This information can help education, advertising and workplace safety efforts. Educating the community about the impact of sleepiness on driving performance, and introspective judgements of our performance and sleepiness levels, may help to increase awareness of the risks of driving when sleepy, and reduce road crashes.
CHAPTER 8
SUMMARY OF MAJOR FINDINGS & CONCLUSIONS

The current thesis has demonstrated significant impairments in a range of driving-related processes following 24-hours of sleep deprivation in a sample of professional drivers. The experiments in this thesis examined a range of driving-related processes, using tasks with strong face validity (to the task of driving) but lacking rigorous experimental control, to tasks with high experimental control but lacking practical application. Although some cognitive and electrophysiological measures were immune to sleep loss, a number of sensitive measures were significantly affected by sleep deprivation compared to after a normal night of sleep.

As expected, ratings on a number of mood and sleep-related questionnaires increased (more impaired) significantly over the 24-hour period of sleep deprivation. This sample of drivers was well aware of their subjective state sleepiness, and detected a number of symptoms of sleepiness whilst driving on the simulator. Further to this, they also recognized their performance deterioration on the driving simulator, and when asked whether they felt safe to continue to drive in their current state, the majority of drivers reported that they would have stopped driving.

Impairments on simulated driving measures that reflect real-world driving performance, such as steering and speed variability measures, increased as a function of sleep deprivation. A significant increase in slow eyelid closure with sleep deprivation was demonstrated, using an automated slow eyelid closure monitor, the Copilot. The validity of this type of device is still under investigation, however ocular measures appear to be a promising method of detecting physiological signs of sleepiness in the laboratory setting.

Results from the cognitive domains related to driving suggest that different neuropsychological functions are differentially affected by sleep deprivation. Simple task performance, such as PVT reaction time and lapses in attention, showed a significant decline with sleep loss, whereas other tasks which examine motor function and higher order processing were less vulnerable to the effects of sleep deprivation.
ERP measures were utilised to examine the neural underpinnings of these behavioural changes. After 24-hours of sleep deprivation, there was a decline in performance on a visual reaction time task. This sleep deprivation-related behavioural change was not explained by alterations in early visual processing, but appears to be related to effects on later, higher-order, cognitive processing. Sleep deprivation was also related to slower processing of the parvocellular visual pathway, which involved more sustained processing of detailed visual information. In addition, no sleep-deprivation tunnel vision effects were shown, either in the behavioural or ERP results, suggesting that sleep deprivation affects attention across the entire visual field, rather than specifically causing peripheral deficits as previously reported. Similarly, early auditory processes were unaffected by sleep deprivation, including the startle response and auditory change detection. However, results from the Auditory Oddball Task indicated that later processes, such as the P300, were reduced following 24-hours of sleep deprivation.

The common link between the dysfunction of different aspects of driving performance demonstrated in this thesis is attentional processing. The primary impact of sleep loss appears to relate to how an individual can attend to relevant information in the driving scene. This effect was further examined in Experiment 2, in which the neural activations associated with performing a divided attention task were examined using neuroimaging. As in Experiment 1, Experiment 2 demonstrated significant increases in subjective sleepiness and mood following 27-hours of sleep deprivation. This study demonstrated that divided attention performance, although reduced, was not significantly affected by sleep deprivation. Results from the fMRI data suggested that selectively attending to one modality increased neural activations in the corresponding sensory regions, while simultaneously decreasing activity in the unattended sensory cortices. When attention was divided between two modalities, increased activation in frontal and parietal regions, comprising the brain’s attentional and executive network, increased significantly, compared to attending to either modality alone. Findings from the sleep deprivation session indicate that specific brain regions, located in the parietal cortices, and other sensory and motor regions, (temporal and cerebellum), increase activation, compared to after normal sleep. Behavioural performance following sleep loss was no different to that after normal sleep. This increased parietal activation has also been demonstrated in previous sleep
deprivation studies (Drummond, 2001), and may reflect a compensatory brain region which is activated during higher demand situations, to aid task performance. If this compensatory response fails to occur, for instance when the period of sleep deprivation is extended, or attentional resources are overwhelmed in more task-demanding situations, such as driving, it may lead to a reduction in performance or sensory monitoring. This may be detrimental to a drivers’ ability to drive safely, and could ultimately lead to an accident.

To further investigate the potential causes of sleep-related motor vehicle accidents, the association between sleep deprivation and d-amphetamine on driving-related performance measures was examined. This pilot study examined the effects of a moderate dose of 0.42 mg/kg d-amphetamine as a countermeasure for sleep deprivation. This level of drug produced blood plasma levels within the range found in drivers apprehended for impaired driving, and fatally-injured drivers, however they tended to be much larger than the average level found in such drivers. Subjective sleepiness (KSS, sleepiness symptoms) and mood (VAS) scores were more sensitive to the effects of both sleep deprivation and d-amphetamine, with increased sleepiness and decreased affect reported with sleep deprivation. The negative effects of sleep deprivation on mood and sleepiness ratings were reversed following d-amphetamine administration compared to placebo. This suggested that drivers were able to make introspective assessments of their mood and sleepiness states, and reported improvements in these measures. Subjective ratings of performance were also negatively affected by sleep deprivation. Interestingly, although no performance improvement on the driving simulator was found, participants reported that their driving performance significantly improved following d-amphetamine compared to placebo following sleep deprivation. It was argued that this may indicate an over-estimation of a sleepy individual’s ability or performance following amphetamine use whilst driving, rather than simply an increase in their alertness and attention.

In terms of the cognitive tasks assessed in the current study, the PVT was affected by sleep deprivation, whereas the shorter cognitive tests were unaffected, as reported in Experiment 1. Significant improvements in performance were found following d-amphetamine compared to placebo when drivers were sleep deprived, however these
were restricted to simple reaction time tasks. In sleep deprived individuals, *d*-amphetamine may have differential effects on performance, and subjective sleepiness and mood.

Results from the ERP analyses indicate that early visual and auditory processes were unaffected by sleep deprivation, or *d*-amphetamine. There was, however, a significant reduction in the Auditory Oddball P300 when *d*-amphetamine was consumed compared to placebo, in sleep deprived participants. This may indicate that participants’ in the current study were able to more selectively attend to the target stimulus and reduce processing of the irrelevant stimulus following *d*-amphetamine administration when sleep deprived. These findings support and extend previous studies, which have found that amphetamine improves recognition of the relevant stimulus, and decreases attention to irrelevant stimuli.

The current thesis has highlighted and extended previous literature examining the impact of sleep deprivation on performance. By breaking down the task of driving into its individual components, and examining the impact of sleep loss on each aspect, this thesis has been able to describe where along the information processing chain performance effects occur, and which can potentially cause sleep-related motor vehicle accidents. This thesis has demonstrated that many of these sleep-related neural effects are beyond the conscious control of the driver, and introspectively recognising sleepiness may not be enough to prevent motor vehicle accidents. A clearer understanding of the vulnerabilities of an individual to the effects of sleep deprivation, and awareness of the risks involved when driving following extended wakefulness, will hopefully aid education of drivers and reduce sleep-related motor vehicle accidents.
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Appendix A: Participant Information Sheet

PARTICIPANT INFORMATION SHEET

EEG Control Group

THE EFFECTS OF SLEEP DEPRIVATION AND DEXAMPHETAMINE ON NEUROPSYCHOLOGICAL FUNCTION, DRIVING PERFORMANCE AND BRAIN ACTIVITY IN PROFESSIONAL DRIVERS

Principal Researchers: Associate Professor R. Croft, Professor R.J. Pierce
Associate Researchers: Ms M. Jackson, Dr M. Howard, Dr K. Papafotiou, Dr G. Kennedy

You are invited to take part in a research study looking at the ability of professional drivers to judge the effects of sleepiness and dexamphetamine use on their driving. This Participant Information is 4 pages long. Please make sure you have all four pages.

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 the Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative, friend, your local health worker or your union representative. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from 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 a 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 Forms 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 Committees of Austin Health and Swinburne University.
Purpose of Study

This study will look at the effects of sleepiness on brain activity and on driving performance of professional drivers. Sleepiness impairs performance and increases accident risk. It is not known how sleepiness affects driving performance and brain activity, or if drivers can judge when their performance is deteriorating. This study will address these questions.

Your Involvement in the Study

You will be asked to attend three separate sessions at the sleep laboratory. These sessions will be approximately 1 week apart.

What is involved in each session?

Initial Screening session: The first session will be a brief visit of one hour at Austin Health to discuss the project, have a medical check-up, sign the consent forms, complete some questionnaires about sleep habits, and practice the driving simulator task and neuropsychological tests.

Session 1: This session will take 5 hours, starting at 09:30am and finishing at 3:00pm.
- You will be asked to arrive at the Centre for Neuropsychology at Swinburne University, Hawthorn at 9:30am. A taxi voucher will be provided. You will be asked to provide a urine sample for screening purposes.
- You will then be given a capsule that may or may not improve your performance. There are no side effects associated with the substance you will be asked to take. You will not be told what you have been given. A blood sample will be taken 2 hours later.
- You will then complete some neuropsychological tasks, a 30-minute driving task, and fill in some questionnaires about sleepiness and your performance. This will take 1 hr.
- Following this you will be set-up for brain activity EEG analysis. An electrode cap will be placed on your head, and electrodes will be attached using gel. You will then complete some more tests on a computer screen. This will take about 50 minutes.
- You will then complete a sobriety test and have a second blood test. The study will be finished at around 3:00pm, and a taxi voucher will be provided for your trip home.

Session 2: This session will be an overnight session, starting at 10:00pm in the evening and finishing 2:00pm the next day (16 hours).
- You will arrive at the Austin Health sleep laboratory by taxi at 10:00pm following a normal days’ work. A taxi voucher will be provided.
- You will then need to stay awake all night, monitored by staff at the sleep lab. At about 6:00am the next day a research assistant will drive you to Swinburne University. When you arrive, you will be asked to provide a urine sample.
- You will be given a capsule that may or may not improve your performance. There are no side effects associated with the substance you will be asked to take. You will not be told what you have been given. A blood sample will be taken 2 hours later.
- You will then do some neuropsychological tests, a 30-minute driving task and fill in questionnaires on symptoms of sleepiness and driving impairment. This will take 1 hr.
- Following this you will complete some questionnaires while being set-up for brain activity EEG analysis. An electrode cap will be placed on you head, and electrodes will be attached using gel. You will then complete some more tests on a computer screen. This will take about 50 minutes.
- You will then complete a sobriety test. For these sessions you will remain awake until 2:00pm that afternoon and do some brief tasks and questionnaires. A blood sample will be taken every two hours. There are three blood sample in total.
- You will be given cab charges for your taxi trips to the hospital and from Swinburne.

  o You will need to complete a diary of your sleep pattern for the week leading up to each session.
  o You will need to avoid caffeine, any stimulants and alcohol intake from midday on the day before the study and during the study.
  o You will be given cab charges for your taxi trips to and from the hospital.

**What are the tests?**

**Brain Activity tests (electroencephalography - EEG)** - Brain activity will be measured with the EEG and muscle activity via the EMG while you perform a number of sensory and cognitive tasks. To collect the EEG data, a cap (similar to a bathing cap) containing 32 electrodes is placed over the scalp and a small amount of water-soluble gel is used to ensure a good contact between electrode and scalp. Electrodes are also attached to the nose, below the left eye and behind the ear. All auditory stimuli will be delivered to both ears via ear inserts. These are similar to the ear yellow insertable foam earplugs commonly used for hearing protection, with speakers imbedded in them. You will then complete some tests when you have to respond to sounds, or react to objects on the computer screen. This will take about 50 minutes.

**Sleep Diary** – You will be asked to fill in a diary for the week leading up to each session. In the diary we would like you to record what time you think you went to sleep and woke up, how many hours sleep you got, if you woke during the night, and your caffeine and alcohol intake each day.

**Driving simulation task** – During the study you will do a 30-minute driving simulation task. This is done on a computer, similar to a computer game, with steering wheel and pedals. You have to steer a vehicle on a dark highway, keeping within the speed limit and avoiding other trucks.

**Neuropsychological tests** – A short set of tests will be done to test your reaction time, attention and memory. Most of these tests will be done on a computer, and some will be pen and paper tests. These tests will take about 20 minutes.

**Sleepiness and performance questionnaires** – Four short questionnaires will be filled out to assess your sleepiness and the occurrence of sleep symptoms. There will also be some questionnaires asking you about your performance on the driving simulator, personality and mood.

**Am I suitable to participate?**

Some people may not be suitable to participate in this study. In order to participate, you must meet the following criteria:

**Inclusion criteria**
- Current drivers licence
- Never used dexamphetamine
- Aged between 18 and 65 years
• English first language

Exclusion criteria
- History of cardiovascular disease, hypertension, epilepsy, diabetes, psychiatric illness
- Pregnancy or attempting to become pregnant
- Heavy smokers
- 5 or more caffeinated beverages per day
- Visual impairment that does not correct with glasses

Are there any risks, inconveniences or side effects?
1. You will need the day off following the night without sleep in order to sleep, so you will have to take 2 days off work.
2. Time involvement will include completing a written sleep diary for the week leading up to each session you attend (5 minutes per day); an initial screening session (1 hour) and two experimental sessions (1 x 16 hour session and 1 x 5 hour session).
3. You may experience some pain and bruising from the IV needle used to take blood.

Voluntary Participation
Your participation in the project is entirely voluntary. You have the right to withdraw from the project at any time, without prejudice to your relationship with and treatment by this hospital.

Payment
As re-imbursement for your time commitment to the study, you will be given a cheque of $200 at the completion of the study. Should you withdraw at any time during the study, you will be given part payment according to how long you participated for.

Confidentiality
Results will remain strictly confidential with individuals being identified by a coded number. Neither individuals nor individual results will be identified in publications. Records of the project will be kept under safe storage, locked in a filing cabinet for 15 years after completion. Records may be inspected for purposes of data audit by authorised persons within the institution (ethics committee), or external regulatory body’s. Information collected in this study can be subpoenaed and accessible for court action.

Questions
If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact Mr. Andrew Crowden, Chairman of the Austin Health Human Research Ethics Committee, Phone (03) 5427 0427.
If you have any questions about the project please do not hesitate to contact Ms Melinda Jackson on 03 9496 3871 or 9496 3688. Out of hours you can contact Rob Pierce on 9496 5000.
Appendix B: Consent Form

Consent Form to Participate in Research Control Group - EEG

Title: THE EFFECTS OF SLEEP DEPRIVATION AND DEXAMPHETAMINE ON NEUROPSYCHOLOGICAL FUNCTION, DRIVING PERFORMANCE AND BRAIN ACTIVITY IN PROFESSIONAL DRIVERS

I, ..........................................................., have been invited to participate in the above study, which is being conducted under the direction of Professor Rob Pierce. I understand that while the study will be under his supervision, other relevant and appropriate persons may assist or act on his behalf. My agreement is based on the understanding that the study involves:

- An initial 1 hour visit at Austin Health to discuss the project, sign the consent forms, complete some questionnaires about sleep habits, have a medical check-up, and practice the driving simulator task and neuropsychological tests.

- One half day session starting at 9:30am and finishing at 3:00pm (5.5 hours):
  - I will arrive at Swinburne University at 9:30am by taxi, following a normal nights’ sleep, and provide a urine sample.
  - I will be given a capsule that may or may not improve my performance on the tasks and driving simulator. A blood sample will be taken 2 hours later.
  - I will undertake neuropsychological tests, a 30-minute driving task and report on symptoms of sleepiness and any driving impairment.
  - I will also undergo brain activity analysis via EEG while performing computerised tasks. An electrode cap will be placed on my head, and electrodes will be attached using gel. I will then complete some more tests on a computer screen. This will take about 50 minutes. A second blood sample will then be taken.
  - I will be free to go home by taxi at around 3:00pm.

- One overnight session starting at 10:00pm and finishing at 2:00pm the next day (16hrs):
  - I will arrive at Austin Health sleep laboratory at 10:00pm after a normal days work.
  - I will be required to remain awake all night in the sleep laboratory.
  - At 6:00am I will be taken to Swinburne University by taxi, and provide a urine sample.
  - I will be given a capsule that may or may not improve my performance on the tasks and driving simulator. A blood sample will be taken 2 hours later.
  - I will then do the driving task, neuropsychological tests and questionnaires and EEG analysis. I will remain awake until 2:00pm and complete some brief tasks every 2 hours. Blood samples will be taken every two hours. There will be 3 blood tests in total.
  - I will be given cab charges for my taxi trips to the hospital and from Swinburne.

I will complete a diary of my sleep patterns for the week prior to the session and avoid caffeine intake on the day of the study. I am aware that I will need the day off after the overnight test sessions.
My agreement is based on the understanding that the research study looks at how different parts of the brain work when people perform tasks. The neuropsychological tests and EEG will take about 2 hours all together.

Is this a drug trial? No

The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

- Lack of sleep increases the risk of accidents. In order to minimise this risk, transport will be organised to and from the department.
- Time involvement will include: approximately five minutes per day to complete the sleep diary for one week prior to the overnight session; a single one hour period during a day to complete baseline tests; one 5 hour half-day session, and one 16 hour overnight session. You will need the day off following the night without sleep, in order to sleep (ie. two days off).
- Some participants may experience pain and/or bruising from the IV butterfly needle, used to take blood.
- 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 have read and understand the sections in the attached ‘Participant Information Sheet’ describing the tasks that I may be required to perform, possible risks, inconveniences and discomforts, which have also been explained to me. In particular, I understand that the scanner is noisy and a bit tight for space.
- I have read and understand the sections in the attached ‘Participant Information Sheet’ describing the procedure that will be followed should abnormal findings be discovered in my scans. I understand that because these images are taken only for research purposes, not all abnormalities that might be detectable with MR scans are always seen.
- I understand that I can refuse to consent or withdraw from the study at any time without explanation, and that I can be withdrawn by the Principal Investigator from this study at any time, and this will not affect my access to the best available treatment and care from Austin Health.
- 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:

One copy to be given to participant, one copy filed in participants medical record
Appendix C: Medical Examination Questionnaire

Medical Examination for Participants

Name: ........................................
Date: / /
Doctor: ......................................

Height: cm
Weight: kg
BP:

✓ Current drivers licence
✓ Recreational use of dexamphetamine
  at least weekly for at least 6 months and
  at least three days free from dex per week
  OR
✓ Never used dexamphetamine

Exclusion criteria:

History of cardiovascular disease ........................................
Hypertension ......................................................................
......................................................................................
Epilepsy ...........................................................................
......................................................................................
Diabetes ............................................................................
......................................................................................
Liver disease.....................................................................
......................................................................................
Kidney disease..................................................................
......................................................................................
Anaemia...........................................................................
......................................................................................

Lactose intolerant? yes / no

Psychiatric illness, or illness in immediate family ..................
......................................................................................

Claustrophobia ..............................................................
Pregnancy or attempting to become pregnant

Any surgical procedures? .................................................................
.................................................................................................
.................................................................................................

- Pace maker, cardiac valve, vascular surgery clips
- Inner ear implants
- Eye injury involving metal fragments
- Smoker? ....................................................................................

- < 5 caffeine beverages per day?
- Visual impairment that does not correct with glasses?

---

**Appendix D: Demographics Questionnaire**

**Screening Questionnaire**

Name:  

Date:  

1. Gender:  Male / Female

2. Age:  ........... years
3. BMI: Height …….cm      Weight …………..kg

4. Is English your first language? Yes / No

5. Do you have a current drivers license? Yes / No

6. How many hours do you spend driving for work per week? ……….. hours

7. Are you on any medication? Please list …………………………………

8. Do you drink alcohol? Yes / No

   If yes, how many standard drinks do you consume on workdays?
   How many standard drinks do you consume on weekends? ……………..

9. Do you smoke? Yes / No

   If yes, how many cigarettes do you smoke per day? …………………

10. Do you drink caffienated beverages (i.e. Coffee, tea, cola)? Yes / No

    If yes, how many caffienated drinks do you consume per day? ……….

11. Do you use any stimulants while driving (i.e. amphetamine)? Yes / No

    If yes, how often do you use stimulants? ………………………
    How many days per week do you not use stimulants? ……………..

12. Do you suffer from any of the following?

    - History of cardiovascular disease or stroke
    - Hypertension
    - Epilepsy
    - Diabetes
    - Psychiatric illness
    - Pace maker
    - Claustrophobia
    - Visual impairment that does not correct with glasses

---

**Appendix E: Drug History Questionnaire**

Subject No.
Date:
Time:

282
Drug History Questionnaire

Please fill out the following information about your use of the following substances.
Note: If the questions are not applicable to you please write N/A.

1. Have you ever consumed alcohol?  
   Yes / No
   1.1 When was the last time you consumed alcohol? Please tick a box
   - Hours ago
   - Days ago
   - More than 1 week ago
   - More than a month ago
   - Other. Please specify ___________________________________________________

1.2 How frequently do you consume alcohol? Please tick a box
   - Daily or almost daily
   - One or two times a Week
   - Two or three times a Month
   - Once a month
   - Other. Please specify ___________________________________________________

1.3 How many standard drinks do you typically consume in a drinking session?

1.4 How often during the last year have you needed a drink in the morning to get yourself going after a heavy drinking session? Please tick a box
   - Daily or almost daily
   - Once or twice a Week
   - Two or three times a Month
   - Once a month
   - Other. Please specify ___________________________________________________

1.6 How long have you been drinking alcohol for?

2. Have you ever consumed cannabis (marijuana)?  
   Yes / No
   2.1 When was the last time you consumed cannabis? Please tick a box
   - Hours ago
2.2 How frequently do you consume cannabis? *Please tick a box*

- Daily or almost daily
- One or two times a Week
- Two or three times a Month
- Once a month
- Other. *Please specify*

2.3 When you consume cannabis, how much do you typically have? (i.e. One joint, 3 bongs)

__________________________________________________________

2.4 How long have you or did you use cannabis for?

__________________________________________________________

3. Have you ever consumed amphetamines (speed)?

- Yes / No

3.1 When was the last time you consumed amphetamines? *Please tick a box*

- Hours ago
- Days ago
- More than 1 week ago
- More than a month ago
- Other. *Please specify*

3.2 How frequently do you consume amphetamines? *Please tick a box*

- Daily or almost daily
- One or two times a Week
- Two or three times a Month
- Once a month
- Other *Please specify*

3.3 When you consume amphetamines, how much do you typically have? (i.e. One line, 1 point)

__________________________________________________________

3.4 How long have you or did you use amphetamines for?

__________________________________________________________
4. Have you ever consumed MDMA (Ecstasy)?
   Yes / No

4.1 When was the last time you consumed ecstasy? Please tick a box
   - [ ] Hours ago
   - [ ] Days ago
   - [ ] More than 1 week ago
   - [ ] More than a month ago
   - [ ] Other. Please specify

4.2 How often do you consume ecstasy? Please tick a box
   - [ ] Daily or almost daily
   - [ ] One or two times a Week
   - [ ] Two or three times a Month
   - [ ] Once a month
   - [ ] Other Please specify

4.3 When you consume ecstasy, how many tablets do you typically have?

4.4 How long have you or did you use ecstasy for?

5. Have you ever consumed cocaine?
   Yes / No

5.1 When was the last time you consumed cocaine? Please tick a box
   - [ ] Hours ago
   - [ ] Days ago
   - [ ] More than 1 week ago
   - [ ] More than a month ago
   - [ ] Other. Please specify

5.2 How frequently do you consume cocaine? Please tick a box
   - [ ] Daily or almost daily
   - [ ] One or two times a Week
   - [ ] Two or three times a Month
   - [ ] Once a month
   - [ ] Other Please specify
5.3 When you consume cocaine, how much do you typically have? (i.e. One line, 1 point)


5.4 How long have you or did you use cocaine for?


6. Have you ever consumed heroin?
   Yes / No

6.1 When was the last time you consumed heroin? Please tick a box

☐ Hours ago
☐ Days ago
☐ More than 1 week ago
☐ More than a month ago
☐ Other. Please specify

6.2 How frequently do you consume heroin? Please tick a box

☐ Daily or almost daily
☐ One or two times a Week
☐ Two or three times a Month
☐ Once a month
☐ Other Please specify

6.3 When you consume heroin, how much do you typically have? (i.e. one hit)


6.5 How long have you or did you use heroin for?


7. Have you ever used inhalants (petrol, glue, etc)?
   Yes / No

Please specify what type

7.1 When was the last time you consumed inhalants? Please tick a box

☐ Hours ago
☐ Days ago
☐ More than 1 week ago
☐ More than a month ago
☐ Other. Please specify
7.2 How frequently do you consume inhalants? *Please tick a box*

- [ ] Daily or almost daily
- [ ] One or two times a Week
- [ ] Two or three times a Month
- [ ] Once a month
- [ ] Other *Please specify*

7.3 When you consume inhalants, how much do you typically have?

__________________________________________________________________________________

7.4 How long have you or did you use inhalants for?

__________________________________________________________________________________

*Appendix F: Randomisation Schedules*
### Experiment 1

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<th>Task order</th>
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<th>Session 2</th>
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Appendix G: Sleep Diary

Code number:_________ Please complete this diary of your sleep and work habits for two weeks prior to your sleep study

Each Morning Complete The Following (see example below):
1. Write in the day and date
2. With an arrow pointing down mark the time you got into bed last night
3. With a plain line mark the time you think you fell asleep and woke up in the morning
4. With plain lines, mark times when you woke up and went back to sleep during the night
5. With an arrow pointing up mark when you got out of bed
6. With plain lines mark any naps you have during the day
7. With an X mark hours that you were at work
8. With an A and a number mark the number of glasses of alcohol you had during the day
9. With a C and a number mark the number of cups of coffee, tea or cola you had during the day

| Day | Date | 8 pm | 9 pm | 10 pm | 11 pm | 12 pm | 1 am | 2 am | 3 am | 4 am | 5 am | 6 am | 7 am | 8 am | 9 am | 10 am | 11 am | 12 noon | 1 pm | 2 pm | 3 pm | 4 pm | 5 pm | 6 pm | 7 pm | 8 pm |
|-----|------|------|------|-------|-------|-------|------|------|------|------|------|------|------|------|------|-------|-------|------|------|------|------|------|------|------|------|
| 1   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 2   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 3   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 4   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 5   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 6   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 7   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 8   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 9   |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 10  |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 11  |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 12  |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 13  |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |
| 14  |      |      |      |       |       |       |      |      |      |      |      |      |      |      |      |      |       |       |      |      |      |      |      |      |      |      |

List for question 5 above: did any of the following keep you awake at night
1. Noise in the neighbourhood or house
2. Children
3. Pain
4. Too hot or cold
5. Sleeping partner
6. Mind too active
7. Need to go to the toilet
8. Other
Appendix H: Sleepiness Symptoms Questionnaire

Did you notice any of the following during your last driving session? Please rate how often.
(TICK ONE BOX IN EACH ROW)

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<th>Some of the time</th>
<th>Most of the time</th>
</tr>
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1. Struggling to keep your eyes open
2. Vision becoming blurred
3. Nodding off to sleep
4. Difficulty keeping to the middle of the road
5. Difficulty maintaining the correct speed
6. Mind wandering to other things
7. Reactions were slow
8. Head dropping down
Appendix I: Performance Questionnaire

PERFORMANCE QUESTIONNAIRE

Compared to your first performance on the driving simulator, how would you rate your current performance?

(TICK ONE BOX)

1. □ Significantly impaired
2. □
3. □ Slightly impaired
4. □
5. □ No difference
6. □
7. □ Slightly improved
8. □
9. □ Significantly improved
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.

(TICK ONE BOX)

1. I would continue driving
2. I would continue driving only if pressured 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.

(TICK ONE BOX)

1. I would continue driving
2. I would continue driving only if pressured to do so
3. I would stop driving now even if under pressure to continue
4. I would have stopped driving some time ago
5.
Appendix K: Participant Information Sheet - Experiment 2

PARTICIPANT INFORMATION SHEET

fMRI Experimental Group

THE EFFECTS OF SLEEP DEPRIVATION & DEXAMPHETAMINE ON NEUROPSYCHOLOGICAL FUNCTION, DRIVING PERFORMANCE & BRAIN ACTIVITY IN PROFESSIONAL DRIVERS

Principal Researcher: Professor R.J. Pierce
Associate Researchers: M. Jackson, Dr. G. Kennedy, Dr. M. Howard, Dr K. Papafotiou

You are invited to take part in a research study looking at the ability of professional drivers to judge the effects of sleepiness and dexamphetamine on brain activity. This Participant Information Form is 4 pages long. During the study you will have four Magnetic Resonance Imaging (MRI) brain scans. There is a separate 3-page MRI information sheet that explains the scanning procedure. Please make sure you have all seven pages.

These Participant Information Forms contain detailed information about the research project. Their 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 the Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative, friend, local health worker or your union representative. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from 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 a 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 Forms 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 Austin Health and Swinburne University.
Purpose of the Study

This study will look at the effects of sleepiness and amphetamines on the driving ability of professional drivers and on their brain activity. Sleepiness impairs performance and increases accident risk. Amphetamines are often used by drivers to try to stay awake during times of sleepiness. It is not known how the combination of sleepiness and amphetamine affects driving performance, or if drivers can judge when their performance is deteriorating. This study will address these questions.

Your Involvement in the Study

You will be asked to attend four separate sessions at the sleep laboratory. Each session will be approximately 1 week apart. All participants will be given either dexamphetamine or a sugar capsule during sessions 1, 2, 3 and 4. Neither you nor the researcher will know what capsule you have been given. Some people will not be able to participate if they do not meet all the selection criteria. Exclusion criteria for this study are people:

- With a history of cardiovascular disease, hypertension, epilepsy, diabetes, psychiatric illness
- Who have a pacemaker
- Who are pregnant or attempting to become pregnant
- Who are claustrophobic
- Who smoke
- Who drink 5 or more caffeinated beverages per day
- Who have visual impairment that does not correct with glasses

What is involved in each session?

Sessions 1 & 2: These two sessions will take half a day each, starting at 8:00am and finishing at midday (4 hours).

- You will arrive at the Brain Research Institute at Austin Health by taxi at 8:00am, following a normal night’s sleep. A taxi voucher will be provided. You will be asked to provide a urine sample and will be given a breath test for alcohol.
- You will then be given a capsule that may or may not improve your performance. You will not be told what you have been given. A blood sample will then be taken 2 hours later.
- You will then have an fMRI brain scan while performing two tasks. This will take about 1 hour.
- You will be given a taxi voucher for your trip home at around 12:00pm.

Sessions 3 & 4: These sessions will be overnight sessions, starting at 10:00pm in the evening and finishing 12:00pm the next day (14 hours).

- You will arrive at the Austin hospital sleep laboratory by taxi at 10:00pm following a normal days’ work. A taxi voucher will be provided.
- You will then need to stay awake all night, monitored by staff at the sleep lab. At about 6:00am the next day you will be asked to provide a urine sample and will be given a breath test for alcohol.
- You will be given a capsule that may or may not improve your performance. You will not be told what you have been given. A blood sample will be taken 2 hours later.
- You will then have an fMRI brain scan while performing two tasks. This will take about 1 hour.
• You will be given cab charges for your taxi trips to and from the hospital.

- You will need to complete a diary of your sleep pattern for the week leading up to each session
- You will need to avoid caffeine, any stimulants and alcohol intake from midday on the day before the study and during the study.
- You will be given cab charges for your taxi trips to and from the hospital.

**What are the tests?**

**Brain Scan** – You will have four Magnetic Resonance Imaging (MRI) brain scans during the study. The MR procedure will take about 45 minutes to 1 hour. During this time you will need to remain still on a comfortable padded table that goes into a large tunnel inside the scanner. While you are lying in the scanner, you will do a computerised task that will be displayed on a screen in front of you, and you respond by pressing buttons on a keyboard. You will be able to practice the task before you go in the scanner.

**Sleep Diary** – You will be asked to fill in a diary for the week leading up to each session. In the diary we would like you to record what time you think you went to sleep and woke up, how many hours sleep you got, if you woke during the night, and your caffeine and alcohol intake each day.

**Sleepiness and performance questionnaires** – Four short questionnaires will be filled out to assess your sleepiness and the occurrence of sleep symptoms.

**Are there any risks, inconveniences or side effects?**

You will need the day off following the nights without sleep in order to sleep, ie. you will have to take 2 days off work.

Side effects of amphetamine may include:

- Effects on the heart - Rapid heart rate, heart palpitations, increased blood pressure
- Effects on the brain - restlessness, dizziness, headache, agitation, difficulty sleeping
- Other – dry mouth, unpleasant taste, diarrhoea, constipation, rash, or changes in libido.

A doctor will be available at all times should you require medical attention. The effects of the amphetamines should wear off within a few hours after the study has finished (about 10 hours). If at any time you do not feel well and do not want to complete the study, you are free to withdraw.

Time involvement will include completing a written sleep diary for the week leading up to each session you attend (5 minutes per day) and four experimental sessions (2 x 16 hour sessions and 2 x 5 hour sessions).

You may experience some pain and bruising from the IV needle used to take blood.

The MRI scanner is shaped like a tunnel and is a bit tight for space. Some people find it uncomfortable lying flat in the scanner. The MRI scanner is noisy, but you will be able to
wear headphones.

**Voluntary Participation**
Your participation in the project is entirely voluntary. You have the right to withdraw from the project at any time, without prejudice to your relationship with and treatment by this hospital.

**Payment**
As re-imbursement for your time commitment to the study, you will be given a cheque for $400 at the completion of the study. Should you withdraw at any time during the study, you will be given part payment according to how long you participated for.

**Confidentiality**
Knowledge of any drug use you make known to the researchers will not be disclosed to any other persons, including employees, health workers etc. Results will remain strictly confidential with individuals being identified by a coded number. Neither individuals nor individual results will be identified in publications. Records of the project will be kept under safe storage, locked in a filing cabinet for 7 years after completion. Records may be inspected for purposes of data audit by authorised persons within the institution (ethics committee), or external regulatory body’s.

**Questions**
If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact:

Mr. Stephen Duns,  
Chairman of the Austin Health Human Research Ethics Committee  
Phone (03) 5427 0427

or

The Chair  
Human Research Ethics Committee  
Swinburne University of Technology  
P O Box 218  
HAWTHORN. VIC. 3122  
Phone: (03) 9214 5223

If you have any questions about the project please do not hesitate to contact me on the following numbers: Ms Melinda Jackson: Ph: 03 9214 5143 or 0407 835 887. Out of hours you can contact Prof. Rob Pierce on 9496 5000.
Appendix L: Consent Form - Experiment 2

Consent Form to Participate in Research  Control Group - fMRI

Title: THE EFFECTS OF SLEEP DEPRIVATION AND DEXAMPHETAMINE ON NEUROPSYCHOLOGICAL FUNCTION, DRIVING PERFORMANCE AND BRAIN ACTIVITY IN PROFESSIONAL DRIVERS

I, ..........................................................., have been invited to participate in the above study, which is being conducted under the direction of Prof Rob Pierce. I understand that while the study will be under his supervision, other relevant and appropriate persons may assist or act on his behalf. My agreement is based on the understanding that the study involves:

- **One half-day session** starting at 8:00am and finishing at 12:00pm (4 hours):
  - I will arrive at the Brain Research Institute at Austin Health by taxi at 8:00am, following a normal night’s sleep. A taxi voucher will be provided. I will be asked to provide a urine sample.
  - I will then be given a capsule that may or may not improve my performance. I will not be told what I have been given. A blood sample will be taken 2 hours later.
  - I will have an fMRI brain scan while performing computer tasks.
  - I will complete some questionnaires and a second blood sample will be taken.
  - I will be free to go home by taxi at around 12:00pm.

- **One overnight session** starting at 10:00pm and finishing at 12:00pm the next day (14hrs)
  - I will arrive at Austin Health sleep laboratory by taxi at 10:00pm after a normal days work.
  - I will be required to remain awake all day and all night, in the sleep laboratory.
  - At about 9:00am the next day I will be asked to provide a urine sample, and be given some breakfast.
  - I will be given a capsule that may or may not improve your performance. I will not be told what I have been given. A blood sample will be taken 2 hours later.
  - I will then be taken to the BRI by shuttle bus and have an fMRI brain scan while performing two tasks. This will take about 1 hour.
  - I will complete some questionnaires and a second blood sample will be taken.
  - I will be given cab charges for my taxi trips to and from Austin Health.

- I will complete a diary of my sleep patterns for the week prior to the sessions and avoid caffeine intake on the day of the study. I am aware that I will need the day off after the overnight test session.

My agreement is based on the understanding that the research study looks at how different parts of the brain work when people perform tasks. MR anatomical, angiographic and spectroscopic scans (all different types of pictures) of my brain will be acquired while I am at rest. Functional MRI will be performed while I do specific tasks. I will be in the scanner for up to 60 minutes. After the scanning session, I will be asked to complete an out-of-scanner task and a questionnaire relating to my experience in the scanner. These tests will take about 20 minutes in total.
Is this a drug trial?  No

The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

- Lack of sleep increases the risk of accidents. In order to minimise this risk, transport will be organised to and from the department.
- Time involvement will include: approximately five minutes per day to complete the sleep diary for one week prior to the overnight session; a single one hour period during a day and one 14 hour overnight session. You will need the day off following the night without sleep, in order to sleep (ie. two days off).
- I may experience some pain and bruising from the IV needle used to take blood.
- The MRI scanner is shaped like a tunnel and is a bit tight for space. I might find it uncomfortable lying flat in the scanner. The MRI scanner is noisy, but I will be able to wear headphones.

- 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 have read and understand the sections in the attached ‘Participant Information Sheet’ describing the tasks that I may be required to perform, possible risks, inconveniences and discomforts, which have also been explained to me. In particular, I understand that the scanner is noisy and a bit tight for space.
- I have read and understand the sections in the attached ‘Participant Information Sheet’ describing the procedure that will be followed should abnormal findings be discovered in my scans. I understand that because these images are taken only for research purposes, not all abnormalities that might be detectable with MR scans are always seen.
- I understand that I can refuse to consent or withdraw from the study at any time without explanation, and that I can be withdrawn by the Principal Investigator from this study at any time, and this will not affect my access to the best available treatment and care from Austin Health.
- 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:

One copy to be given to participant, one copy filed in participants medical record
You are invited to take part in a research study looking at the ability of professional drivers to judge the effects of sleepiness and dexamphetamine use on their driving. This Participant Information and Consent Form is 6 pages long. Please make sure you have all six pages.

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 the Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative, friend, local health worker or your union representative. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from 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 a 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 Forms 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 at Austin Health and Swinburne University.

Purpose of the Study

This study will look at the effects of sleepiness and amphetamines on the driving ability and brain activity of professional drivers. Sleepiness impairs performance and increases accident risk. Amphetamines are often used by drivers to try to stay awake during times of sleepiness. It is not known how the combination of sleepiness and amphetamine affects
driving performance, or if drivers can judge when their performance is deteriorating. This study will address these questions.

**Your Involvement in the study**

You will be asked to attend four separate sessions, and one medical examination and practice session. Each session will be approximately 1 week apart. All participants will be given either dexamphetamine or a sugar capsule during sessions 1, 2, 3 and 4. Neither you nor the researcher will know what capsule you have been given.

**What is involved in each session?**

**Initial screening:** The first session will be a brief visit of one hour at Austin Health to discuss the project, then sign the consent forms, complete some questionnaires about sleep habits, have a medical check-up, and practice the driving simulator task and neuropsychological tests.

**Sessions 1 & 2:** These two sessions will take half a day each, starting at 9:30am and finishing at 3:00pm (5.5 hours).
- You will arrive at the Centre for Neuropsychology at Swinburne University by taxi at 7:00am, following a normal night’s sleep. You will be asked to provide a urine sample.
- You will then be given a capsule that may or may not improve your performance. You will not be told what you have been given. A blood sample will then be taken 2 hours later.
- You will then do some neuropsychological tests, a 30-minute driving task and fill in questionnaires on symptoms of sleepiness and any driving impairment. Video monitoring will be performed whilst doing the driving test. This will take about 1 hour.
- Following this you will be set-up for brain activity EEG analysis. An electrode cap will be placed on you head, and electrodes will be attached using gel. You will then complete some tests on a computer screen. This will take about 45 minutes.
- You will then complete a sobriety test and have a second blood test. You will be given a taxi voucher for your trip home at around 3:00pm.

**Sessions 3 & 4:** These sessions will be overnight sessions, starting at 10:00pm in the evening and finishing 3:00pm the next day (17 hours).
- You will arrive at the Austin hospital sleep laboratory by taxi at 10:00pm following a normal days’ work. A taxi voucher will be provided.
- You will then need to stay awake all night, monitored by staff at the sleep lab. At about 6:00am the next day you will be taken to Swinburne University by taxi. When you arrive, you will be asked to provide a urine sample.
- You will be given a capsule that may or may not improve your performance. You will not be told what you have been given. A blood sample will be taken 2 hours later.
- You will then do some neuropsychological tests, a 30-minute driving task and fill in questionnaires on symptoms of sleepiness and any driving impairment. Video monitoring will be performed whilst doing the driving test. This will take about 1 hour.
- Following this you will complete some questionnaires while being set-up for brain activity EEG analysis. An electrode cap will be placed on you head, and electrodes will be attached using gel. You will then complete some more tests on a computer screen. This will take about 45 minutes.
- You will then complete a sobriety test. For these sessions you will remain awake until 3:00pm that afternoon and do some brief tasks and questionnaires. A blood sample will be taken every two hours. There will be three blood samples in total.
- You will be given cab charges for your taxi trips to the hospital and from Swinburne.
• You will need to complete a diary of your sleep pattern for the week leading up to each session.
• You will need to avoid caffeine, any stimulants and alcohol intake from midday on the day before the study and during the study.
• We need you to stop taking any amphetamines for three days before each session.
• You will be given cab charges for all your taxi trips to and from the hospital.

What are the tests?

Brain Activity tests (electroencephalography - EEG) - Brain activity will be measured with the EEG and muscle activity via the EMG while you perform a number of sensory and cognitive tasks. To collect the EEG data, a cap (similar to a bathing cap) containing 32 electrodes is placed over the scalp and a small amount of water-soluble gel is used to ensure a good contact between electrode and scalp. Electrodes are also attached to the earlobes, and four individual electrodes placed near your eyes. Heart rate will be recorded via two electrodes placed on the left side of the chest, which you can attach yourself. All auditory stimuli will be delivered to both ears via EAR inserts. These are similar to the EAR yellow insertable foam earplugs commonly used for hearing protection, with speakers imbedded in them. You will then complete some tests when you have to respond to sounds, or react to objects on the computer screen. This will take about 45 minutes.

Sleep Diary – You will be asked to fill in a diary for the week leading up to each session. In the diary we would like you to record what time you think you went to sleep and woke up, how many hours sleep you got, if you woke during the night, and your caffeine and alcohol intake each day.

Driving simulation task – During the study you will do a 30-minute driving simulation task. This is done on a computer, similar to a computer game, with steering wheel and pedals. You have to steer a vehicle on a dark highway, keeping within the speed limit and avoiding other trucks.

Neuropsychological tests – A short set of tests will be done to test your reaction time, attention and memory. Most of these tests will be done on a computer, and some will be pen and paper tests. These tests will take about 1 hour.

Sleepiness and performance questionnaires – Four short questionnaires will be filled out to assess your sleepiness and the occurrence of sleep symptoms. There will also be 2 questionnaires asking you about your performance on the driving simulator.

Am I suitable to participate?

Some people may not be suitable to participate in this study. In order to participate, you must meet the following criteria:

Inclusion criteria
• Current drivers licence
• Current user of amphetamines
• Aged between 18 and 65 years
• English first language

Exclusion criteria
• History of cardiovascular disease, hypertension, epilepsy, diabetes, psychiatric illness
- Pregnancy or attempting to become pregnant
- Heavy Smokers
- 5 or more caffeinated beverages per day
- Visual impairment that does not correct with glasses

**Are there any risks, inconveniences or side effects?**

4. You will need to take the day off following the nights without sleep in order to sleep, ie. You will have to take 2 days off work. We can arrange for your study to be on a Friday so you have the weekend to recover, and won’t miss work.

5. Amphetamine is a drug of addiction. Side effects of amphetamine may include:
   - Effects on the heart - Rapid heart rate, heart palpitations, increased blood pressure
   - Effects on the brain - restlessness, dizziness, headache, agitation, difficulty sleeping
   - Other – dry mouth, unpleasant taste, diarrhoea, constipation, rash, changes in libido

A doctor will be available at all times should you require medical attention. The effects of the amphetamines should wear off within a few hours after the study has finished (about 10 hours). If at any time you do not feel well and do not want to complete the study, you are free to withdraw.

6. Time involvement will include completing a written sleep diary for the week leading up to each session you attend (5 minutes per day); an initial screening session (1 hour) and four experimental sessions (2 x 17 hour session and 2 x 5.5 hour session).

7. You may experience some pain and bruising from the IV needle used to take blood.

**Voluntary Participation**

Your participation in the project is entirely voluntary. You have the right to withdraw from the project at any time, without prejudice to your relationship with and treatment by this hospital.

**Payment**

As re-imbursement for your time commitment to the study, you will be given a cheque for $400 at the completion of the study. Should you withdraw at any time during the study, you will be given part payment according to how long you participated for.

**Confidentiality**

Knowledge of any drug use you make known to the researchers will not be disclosed to any other persons, including employees, health workers etc. Results will remain strictly confidential with individuals being identified by a coded number. Neither individuals nor individual results will be identified in publications. Records of the project will be kept under safe storage, locked in a filing cabinet for 15 years after completion. Records may be inspected for purposes of data audit by authorised persons within the institution (ethics committee), or external regulatory body’s. Information can be subpoenaed for court action.

**Questions**

If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact Mr. Andrew Crowden, Chairman of the Austin Health HREC Phone (03) 9496 2901. If you have any questions about the project please do not hesitate to contact Ms Melinda Jackson on 03 9214 534.
Appendix N: Consent Form - Experiment 3

**Title:** THE EFFECTS OF SLEEP DEPRIVATION AND DEXAMPHETAMINE ON NEUROPSYCHOLOGICAL FUNCTION, DRIVING PERFORMANCE AND BRAIN ACTIVITY IN PROFESSIONAL DRIVERS

I, ..........................................................., have been invited to participate in the above study, which is being conducted under the direction of Professor Rob Pierce. I understand that while the study will be under his supervision, other relevant and appropriate persons may assist or act on his behalf. My agreement is based on the understanding that the study involves:

- An initial 1 hour visit at Austin Health to discuss the project, sign the consent forms, complete some questionnaires about sleep habits, have a medical check-up, and practice the driving simulator task and neuropsychological tests.
- Two half-day sessions, starting at 9:30am until 3:00pm (5.5 hrs).
  - I will arrive at Swinburne University at 7:00am by taxi, following a normal nights’ sleep, and provide a urine sample.
  - I will be given a capsule that may or may not improve my performance on the tasks and driving simulator. A blood sample will be taken 2 hours later.
  - I will complete some neuropsychological tests, a 30-minute driving task and report on symptoms of sleepiness and any driving impairment. This will take 1 hour.
  - I will also undergo brain activity analysis via EEG while performing computerised tasks. An electrode cap will be placed on my head, and electrodes will be attached using gel. This will take 45 minutes.
  - I will be free to go home by taxi at around 3:00pm.
- Two overnight sessions, starting at 10:00pm and finishing at 3:00pm the next day (17 hrs).
  - I will arrive at Austin Health sleep laboratory at 10:00pm after a normal days work, and provide a urine sample.
  - I will be required to remain awake all night in the sleep laboratory.
  - At 6:00am I will be taken to Swinburne University by taxi. I will be asked to provide a urine sample for screening purposes.
  - I will be given a capsule that may or may not improve my performance on the tasks and driving simulator. A blood sample will be taken 2 hours later.
  - I will then do the driving task, neuropsychological tests, questionnaires and EEG analysis.
  - I will then remain awake until 2:00pm and complete some brief tasks. A blood sample will be taken every two hours. There will be 3 blood tests in total.
    - I will be given cab charges for my taxi trips to Austin Health and from Swinburne.
  - I will complete a diary of my sleep patterns for the week prior to each session and avoid caffeine intake on the day of the study. I am aware that I will need the day off after the two overnight test sessions.

My agreement is based on the understanding that the research study looks at how different parts of the brain work when people perform tasks. The neuropsychological tests and EEG will take about 2 hours all together.
Is this a drug trial?  YES.

I understand I will receive the following drug: dexamphetamine in a dose of 0.42mg per kg body weight. I understand that my participation will assist the investigators in determining the effects of the drug, and that there may be no direct benefit to me.

The study may involve the following risks, inconvenience and discomforts, which have been explained to me:

- Lack of sleep increases the risk of accidents. In order to minimise this risk, transport will be organised to and from the department.
- Time involvement will include: approximately five minutes per day to complete the sleep diary for one week prior to each study session; a single one hour period during a day to complete baseline tests; two 16-hour overnight sessions and two 5-hour day sessions. You will need the day off following the night without sleep, in order to sleep.
- Side effects of amphetamine may include:
  - Effects on the heart - Rapid heart rate, heart palpitations, increased blood pressure
  - Effects on the brain - restlessness, dizziness, headache, agitation, difficulty sleeping
  - Other – dry mouth, unpleasant taste, diarrhoea, constipation, rash, or changes in libido.
  - A doctor will be available at all times should you require medical attention. The effects of the amphetamines should wear off within a few hours after the study has finished (about 10 hours). If at any time you do not feel well and do not want to complete the study, you are free to withdraw.
  - Some participants may experience pain and/or bruising from the IV butterfly needle, used to take blood.
- 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 have read and understand the sections in the attached ‘Participant Information Sheet’ describing the tasks that I may be required to perform, possible risks, inconveniences and discomforts, which have also been explained to me. In particular, I understand that the scanner is noisy and a bit tight for space.
- I have read and understand the sections in the attached ‘Participant Information Sheet’ describing the procedure that will be followed should abnormal findings be discovered in my scans. I understand that because these images are taken only for research purposes, not all abnormalities that might be detectable with MR scans are always seen.
- I understand that I can refuse to consent or withdraw from the study at any time without explanation, and that I can be withdrawn by the Principal Investigator from this study at any time, and this will not affect my access to the best available treatment and care from Austin Health.
- 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:

One copy to be given to participant, one copy filed in participants medical records
The final ethics approval form is included on the following page. All conditions pertaining to the clearance were properly met, and the annual and final reports have been submitted to the ethics committee.