The Acute Effects of \textit{d}-amphetamine and Methamphetamine on Simulated Driving Performance, Cognitive Functioning, Brain Activity, and the Standardised Field Sobriety Tests

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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: (Yvonne) Beata Silber

Signed: ________________________________
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Publications Arising from this Thesis


Abstract

Recently there has been an increase in awareness of the role of drugs other than alcohol in the causation of road accidents and deaths, with the most recent report indicating that 33% of all Victorian (Australia) road fatalities are drug (other than alcohol) related (TAC, 2006). Currently in Victoria, one of the classes of drugs reported to be of most concern is the amphetamines. The epidemiological driving literature highlights a possible association between amphetamine use and road crashes. However, since the cognitive research generally indicates cognitive enhancing properties following amphetamine consumption, it remains unclear how amphetamines may be related to adverse driving. The present thesis was designed to explore this issue.

In response to the increasing number of drug-related road fatalities, the Standardised Field Sobriety Tests (SFSTs), designed and validated for the detection and assessment of impairment associated with alcohol intoxication, are currently being employed by the Victoria Police (Australia) for the identification of driving impairment associated with drugs other than alcohol. The present thesis was designed to evaluate whether the SFSTs are a sensitive measure for identifying impairment associated with a single acute therapeutic amphetamine dose. Furthermore, the accuracy of using the SFSTs to detect driving impairment associated with these amphetamine doses was also evaluated.

The present thesis examined the effects of a single acute therapeutic dose of various amphetamine preparations, on simulated driving performance, driving-related cognitive processes (assessed using standard cognitive tasks and the electroencephalogram [EEG]), and performance on the SFSTs, in healthy, stimulant-using, non-fatigued adults. The present thesis consisted of five separate experiments. The first three experiments examined the effects of d-amphetamine, d,l-methamphetamine, and d-methamphetamine, on simulated driving performance, driving-related cognitive processes, and performance on the SFSTs. Experiment 4 and Experiment 5 assessed the effects of d-amphetamine and d-methamphetamine on visual and auditory cognitive processes using the EEG. These forms of amphetamines were selected as they are commonly used recreationally by young adult drivers, and occupationally by truck drivers.
Experiment 1, Experiment 2, and Experiment 3 employed a repeated-measures, counter-balanced, double blind, placebo-controlled design. In each experiment, twenty different (i.e. 60 participants in total) healthy volunteers (10 males and 10 females) completed two treatment conditions i) placebo and ii) 0.42mg/kg amphetamine (~30mg). Driving performance was assessed using a driving simulator task, which consisted of four driving tasks; ‘freeway traffic driving’ and ‘city traffic driving’ in both day and night conditions. Cognitive performance was assessed using a range of computer and pen and paper tasks designed to assess attention, psychomotor performance, and perceptual speed. Specifically, the tasks were: the Digit Span Test; aDigit Vigilance task; a Movement Estimation Task; the Digit Symbol Substitution Test; a Tracking Task; the Trail-Making Test; and the Inspection Time task. SFSTs performance was assessed using the Horizontal Gaze Nystagmus (HGN) test, the Walk and Turn (WAT) test, and the One Leg Stand (OLS) test. Three blood and saliva samples were obtained throughout all experimental sessions (120, 170, and 240 minutes after drug administration).

The results indicated that 0.42mg/kg \( d \)-amphetamine significantly impaired simulated driving performance, in recreational stimulant users, 2-3 hours post-drug administration, when mean blood amphetamine concentrations were approximately 90ng/mL. No significant driving decrements were observed following \( d,l \)-methamphetamine or \( d \)-methamphetamine, when methamphetamine blood concentrations were 90ng/mL and 70ng/mL, respectively. There were only few driving behaviours that were found to be significantly reduced with \( d \)-amphetamine, such as reductions in signalling adherence and driving too fast for the traffic conditions. However, during all three amphetamine conditions, drivers travelled at a slower speed on the freeway at the time that an emergency situation occurred, relative to the placebo condition. It was argued that either this may result from more cautious driving, or that the reduction in speed acted as a compensatory mechanism to permit drivers to attend to other aspects of driving. Overall, the present results indicate that a therapeutic dose of amphetamine does not produce considerable impairment to driving, as only minimal amphetamine effects were observed on driving performance.

In terms of cognitive performance, the results indicated that a therapeutic dose of various amphetamines has minimal effect on driving-related cognitive functioning, with some significant improvements noted in aspects of attention, psychomotor functioning and
perceptual speed. This is consistent with the failure to identify significant driving impairments, described above, following a similar dose. However, the ability to perceive and predict motion and estimate ‘time to contact’, assessed using a movement estimation task, was affected following \textit{d}-amphetamine and \textit{d}-methamphetamine consumption.

In terms of performance on the SFSTs, the present thesis demonstrated that following the administration of low-level \textit{d}-amphetamine, \textit{d,\textit{l}}-methamphetamine, and \textit{d}-methamphetamine, performance on the SFSTs was not impaired. Using the SFSTs, impairment associated with low dose \textit{d}-amphetamine was identified in only 5\% of cases, \textit{d}-methamphetamine in 5\% of cases, and \textit{d,\textit{l}}-methamphetamine in 0\% of cases. These findings indicate that the degree of impairment produced with the low amphetamine dosing conditions was below the threshold of sensitivity of the SFSTs. However, as significant impairments in driving were not observed with amphetamines, the present SFSTs findings highlight that these tests are unlikely to produce false positive results during police drug evaluation procedures for amphetamine-related impairments.

Experiment 4 and Experiment 5 similarly employed a repeated-measures, counter-balanced, double blind, placebo-controlled design. In each experiment, twenty healthy volunteers (10 males and 10 females) completed two treatment conditions i) placebo and ii) 0.42mg/kg amphetamine (~30mg). Tasks designed to assess visual and auditory cognitive functions relevant to driving were administered. Specifically, these processes were: divergent visual system pathways (magnocellular and parvocellular pathways); aspects of visual field processing (central and peripheral visual fields); mismatch negativity (MMN); prepulse inhibition (PPI); selective attention; resource allocation; and speed of processing. Two blood and saliva samples were obtained throughout all experimental session (120 and 200 minutes after drug administration).

\textit{d}-amphetamine and \textit{d}-methamphetamine generally improved cognitive functioning, as assessed with visual and auditory ERP indices. Specifically, the results demonstrated that a low-level acute dose of \textit{d}-amphetamine and \textit{d}-methamphetamine improved early processing of visual information (indexed by improvements to the P100 component for the magnocellular and parvocellular visual pathways). In addition, \textit{d}-methamphetamine improved the speed at which visual information was evaluated and processed (indexed by decreases in P300 latency), which was consistent with \textit{d}-methamphetamine-related
improvements in reaction time. There was a trend for \textit{d}-amphetamine to improve the speed that changes in auditory stimulation were automatically detected (indexed by decreases in MMN latency). In addition, \textit{d}-methamphetamine improved the ability to automatically ‘screen out’ irrelevant and intrusive auditory information (indexed by increases in PPI of the startle response). \textit{d}-amphetamine was found to improve the speed at which auditory information was evaluated and processed (indexed by decreases in P300 latency), which was substantiated with corresponding improvements in reaction time and accuracy.

Although amphetamines were generally shown to enhance ERP indices, a trend was found for \textit{d}-amphetamine to differentially affect different regions of the visual field, in terms of selective attention. Specifically, there was a trend-level indication that \textit{d}-amphetamine improved indices of selective attention (denoted by increases in N200 amplitude) for information presented centrally, but impaired indices of selective attention (denoted by decreases in N200 amplitude) for information presented in the periphery. Although impairments to the peripheral visual field were not similarly observed with \textit{d}-methamphetamine, decrements to indices of selective attention (denoted by decreases in N200 amplitude) were also found with \textit{d}-methamphetamine during the auditory oddball task. In terms of driving, these results suggest that drivers dosed with low-level amphetamine may not selectively attend to and discriminate changes within the traffic environment, although further research is required to confirm this.

In conclusion, the present thesis has demonstrated that a single acute therapeutic dose of amphetamine produces minimal and inconsistent effects to driving. However, some (inconsistent) evidence was found that suggests that there may be mild impairments such as decreased ability to perceive and predict motion, tunnel vision effects, and decrements to selective attention. In addition, the present thesis highlights that at therapeutic doses, amphetamines do not impair SFSTs performance, which is in accordance with the failure to identify substantive amphetamine-related decrements to driving and cognitive functioning observed in the present thesis.
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1.1 Drug Related Road Accidents and Deaths in Victoria, Australia

Over the past 50 years the number of road accidents and deaths has been documented in Victoria, Australia, and more recent research has reported road crashes specifically associated with the presence of alcohol and other drugs (Drummer, 1994; Drummer, 1998; Drummer & Gerostamoulos, 1999; Drummer et al., 2003ab). Currently in Victoria the drugs reported to be of most concern are alcohol, cannabis, amphetamines and other stimulants, benzodiazepines, and opiates (Road Safety Committee, Parliament of Victoria, 2005).

Since 1989 there has been an overall decrease in the Victorian road toll by more than half, from 776 in 1989 to 346 in 2005 (Transport Accident Commission (TAC), 2006). Over these years alcohol has been considered to be a leading contributor to road fatalities (Drummer et al., 2003b). However, as a result of the introduction of specific countermeasures aimed at reducing the number of alcohol-related road fatalities, such as random breath testing, education programs, and mass media campaigns, there has been a significant decrease in the number of alcohol related road incidents in Victoria (TAC, 2006). This is clearly illustrated in the road fatality statistics, where in 1987 38% of drivers killed on Victorian roads were under the influence of alcohol (blood alcohol level 0.05% or above), whereas in 2004 this figure decreased to 23% (TAC, 2006).

Although alcohol related road crashes have reduced considerably, over the last decade there has been an increase in the role of drugs other than alcohol in road crashes and deaths (Drummer et al., 2003ab). This is exemplified in the road fatality statistics, where from 1990 to 1993, 22% of all Victorian drivers killed tested positive for the presence of drugs other than alcohol (where 9.6% involved cannabis, 3.9% amphetamines and other stimulants, 4.5% benzodiazepines, and 3.3% opioids), whereas this percentage increased to 33% in 2004 (where 12.6% involved cannabis, 4.9% amphetamines and other stimulants, 4.4% benzodiazepines, and 7.1% opioids) (Drummer, 1994, 1998; TAC, 2006). These recent figures indicate that drugs other than alcohol are present in over one quarter of Victorian driver fatalities, and more alarmingly, the percentage of drug-related road fatalities (other than alcohol) has surpassed that of alcohol-related fatalities.
Considerable attention has recently been directed to the issue of the presence of amphetamine in drivers involved in road crashes. In truck drivers, in particular, amphetamine use has become a major issue of public concern following a recent report indicating that 23% of Australian truck drivers involved in fatal crashes tested positive to stimulants (Drummer et al., 2003a). This is an alarming figure considering that 20% of Australian road deaths involve heavy vehicles (Australian Transport Safety Bureau, 2004).

While the road fatality statistics indicate a possible association between amphetamine use and road crashes, it is difficult on this evidence alone to infer that amphetamine use ‘causes’ these road fatalities. For instance, there are other factors that may be associated with amphetamine-related road crashes, such as fatigue caused by excessive sleep loss (resulting from amphetamine use), or the “withdrawal” or “crash” phase following several days of amphetamine binging, that can result in fatigue, exhaustion, restlessness, and possible psychosis (Logan, 2002). It is therefore necessary to investigate how the acute effects of amphetamine affect driving performance and specific cognitive functions involved in the process of driving, in order to clarify how amphetamine may be associated with road fatalities.

1.2 Research Question

Determining the relationship between drug consumption and driving impairment is intrinsically fraught with difficulties. The effects of amphetamine on driving ability are generally investigated using two approaches. The first approach is to examine the epidemiology of drivers involved in traffic violations. Epidemiological studies provide the most accurate representation of driving patterns in situ, however, as they lack experimental control, inferring causation remains problematic. Thus, although epidemiological studies provide evidence of an association of drugs with crashes, these methods cannot establish that drug use ‘causes’ adverse driving events. In contrast, the second approach, the experimental approach, allows researchers to examine the acute effects of amphetamine on specific processes related to driving. Therefore, these experimental studies have the advantage of greater control over causation, although they may not easily translate to real-life driving situations. Experimental studies typically involve examining the acute effects of amphetamine on driving simulator performance and cognitive processes related to driving. However, the experimental research, hitherto, that has investigated the effects of
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amphetamine on driving performance, and the specific mechanisms involved in this process, is limited and inconsistent with the epidemiological research.

The epidemiological driving literature highlights an association between amphetamine use and road crashes (refer to the previous section 1.1 and Chapter 3 for detail), however, it remains unclear why amphetamine should be related to adverse driving due to the findings from experimental research that generally indicate that amphetamine has cognitive enhancing properties (refer to Chapter 4 for a review of the amphetamine cognitive literature). There are, thus, inconsistencies between the outcomes of these two approaches, as the epidemiological literature indicates possible amphetamine-related impairments in driving ability, whereas the experimental literature suggests amphetamine-related improvements in cognitive processes related to driving.

There are several factors that may explain the inconsistency pertaining to the epidemiological and experimental findings. For instance, the discrepancy may reflect that amphetamine-related road crashes are associated with factors other than acute amphetamine effects, such as fatigue or the “withdrawal” phase, which have not, to the author’s knowledge, previously been examined using the experimental approach. Alternatively, the inconsistency in the literature may be due to the lack of sensitivity in the cognitive testing methods employed. For example, it may be that the sensory and cognitive tasks previously administered are not assessing abilities important to driving, or that impairments related to amphetamine use may be too subtle to be detected in such experimental sessions. In addition, the doses administered in previous cognitive studies may have been too low to observe decrements in cognitive performance.

This thesis will address several of these issues in order to establish how amphetamine use may be associated with road fatalities. Administering tasks that specifically assess driving ability and processes important to driving following the administration of amphetamine may help resolve some of the inconsistencies and ambiguities that exist in the amphetamine literature. Furthermore, employing more sensitive techniques, such as derivations of the electroencephalogram (EEG), may also help clarify these issues (discussed in Chapter 5), and possibly establish if there are particularly subtle neural mechanisms that affect driving performance following amphetamine administration. This thesis will, thus, assess the acute effects of amphetamine on simulated driving performance.
and specific cognitive processes that are important to driving. In addition, this thesis will assess cognitive functioning using the EEG in order to identify the more subtle effects that amphetamine may have on driving performance, but that may not be detected using standard cognitive tasks. It should, however, be noted that due to the toxic nature of the drug, it is ethically problematic to administer amphetamine doses as high as those typically encountered in apprehended and fatally injured drivers. Therefore, the results of the present thesis will represent an evaluation of a single acute therapeutic dose of various amphetamine preparations, which will provide a useful indication of the effects of therapeutic amphetamine doses, and which subsequently may be useful in considering the effects of high amphetamine concentrations on driving. It is also important to note that as the present thesis is employing subtle measures (cognitive tasks and EEG) to investigate the effects of various single therapeutic doses of amphetamine on human functioning, any impairment found may provide useful insight into the possible impairments that may be produced at higher amphetamine concentrations.

Although the experimental literature does not indicate that amphetamine use ‘causes’ road crashes, the epidemiological literature does suggest that there is an association with amphetamine use and road fatalities and that there has been a general increase in the number of drivers driving while intoxicated with amphetamine. This has raised much public and government concern and it is, therefore, necessary that law enforcement strategies aimed at reducing the percentage of drivers driving while under the influence of amphetamine be implemented.

As early as 1967, the Victorian Government (Australia) has enforced driving laws that have resulted in a substantial and sustained decrease in road deaths, including; compulsory wearing of seat belts in 1970; the introduction of random breath testing stations in 1976; radar speed detectors in 1981; red light cameras in 1983; zero blood alcohol content for probationary license drivers in 1984; introduction of high profile “booze” buses in 1990; the establishment of Road Safety Councils in 1991; the introduction of breath analysis instruments in all police vehicles in 1997; implementation of the Standardised Field Sobriety Tests (SFSTs) to detect driving impairment associated with the consumption of a drug other than alcohol in 2000; and finally, more recently, random saliva drug testing in 2004.
Similar to the successful process enforced to reduce the number of drivers operating a motor vehicle while intoxicated with alcohol (i.e. random alcohol breath testing), the SFSTs were introduced in 2000 to detect driving impairment associated with the consumption of a drug other than alcohol. Similar to the rationale for introducing random alcohol breath tests, the SFSTs were implemented as a means of identifying and removing drug-impaired drivers, and deterring drivers from driving after having consumed drugs other than alcohol.

The SFSTs were, however, initially designed specifically for the detection and assessment of alcohol intoxication (Burns & Moskowitz, 1977), and only limited empirical research has been conducted to assess whether the SFSTs are efficient in identifying impairment associated with the consumption of drug/s other than alcohol (refer to Chapter 6 for a review of the literature). Pharmacologically and physiologically the effects of amphetamine on human performance are considerably different to that of alcohol (for example, amphetamine is a central nervous system stimulant, whereas alcohol is a central nervous system depressant). Thus, there is reason to expect that performance on the SFSTs would be different for drivers intoxicated with amphetamine compared to drivers intoxicated with alcohol. Therefore, research needs to be conducted to investigate the efficiency of the SFSTs in identifying impairment associated with amphetamine use in order to determine that the SFSTs are an appropriate measure for detecting amphetamine-related impairment in drivers. Thus, this thesis will test whether using the SFSTs is appropriate for detecting any impairment following a single acute therapeutic dose of amphetamine in drivers.

1.3 Project Aims

In order to address the issues discussed above in section 1.2, the present thesis was designed primarily to assess whether a single acute therapeutic dose of various amphetamine preparations impairs simulated driving performance, and to establish which specific sensory and cognitive processes are affected following the administration of amphetamine in healthy, stimulant-using, non-fatigued adults. To test this, the acute effects of a single therapeutic dose of various amphetamine preparations were tested on simulated driving performance, cognitive processes related to driving, and visual and auditory cognitive processes assessed with the electroencephalogram EEG, using a series of repeated-measures, counter-balanced, double blind, placebo-controlled studies. A second
The aim of the present thesis was to investigate the accuracy of the SFSTs in identifying amphetamine-related impairment in healthy, stimulant-using, non-fatigued adults. To test this, the effects of a single acute therapeutic dose of various amphetamine preparations on SFSTs performance were examined, using a series of repeated-measures, counter-balanced, double blind, placebo-controlled studies. The extent to which the SFSTs successfully identify impairment associated with amphetamine use will provide an indication of the efficiency of these tests in detecting impairment following a single therapeutic dose of amphetamine. However, it should be noted that it is likely that performance on the SFSTs will not be impaired following a single therapeutic dose of amphetamine, as any amphetamine-related impairments associated with these low doses should be far below the threshold of the sensitivity of the SFSTs, which were designed to detect gross impairment. However, as no previous research has investigated the sensitivity of the SFST in detecting impairment following any dose of amphetamine, the present results will provide a useful indication of the sensitivity of the SFSTs at therapeutic doses.

The above experiments were performed with three forms of amphetamine. These were \( d \)-amphetamine, \( d,l \)-methamphetamine, and \( d \)-methamphetamine. These forms of amphetamine were administered as they are commonly used recreationally by young adult drivers and occupationally by truck drivers. Specifically, methamphetamine is considered to be one of the most popular abused stimulants. Within the transport industry, particularly long-distance drivers, methamphetamine has long been used for its function of allowing longer and more sustained work performance. Methamphetamine exists in two isomeric forms, dextro (\( d \)-) and levo (\( l \)-) (Logan, 2002), with the \( d \)-isomer having greater central nervous system potency than the \( l \)-isomer (Hardman & Limbird, 1996). A racemic mixture of methamphetamine (\( d,l \)-) is less potent than the \( d \)-isomeric form and more potent than the \( l \)-isomeric form, however, the symptoms and side effects are similar to that of the \( d \)-methamphetamine. Therefore, the present thesis examined the effects of both \( d \)-methamphetamine and \( d,l \)-methamphetamine. \( d \)-amphetamine is also a commonly used stimulant amongst truck drivers as it is more readily available and easier to self-administer than methamphetamine. Thus, it is for these reasons the present thesis examined the effects of these three forms of amphetamine on human functioning.

In order to simulate as close to real-life amphetamine-induced effects as is ethically viable, the present thesis administered single oral doses of 0.42mg/kg amphetamine as it is one of
the highest approved (by Research Ethics Committees) doses administered to humans for controlled experimental research purposes. It is important to note that although low range concentrations of amphetamines are found in apprehended and fatally injured drivers (Logan et al., 1998; Drummer et al., 2003a), this generally results from the withdrawal phase of the drug, and thus the effect profile is considerably different to that of the present study. Therefore, although there will be some overlap in blood amphetamine concentrations in the present thesis with those seen recreationally, a claim of parity for these two groups is not warranted.

1.4 Hypotheses
As there has been limited research that has investigated the acute effects of amphetamine on performance, few specific hypotheses were generated in the present thesis. For most aspects of the thesis the research was exploratory. Specifically,

- It was predicted that a single acute therapeutic dose of amphetamine would impair overall simulated driving performance. However, no hypotheses were made as to the effect of amphetamine on specific driving behaviours. These latter analyses were exploratory.

- No specific hypotheses were made in terms of the effects of a single acute therapeutic dose of amphetamine on standard cognitive tasks measuring attention, psychomotor performance and perceptual speed, as previous research has generally administered doses considerably lower than the average dose administered in the present thesis. Therefore, it was not clear whether the dose administered in the present thesis would improve cognitive performance (as has previously been reported), or impair cognitive performance due to the inverted-U response (which suggests that when an individual passes a critical level of dopamine tone, aspects of cognitive functioning become impaired).

- As there have been limited investigations that have explored the effects of a single acute therapeutic dose of amphetamine on visual and auditory cognitive functions using EEG, no hypotheses were made as to the specific effects of acute amphetamine on cognitive functioning using the EEG.
• Finally, it was predicted that following a single acute therapeutic dose of amphetamine, performance on the SFSTs would not be impaired.
Chapter 2. Amphetamine

2.1 What is Amphetamine?
Amphetamines are popular recreational drugs that have some legitimate therapeutic properties, but are primarily drugs of abuse. The amphetamines are commonly abused for their central nervous system stimulant properties that induce profound behavioural effects. Their ability to enhance mood, energy and alertness characterises their actions, as does their ability to cause depression and fatigue during the withdrawal phase (1-7 days).

Amphetamine was first synthesised in 1887, but it was not until the 1920s that its use as a nasal decongestant was recognised. A few years later, its benefits were further recognised in its ability to combat fatigue, suppress appetite, and treat narcolepsy and hyperactivity in children. However, by the 1940s, its potential for abuse became apparent and it is now generally classed as a drug of abuse with some therapeutic value (Logan, 2002).

damphetamine and methamphetamine are two of the more commonly known amphetamines. Methamphetamine is considered to be a more potent central psychostimulant than d-amphetamine (Shoblock et al., 2003). A brief summary of the chemistry, pharmacology, pharmacokinetics, and pharmacodynamics of these drugs are discussed in sections 2.1.1 and 2.1.2.

2.1.1 d-amphetamine
d-amphetamine is a stimulant drug often prescribed in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

ADHD is a common childhood behavioural disorder, which is characterised by problems with attention, hyperactivity, and impulsivity. d-amphetamine is often used as an integral component of treatment programs, typically in combination with psychological, educational, or social measures, for a stabilizing effect in children exhibiting the relevant symptoms. d-amphetamine is prescribed to treat the behavioural and cognitive impairments associated with ADHD, such as, inattention and restlessness (Fillmore et al., 2005), with daily oral doses of d-amphetamine (Dexamphetamine Tablets) that range from 2.5 to 40mg (typically administered in two divided doses) (MIMS, 2002).
Narcolepsy is principally characterized by a permanent and overwhelming feeling of sleepiness and fatigue. Other symptoms involve abnormalities of dream sleep, such as, dream-like hallucinations and finding oneself physically weak or paralysed for a few seconds. The symptom of sleepiness is generally treated with daily oral doses of \(d\)-amphetamine (Dexamphetamine Tablets) that range from 5 to 60mg (administered in divided doses) for optimal response (MIMS, 2002).

2.1.1.1 Chemistry

Dexamphetamine Tablets contain the dextro isomer of \(d,l\)-amphetamine sulphate. The chemical name for \(d\)-amphetamine is (s)-alpha-methylphenethylamine sulphate with a molecular formula of \((C_{19}H_{13}N)_{2}H_{2}SO_{4}\) and a molecular weight of 368.5 (MIMS, 2002). It is soluble in approximately 1:10 in water, 1:500 in alcohol 95% and readily soluble in acids (MIMS, 2002). The chemical structure is represented in Figure 2.1.

![Figure 2.1 d-amphetamine Chemical Structure](image)

2.1.1.2 Pharmacology

The pharmacology of amphetamines is complex and involves both central and peripheral actions. \(d\)-amphetamine is a non-catecholamine, sympathomimetic amine with central nervous system (CNS) stimulant activity (MIMS, 2002). The most typical action of \(d\)-amphetamine is to facilitate the action of dopamine and norepinephrine by blocking re-uptake from the synapse, inhibiting the action of monoamine oxidase (MAO), and facilitating the release of dopamine and noradrenaline (Feldman et al., 1997). Amphetamines also increase synaptic levels of the neurotransmitter serotonin, however, its influence on mood and behaviour is thought to result primarily through the enhancement of dopamine and norepinephrine activity (Servan-Shreiber et al., 1998). Peripherally, \(d\)-amphetamine stimulates both alpha and beta-adrenergic receptors (MIMS, 2002). Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action (MIMS, 2002). It causes pronounced
stimulation of the cortex and the respiratory and vasomotor centres. It increases motor activity, mental activity, wakefulness and produces euphoria (MIMS, 2002).

2.1.1.3 Pharmacokinetics

*d*-amphetamine is generally well absorbed orally, which is the major route of administration. Following oral ingestion, peak blood concentrations of *d*-amphetamine occur generally within 2-4 hours (Angrist *et al.*, 1987; Kupietz *et al.*, 1985; Brauer *et al.*, 1996; MIMS, 2002) (varying with the degree of physical activity and the amount of food in the stomach). *d*-amphetamine is readily absorbed from the gastrointestinal tract and rapidly distributed into most of the body tissues. *d*-amphetamine is concentrated in the brain, lung and kidneys (MIMS, 2002). Protein-binding and volume of distribution varies widely, but the average volume of distribution (distribution of amphetamine throughout the body) is 2-3L/Kg body weight (MIMS, 2002). Thirty to forty percent is metabolised by the liver. The remainder is excreted directly by the kidneys (MIMS, 2002). The approximate plasma half life is 10.25 hours (MIMS, 2002), however, excretion of *d*-amphetamine is pH dependant, where it is excreted rapidly if urine is acidic and slowed if urine is alkaline. At normal urinary pH, approximately 30% of an oral dose is excreted unchanged. The half-life is 16-31 hours in urine with a pH greater than 7.5 and decreases to 6-8 hours when the urinary pH is 5.0 or less. The average urinary recovery (return to normal urine conditions) is 45% within 48 hours (MIMS, 2002).

2.1.1.4 *d*-amphetamine Levels in Blood

Research has shown that levels of *d*-amphetamine in plasma, when administered orally, peak at approximately 2-4 hours post-administration (Kupietz *et al.*, 1985; Angrist *et al.*, 1987; Brauer *et al.*, 1996; Mills *et al.*, 2001), and subsequently drop at 5 hours after *d*-amphetamine administration (Angrist *et al.*, 1987; Brauer, *et al.*, 1996). This variability in time of plasma level appears to be associated with the dose of amphetamine consumed. Angrist *et al.* (1987) reported that peak plasma level occurred at 2-3hr in a low-dose group (0.25mg/kg), and at 3-4hr in a high-dose group (0.5mg/kg). Similarly, Brown *et al.* (1979 ab) noted that plasma drug levels peak at 3-4hr after the administration of doses 0.43 mg/kg and 0.45 mg/kg in children. This is roughly comparable to the 2.5hr peak observed by Ebert *et al.* (1976) following dose equivalents of 30 mg *d*-amphetamine. However, Brauer *et al.* (1996) noted that the level of *d*-amphetamine in plasma reached peak at four hours after the administration of 20mg *d*-amphetamine. Although peak plasma levels vary
substantially between participants, this variability can be reduced by adjusting the administered dose by the body weight of the individual. However, factors such as physiological state, food consumption, and metabolism, will inevitably vary peak plasma levels across individuals.

2.1.1.5 Pharmacodynamics
At low therapeutic doses, \(d\)-amphetamine can reduce appetite, increase alertness and energy, combat fatigue and drowsiness, increase psychomotor activity, and promote a sense of well-being (MIMS, 2002). Cardiovascular reactions can include palpitations, and an increase in heart rate and blood pressure. Individuals may also experience restlessness, agitation, dizziness, headache, overstimulation, insomnia, mild confusion, and in rare cases psychotic episodes. Gastrointestinal reactions include dry mouth, unpleasant taste, diarrhoea, constipation, and other gastrointestinal disturbances (MIMS, 2002).

At higher than therapeutic doses, \(d\)-amphetamine symptoms include dilated and slowed reactive pupils, shallow rapid respiration, fever, chills and sweating. Other effects may include restlessness, aggressiveness, anxiety, confusion, delirium, hallucinations, and panic attacks. The stimulant effect is generally followed by depression, lethargy and exhaustion (MIMS, 2002), which is commonly referred to as the “crash”, “withdrawal” phase, or “hangover” period.

2.1.2 Methamphetamine
Methamphetamine, a potent and highly addictive stimulant, was synthesised for therapeutic use in the early 1900’s (Logan, 2002). It is an amphetamine derivative which has some legitimate therapeutic properties but it also has a tremendous potential for abuse. Methamphetamine is a schedule controlled substance (Dexedrine) (in Australia it is a Schedule 9 controlled substance which is the equivalent to Schedule I in the United States), and is available in tablet form. Medicinally, methamphetamine is prescribed for ADHD and Narcolepsy (Couper & Logan, 2004), and is used in treatment similarly to that of \(d\)-amphetamine. Methamphetamine is also prescribed for exogenous obesity, where it is used as a short term (few weeks) adjunct in a regimen of weight reduction based on caloric restriction. Methamphetamine is prescribed for patients in whom obesity is refractory to alternative therapy (e.g. repeated diets, group programs, and other drugs).
Methamphetamine (Dexedrine) is administered orally with doses up to 25mg/day in the treatment of ADHD, 5-60mg/day (in divided doses) for the treatment of Narcolepsy, and up to 15mg/day in the treatment of obesity (Logan, 1996).

2.1.2.1 Chemistry

The chemical name for methamphetamine is $N,\alpha$-dimethylphenethylamine, also referred to as desoxyephedrine, methylamphetamine, or phenylisopropylmethylamine (Logan, 2002). The more popular terms used to refer to methamphetamine consumed non-therapeutically include, crank, crystal, crystal meth, ice, and speed (Drummer, 2001). The molecular formula of methamphetamine is $C_{10}H_{15}N$ and has a molecular weight of 149.24 (Logan, 2002; Drummer, 2001). The chemical structure is represented in Figure 2.2.

![Methamphetamine Chemical Structure](image)

Figure 2.2 Methamphetamine Chemical Structure

Methamphetamine exists in two isomeric forms, dextro ($d$-) and levo ($l$-) (Logan, 2002). The $l$-isomer has CNS activity of approximately 25-33% to that of the $d$-isomer (Logan, 2002) and produces little or no physiological effect when ingested. This form of amphetamine is generally used as a nasal decongestant (Drummer, 2001). It may raise the blood pressure and cause the heart to beat rapidly, but generally does not increase alertness. The $d$-isomer is the more potent and widely abused form of methamphetamine due to its greater CNS activity (Hardman & Limbird, 1996). A racemic mixture of methamphetamine ($d,l$-) is less potent than the $d$-isomeric form and more potent than the $l$-isomeric form. However, the symptoms and side effects are similar to that of $d$-methamphetamine.

2.1.2.2 Pharmacology

Methamphetamine, like other amphetamines, is a non-catecholamine, sympathomimetic amine with CNS stimulant effects (Logan, 2002). As described earlier with $d$-amphetamine, methamphetamine involves both central and peripheral activity (Drummer, 2001). Methamphetamine works centrally by increasing the release of dopamine and
norepinephrine by blocking re-uptake from the synapse, inhibiting the action of monoamine oxidase (MAO), and facilitating the release of dopamine and noradrenaline (Feldman et al., 1997; Logan, 2002). Central methamphetamine effects result in euphoria, mood elevation, increased alertness, and locomotor stimulating effects (Drummer, 2001; Logan, 2001). Peripheral effects of methamphetamine are more marked with the \( l \)-isomers, and occur mainly through stimulating both alpha and beta-adrenergic receptors. Peripheral characteristic effects of methamphetamine include increased pulse and blood pressure and mydriasis (pupillary dilation) (Drummer, 2001; Logan, 2001).

2.1.2.3 Pharmacokinetics

Methamphetamine can be administered intranasally, orally, intravenously, or smoked (Logan, 2002). Following oral ingestion, peak methamphetamine concentrations are seen within 2-4 hours (Cook et al., 1992) (varying with the degree of physical activity and the amount of food in the stomach). Methamphetamine is highly lipid soluble and is very well absorbed. Methamphetamine is readily absorbed from the gastrointestinal tract after oral administration. Methamphetamine is concentrated in the kidney, lungs, cerebrospinal fluid and brain. It readily crosses the blood-brain barrier. Plasma protein-binding and volume of distribution varies widely, but the average distribution of amphetamine throughout the body (volume of distribution) is 3-4L/kg body weight (Drummer, 2001). The mean elimination half life of orally administered methamphetamine has been reported to be 10.1 hours (range 6.4–15 hours) (Cook et al., 1992). Methamphetamine is almost entirely eliminated in urine (90%) (Schepers et al., 2003). Under normal conditions between 30% and 54% of an oral dose of methamphetamine is excreted unchanged in the urine, and between 10% and 23% is excreted as amphetamine (Cook et al., 1992). Urinary excretion of the drug is markedly affected by urinary pH (Cook et al., 1992; Couper & Logan, 2004), as discussed in section 2.1.1.3.

2.1.2.4 Methamphetamine Levels in Blood

Methamphetamine blood concentrations can generally be used to distinguish therapeutic use from drug abuse. However, these concentrations can vary considerably across individuals. Concentrations of 0.02-0.05 mg/L are typically found following therapeutic use, however, up to 0.2 mg/L have also been reported (Cook et al., 1992; Couper & Logan, 2004; Baselt et al., 1995; Mitler et al., 1993). Experimental studies have shown that therapeutic doses of 18mg and 30mg methamphetamine result in peak plasma
concentrations of 0.02 mg/L and 0.04 mg/L, respectively (Drummer, 2001). Although, Cook et al. (1992) found 0.125 mg/kg and 0.250 mg/kg d-methamphetamine (equivalent to 8.75 mg and 17.5 mg, respectively, in a 70 kg subject) also produced average peak plasma concentrations of 0.02 mg/L and 0.04 mg/L, respectively. Concentrations greater than these doses are generally viewed as drug abuse, and particularly high concentrations can be life threatening. Average concentrations in recreational use range between 0.01 to 2.5 mg/L (median 0.6mg/L) (Couper & Logan, 2004), however, levels as high as 9.3 mg/L have also been previously reported (Logan, 1996; Logan et al., 1998).

2.1.2.5 Methamphetamine Levels in Saliva
Methamphetamine levels in saliva have also been reported to be highly variable (Cook et al., 1992; Schepers et al., 2003), as factors such as pH, salivary flow rate and lipid solubility of amphetamine affect the levels of amphetamine found in saliva (Skopp & Pötsch, 1999). Following the administration of 10 mg methamphetamine, peak concentrations in saliva have been found to range between 25 and 312 μg/L (mean 106 μg/L), 4-8 hours (mean 5 hours) post drug administration (Schepers et al., 2003). Following the administration of 20 mg methamphetamine, peak concentrations in saliva have been found to range between 75 and 322 μg/L (mean 192 μg/L), 2-12 hours (mean 5 hours) post drug administration (Schepers et al., 2003). Although there is limited research available reporting methamphetamine concentrations in saliva of recreational users, previous reports have found levels to be as high as 12.6 mg/L in saliva (Samyn & van Haeren, 2000).

2.1.2.6 Pharmacodynamics
Symptoms associated with therapeutic doses (10-60 mg) of methamphetamine include loss of appetite, alertness, irritability, nervousness, insomnia, headache and increased activity. Acute physiological symptoms may include increased heart rate, increased blood pressure, increased respiration rate, elevated body temperature, palpitations, irregular heartbeat, dry mouth, suppressed appetite, and dilated pupils. Higher doses of methamphetamine (generally distinguished based on blood concentrations) can cause intense exhilaration and euphoria, extreme wakefulness, rapid flow of thoughts, talkativeness, rapid speech, confusion, irritability, sweating, tremor, hallucinations, and paranoia (Kramer, 1969; Kramer et al., 1967).
Chapter 3. Amphetamine and Driving

Epidemiological research demonstrating the relationship between amphetamine use and driving performance has involved the analysis of driver blood and saliva specimens and driving behaviours observed in drivers that have been arrested for traffic violations or killed in road crashes. Such data generally includes all subtypes of amphetamines as a class, ignoring subtle differences between the related compounds. Therefore, there is limited epidemiological research available on the effects of d-amphetamine and methamphetamine independently, and the present review of the amphetamine-related driving literature will, thus, also discuss stimulants as a drug class, and ignore the differences within this drug class.

3.1 Epidemiological Driving Studies

In two separate appraisals, Hurst (1976, 1987) reviewed the effects of amphetamine on driving-related cognitive performance and its implications to traffic safety. Hurst (1976, 1987) appraised the available experimental literature and epidemiological data, and concluded that there was little evidence to suggest a causal link between amphetamine use and road crashes. Hurst argued that the experimental research provided little indication that amphetamine use should have a negative impact on traffic safety and claimed that the epidemiological research highlighted that the prevalence of amphetamine use in the driving population was rare. However, Hurst (Hurst, 1976, 1987) argued that the epidemiological evidence was insufficient to be able to implicate amphetamine negatively in terms of road crashes, due to the lack of large case-controlled studies.

In contrast, a decade earlier, Smart (1969) examined the prevalence of various drug users involved in traffic accidents and reported a high rate of accidents (55%) among amphetamine users. Consistent with this, other studies that have examined driver populations have also reported a considerably high incidence of traffic accidents associated with amphetamine use (Lund et al., 1988; Crouch et al., 1993; Kirby et al., 1992; Logan & Schwilke, 1996). Lund et al. (1988) found that 2% of US drivers who voluntarily participated in their study tested positive to methamphetamine. It should, however, be noted, that the refusal rate was 12%. This suggests that the percentage of drivers intoxicated with methamphetamine may have been higher as refusal to participate in the
study may have occurred because some drivers were unwilling to participate for fear of perceived legal ramifications related to driving while under the influence of methamphetamine. However, similar percentages were reported by Logan & Schwilke (1996), who found that amphetamine accounted for 2% of samples obtained from fatally injured drivers in Washington State, USA, and also by Crouch et al. (1993), who reported the prevalence of drug use in fatally injured truck drivers, and found amphetamine or methamphetamine in 7% of cases. Although providing a useful indication, a fundamental problem with all these studies was that control groups were not employed, making it difficult to compare the prevalence of amphetamine use in traffic accidents to that of the general driving population. Therefore, interpretation of the results is difficult.

In 1992, the National Highway Traffic Safety Administration released a report of drug prevalence and driving behaviours in fatally injured drivers in the United States which included a control group of drug-free drivers. It was reported that 83.3% of amphetamine-positive drivers were deemed culpable for the accident, relative to 67.7% in the drug-free control group, and 93.9% in drivers with a blood alcohol concentration greater than 0.09 g/100mL. Furthermore, the most frequent type of accident noted among the drivers testing positive to amphetamines was a “non collision” or “drive-off-the-road” type accident. These results indicate an association between amphetamine use and traffic accidents, however, the cause of the accidents is difficult to determine based on this evidence alone.

More recently, culpability studies in Australia have compared drug levels in fatally injured drivers, indicating that specific drugs are associated with an increase in fatal collision risk (Drummer et al., 2003b; Longo et al., 2000b). In a major multi-centre case-control study, conducted at Victorian Institute of Forensic Medicine, the effects of alcohol and drug use on crash risk were assessed using 3398 fatally-injured Australian drivers. Over a ten year period, stimulants were detected in 4.1% of all drivers and 23% of all truck drivers (Drummer et al., 2003a). In terms of accident risk, 90.6% of drivers who tested positive to stimulants were argued to be fully or partly responsible for their death. A culpability index, an ‘odds ratio’, was calculated for each drug category and compared to a drug-free driver group. The odds ratio provided an index of whether the presence of a specific drug was associated with an increase in the risk of a driver causing a crash. For instance, an odds ratio of 1 indicates no increased risk relative to a reference group, and an odds ratio of 1.5 indicates a 50% increase in risk (relative to a reference group) of a driver causing a crash.
Relative to drug and alcohol free drivers, the odds ratio of drivers using stimulants overall was 2.3, indicating that drivers under the influence of stimulants were more than twice as likely to be at risk of causing an accident. This ratio was found to increase to 8.8 in truck drivers, indicating that truck drivers intoxicated with stimulants were almost nine times as likely to be at risk of causing a crash relative to drug and alcohol free drivers (Drummer et al., 2003b). However, it is worth noting that this increase in odds ratio found with truck drivers may be related to the longer hours spent on the road compared to other drivers, as the probability of being involved in a road crash increases with more time spent driving. In addition, fatigue in truck drivers may have also contributed to the increase in road accidents (Swann, 2002), as these were factors that were not addressed in the study by Drummer et al. (2003ab). Based on these results, Drummer et al. (2003b) concluded that stimulant use was associated with an increase in drivers’ risk of a serious road crash as these drivers were more likely to be responsible for the motor vehicle crash than drivers who were drug and alcohol free.

Although these findings appear to suggest a causal relationship between stimulant use and driver fatality, they should be interpreted with some caution, as the size of the association, as determined by the odds ratio, cannot be used to directly infer causality. These results only suggest that drivers intoxicated with stimulants have an increased risk of causing and dying in a crash. However, it is possible that the presence of stimulants in driver’s blood is a proxy for other factors, such as fatigue or withdrawal effects, resulting from stimulant use that subsequently increased the likelihood of culpability.

In contrast to the findings of Drummer et al. (2003ab), in a study examining driver culpability in 2500 injured drivers in South Australia, Longo et al. (2000b) found stimulants alone in only 0.8% of drivers and stimulants in combination with other drugs in only 1.3% of cases (Longo et al., 2000a). In terms of driver culpability, there was some suggestion of increased culpability amongst drivers testing positive for stimulants (odds ratio = 2), however, this was not found to be statistically significant (Longo et al., 2000b). The authors argued that a much larger sample would need to be used to confirm whether there is an association between stimulant use and crash risk as only 19 drivers tested positive to stimulants.
Although there are some inconsistencies in the epidemiological research discussed thus far, for example, Longo et al. (2000ab) and Drummer et al. (2003ab), the reports do generally indicate that there is some association between amphetamine use and road fatalities. However, these reports cannot be used to directly infer causality. These results merely highlight the prevalence of amphetamine use in drivers involved in road crashes, and that amphetamine use is associated with an increase in drivers’ risk of a road crash. The findings do not indicate whether road fatalities involving drivers intoxicated with amphetamine are attributed to the acute effects of amphetamine itself or whether the presence of amphetamine in driver’s blood is a proxy for other factors, such as, fatigue or withdrawal effects resulting from stimulant use. Therefore, examining the circumstances surrounding traffic arrests or accidents, such as the driving behaviours resulting in the traffic violations, may provide further information as to how amphetamine use is associated with road crashes.

3.2 Epidemiological-Behavioural Driving Studies
Logan (1996) examined the records of 28 drivers arrested or killed in traffic accidents that tested positive to methamphetamine. Circumstances surrounding the accidents or arrests were explored and assessments of driver culpability were also determined. Logan reported that 61% of drivers (n=17) included in the study were involved in an accident, of which 16 drivers were responsible for the accident. The most typical driving behaviour that resulted in these accidents was drifting out of the lane of travel onto the shoulder, into stationary objects, or into oncoming traffic. Logan (1996) argued that this was due to a lack of attention that caused impaired judgement and increased risk taking behaviour, and was likely to be attributed to withdrawal-related fatigue following extended methamphetamine use, rather than from the acute effects of methamphetamine, which, has generally been shown to enhance attention (refer to Chapter 4 for review of the effects of amphetamine on attention and cognitive performance). Other accidents reported by Logan (1996) were caused by errors in judgement by the driver, entering traffic flow inappropriately, failing to stop at stop signs, high speed collisions, erratic driving, weaving, and speeding. Logan argued that methamphetamine concentrations required to elicit these behaviours varied across individuals (range 0.05 to 2.6 mg/L) as a result of differences in patterns of drug use, drug tolerance, fatigue, and alcohol or other drug use. Although specific driving behaviours were noted as likely causes of the accidents, it cannot be inferred from these findings that amphetamine use directly ‘caused’ the accidents. Similarly, although Logan
(1996) argued that sleep deprivation resulting from extended methamphetamine use appears to be the most probable cause for most of the accidents reported, this was not directly assessed and cannot be confirmed from that research.

In a later study, Logan et al. (1998) reviewed the ‘cause’ and ‘manner’ of 146 deaths involving methamphetamine. Of these cases, 52 were defined as “drug caused”, whereby the drug was thought to contribute to the death, and 92 were defined as “drug related”, where the drug was not thought to be directly responsible for the death. Within the “drug related” category, 17 cases were road fatalities. Logan et al. (1998) noted that typical driving behaviours observed in these drivers were consistent with previous reports (Logan, 1996), including drifting out of the lane of travel, high speed and reckless driving, drifting off the road, collisions, erratic driving, and increased risk taking. Furthermore, similar to previous reports, methamphetamine blood concentrations found in drivers eliciting these driving behaviours varied considerably across individuals (Logan, 1996), with methamphetamine concentration levels ranging between 0.05 to 2.6 mg/L. These results support Logan’s (1996) earlier findings, which indicate that either methamphetamine itself or fatigue and related symptoms experienced during the methamphetamine withdrawal phase were associated with the road fatalities. Although Logan et al. (1998) argues that the effects of methamphetamine use most likely contributed to the accident, it cannot be determined based on this evidence alone how methamphetamine use was specifically associated with the accidents.

In summary, the epidemiological research demonstrates that there is some association between amphetamine use and road fatalities, however, it is difficult to infer a causal link based on the evidence discussed in the present chapter. The epidemiological literature indicates that amphetamine use is prevalent amongst drivers involved in road crashes and that amphetamine use is associated with an increase in the risk of the driver causing a road accident. The epidemiological findings do not, however, indicate whether road fatalities involving drivers intoxicated with amphetamine are attributable to the acute effects of amphetamine itself, or whether the presence of amphetamine in a driver’s blood is a proxy for other factors, such as, fatigue or withdrawal effects resulting from stimulant use. In order to help clarify these issues it is important to examine the experimental amphetamine driving literature, as this type of research allows the experimenter to have more control
over causation, which subsequently may help elucidate how amphetamine use is associated with road accidents.
Chapter 4. Amphetamine and Driving-Related Cognitive Performance

The epidemiological research discussed in the previous chapter (Chapter 3 Amphetamine and Driving Performance) highlighted that amphetamine use is prevalent amongst drivers involved in road crashes and that amphetamine use is associated with an increase in the risk of the driver having the cause of a road accident attributed to them. However, the epidemiological literature does not indicate whether amphetamine-related road fatalities are attributed to the acute effects of amphetamine itself or whether the presence of amphetamine in driver’s blood is a proxy for other factors, such as, fatigue or withdrawal effects resulting from amphetamine use. In order to help clarify these issues, studies employing experimental designs will be reviewed. Experimental studies have greater control over causation as the acute effects of amphetamine on processes related to driving can be specifically assessed and compared to performance when no drug (placebo) is consumed.

Simulated driving studies are an important type of experimental research for examining the effects of amphetamine on driving performance, as they provide a surrogate for real life driving ability and still have the advantage of control over causation. Research addressing the effects of amphetamine on simulated driving performance is scarce, and to the author’s knowledge, there has only been one study that has explored this (Mitler et al., 1993). Mitler et al. (1993) investigated the effects of methamphetamine on narcoleptic patients and controls. Included in the protocol was a simple 30 minute computer-based driving simulator task. A dose of up to 60mg methamphetamine was administered to the narcoleptic patients and up to 10mg methamphetamine was administered to the control sample. The authors reported a dose-dependent improvement in driving performance across both groups. However, the authors did not examine whether this improvement in driving ability would be maintained following the administration of higher methamphetamine doses. It is difficult to relate these findings to the epidemiological research as it has been argued that such low amphetamine doses (5-10 mg) have little effect on general functioning that, subsequently, would impair performance (Logan, 2002). Furthermore, these low doses are not a common pattern of abuse among drivers involved in road incidents, therefore, it is difficult to make direct comparisons with them (Logan, 2002).
In contrast to the limited simulated driving studies, there are a considerable number of experimental studies that have assessed the acute effects of amphetamine on cognitive processes related to driving. Although it is argued that employing driving-related cognitive tasks to examine the effects of amphetamine on driving performance does not easily translate to real-life driving, these tasks are more likely to detect underlying impairments that may not be easily observable in real-life driving or driving simulator tasks. This chapter will therefore review the amphetamine cognitive literature related to driving to help identify the underlying cognitive processes that may be affected following amphetamine consumption.


### 4.1 Amphetamine-Induced Enhancements of Cognitive Functioning

Amongst the cognitive domains modulated by amphetamines, the most consistent findings are of amphetamine-related improvements on tasks that assess attention, psychomotor function and perceptual speed, all processes important in driving (Hurst, 1987). These will now be discussed in detail.

In terms of attention, although there have been some null findings (Comer *et al.*, 1996; Pickworth *et al.*, 1997; Comer *et al.*, 2001), in general, significant improvements have been observed in vigilance tasks (both in accuracy and speed) following the administration of 5-15 mg d-amphetamine (Comer *et al.*, 1996; Koelega 1993; Kelly *et al.*, 1991). Comer...
et al. (1996) found that 10mg d-amphetamine improved vigilance performance on a divided attention task. The authors reported that in the d-amphetamine condition the number of times subjects correctly identified the presence of a target increased, and the mean response time and the number of times a target was missed decreased, relative to placebo. The authors concluded that consistent with other reports d-amphetamine improves performance on tasks in which reaction time and/or vigilance are required. Similarly, Kelly et al. (1991) found that 10mg/70kg d-amphetamine increased accuracy on a vigilance task. In a review addressing the effects of stimulant drugs (amphetamine, methylphenidate, caffeine, and nicotine) on vigilance performance, Koelega (1993) concluded that amphetamines enhance vigilance performance, by improving overall performance (accuracy and speed), and preventing decrements in performance over time.

Other tasks that assess attention have also shown improvements in attentional functions following amphetamine ingestion. de Wit et al. (2002) reported an enhancement of attention following the consumption of d-amphetamine (10mg and 20mg) on the Digit Symbol Substitution Test (DSST) (also a measure of psychomotor ability) and the Digit Span test (also a measure of working memory). Similar improvements in DSST performance have been reported by other researchers using doses ranging from 10mg/70kg to 20mg d-amphetamine, and 40mg d,l-amphetamine (Wachtel & de Wit, 1999; Kelly et al., 1991; Ward et al., 1997; Cami et al., 2000). Wachtel & de Wit (1999) found that 20mg d-amphetamine increased response rate on the DSST. Similarly, Ward et al. (1997) found that 5mg/70kg and 10mg/70kg d-amphetamine increased response rate on the DSST without affecting accuracy, and Kelly et al. (1991) reported a decrease in error rates on the DSST following 10mg/70kg d-amphetamine.

Further support for amphetamine-related improvements in attentional functioning has been shown using the Rapid Visual Information Processing Task (RVIPT) after the administration of 20mg d-amphetamine (Johnson et al., 1996). Johnson et al. (1996) found that while d-amphetamine increased the number of correct responses it did not improve reaction time. These findings were substantiated in a later study, where Johnson et al. (2000) reported improved attention on the RVIPT following a low (0.21mg/kg) and moderate (0.42mg/kg) dose of d-methamphetamine. Specifically, the authors found that the number of correct responses increased significantly in the methamphetamine conditions, however, unlike in their earlier study, a significant decrease in reaction time and false
alarm rates were also noted. This inconsistency in results between the two studies in reaction time performance on the RVIPs may be attributable to differences in the type of amphetamine administered or differences in the dose administered.

Amphetamine-related enhancements in attention have also been observed using auditory tasks. McKetin et al. (1999) examined the effect of 10mg and 20mg d-amphetamine on selective attention using a complex auditory selective attention task. Subjects were required to respond as quickly as possible to infrequent target tones that were presented amongst other tones that varied on several parameters. The authors reported an increase in correct responses and decreases in reaction time in both amphetamine conditions. Furthermore, d-amphetamine produced a linear dose response increase in hit rate and decrease in reaction time. No changes in false alarm rates were noted in any condition, thus suggesting that the increased response rate associated with the presence of amphetamine was not attributed to subjects responding more liberally.

The amphetamine cognitive literature discussed thus far indicates that low amphetamine doses enhance attention. Furthermore, the present review illustrates that similar amphetamine-related improvements in attention are manifested across a range of tasks that assess different aspects of attention (e.g. divided attention and vigilance), and that vary in task demand and modality (visual and auditory). These findings, therefore provide strong evidence to conclude that low amphetamine doses improve overall attentional functioning.

In terms of psychomotor performance, improvements on psychomotor tasks other than DSST, such as motor speed and coordination, have also been observed with low dose amphetamine use (Kennedy et al., 1990). Kennedy et al. (1990) found that 10mg d-amphetamine enhanced tapping speed on the Two-handed Tapping Task, a measure of motor performance. The authors concluded that d-amphetamine had a positive effect on speed-based performance tests which emphasise motor skills. Pickworth et al. (1997) found that 10mg d-amphetamine produced a small decrease in psychomotor performance on a ‘circular lights’ task, whereas 30mg d-amphetamine produced an increase. This decrease in performance noted in the low dose amphetamine condition was observed 30 minutes after drug administration, whereas the increase in performance observed in the high dose condition was noted 300 minutes following drug ingestion. These results should, however, be interpreted with caution as few effects have previously been reported 30
minutes following amphetamine ingestion, since peak blood amphetamine levels are generally observed 2-4 hours post drug administration (Kupietz, et al., 1985; Angrist, et al., 1987).

Improvements in psychomotor performance following amphetamine consumption have also been observed with tracking tasks, which are measures of visual-motor coordination and psychomotor ability. Comer et al. (1996) reported improvement in tracking ability on a divided attention task following the administration of 10mg $d$-amphetamine. Performance on tracking tasks has also been examined with sleep-deprived volunteers (Magill et al., 2003; Belleville et al., 1979), where a dose of either 10 or 20 mg $d$-amphetamine significantly improved tracking performance.

Although there are few studies that have explored the acute effects of amphetamine on psychomotor performance, the results generally indicate that amphetamine improves performance. However, it should be noted that with exception to the 30 mg $d$-amphetamine dose administered in the study by Pickworth et al. (1997), the effects of low amphetamine doses (10 mg) were examined in the previous research, and it has been argued that such low doses of amphetamine are unlikely to produce decrements in performance, nor to be representative of doses employed by drivers (Logan, 2002). In regards to the observed improvement in psychomotor performance, reported in the study by Pickworth et al. (1997), following a 30 mg dose of $d$-amphetamine, the results should be interpreted with caution, as performance was assessed 5 hours following drug administration when amphetamine levels in blood have been shown to decline (Brauer et al., 1996).

In terms of perceptual speed, although there have been some null findings (Comer et al., 1996; Comer et al., 2001), overall amphetamines have been shown to enhance aspects of perceptual speed. Kennedy et al. (1990) reported increases in speed-based information processing tasks, such as the Two-handed Tapping Task, following the administration of 10mg $d$-amphetamine. Recently, Fillmore et al. (2005) assessed the effects of 7.5mg/70kg and 15mg/70kg $d$-amphetamine on information processing measured using a working memory task, specifically, the rapid information processing (RIP) task. Consistent with the literature, $d$-amphetamine was found to enhance information processing in a dose-dependant manner, as measured by working memory capacity.
Further support for amphetamine-related improvements in perceptual speed has been shown to occur with tasks that assess reaction time. Specifically, research has consistently demonstrated that following the administration of d-amphetamine reaction time improves (Fillmore et al., 2005; Asghar et al., 2003; McKetin et al., 1999; Servan-Shreiber et al., 1998; Kumari et al., 1997; Ward et al., 1997; Halliday et al., 1994; Fleming et al., 1995; Johnson et al., 2000; Rapoport et al., 1980). This improvement in reaction time has been shown to occur with doses as low as 5mg d-amphetamine (Kumari et al., 1997). Asghar et al. (2003) assessed reaction time on a selective attention task following the administration of 25mg d-amphetamine. The authors found that compared to placebo, d-amphetamine significantly decreased reaction time at 30, 60, 90, 150 and 210 minutes after drug administration. Similarly, Fleming et al. (1995) reported decreases in reaction time on two cognitive measures following 0.25mg/kg d-amphetamine. Halliday et al. (1994) also reported improved reaction time performance following 10mg d-amphetamine. Ward et al. (1997) assessed the effect of 5 mg and 10mg d-amphetamine on a Number Recognition task (a measure of short-term memory), and found that d-amphetamine decreased reaction time and the speed at which subjects recognised targets and distracters, without improving accuracy. Similarly, Callaway et al. (1994) reported that d-amphetamine decreased reaction time with no detrimental effect on accuracy. In contrast, Servan-Shreiber et al. (1998) found that 0.25mg/kg d-amphetamine produced a decrease in overall reaction time and an improvement in accuracy with the decreased reaction times, but only during tasks that required selective attention.

Thus, based on this literature it can be argued that acute low doses of amphetamine enhance perceptual speed. Furthermore, improvements in perceptual speed have consistently been reported across a range of amphetamine doses and task types that vary considerably in task demand. Therefore, there is strong evidence to indicate that low doses of amphetamine improve perceptual speed.

In summary, the literature indicates that at low doses, amphetamine improves performance related to attention, psychomotor function and perceptual speed. Furthermore, improvements in these cognitive functions have been observed with different tasks and amphetamine doses. This provides considerable evidence that at low doses, amphetamine enhances performance on these cognitive processes. In terms of driving, the literature reviewed in the present chapter suggests that the effects of amphetamine on aspects of
attention, psychomotor function and perceptual speed do not appear to be associated with amphetamine-related driving decrements. This indicates that deficits to other driving-related cognitive processes, or factors such as fatigue, resulting from amphetamine use, may be responsible for the amphetamine-related road crashes. However, it is important to note that the experimental studies discussed in the present chapter have examined cognitive functioning following the administration of therapeutic amphetamine doses and not recreational amphetamine doses (Logan, 2002). Therefore, the possibility remains that the experimental research and epidemiological findings are not commensurate, as performance on cognitive tasks following low amphetamine doses cannot be assumed, or are unlikely, to be representative of performance observed following recreational amphetamine doses. However, there are some driving-related cognitive processes that have been shown to be impaired following low amphetamine doses which may help elucidate how amphetamine may be associated with decrements in driving performance. These are discussed below.

4.2 Amphetamine-Induced Impairments of Cognitive Functioning

Contrary to the reported amphetamine-related improvements on attention, psychomotor function and perceptual speed, amphetamine has been shown to have some negative influences with regard to driving behaviour, such as, tendencies towards greater risk-taking behaviours (Hurst, 1962; Hurst et al., 1967), overestimation of one’s own performance (Smith & Beecher, 1964; Hurst et al., 1967), impaired performance on visual scanning tasks (Kennedy et al., 1990), and disruptions in filtering out irrelevant information (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2003; Solomon et al., 1981; Weiner et al., 1988; Bakshi et al., 1995).

In terms of risk taking behaviour, previous research has demonstrated that amphetamine produces increases in this type of behaviour. Hurst (1962) reported increases in risk taking behaviour on a gambling task following the administration of 10mg $d$-amphetamine. In later work, Hurst et al. (1967) supported this finding when the authors examined the effects of 14mg/70kg $d,l$-amphetamine and $d$-amphetamine on judgement and decision making. Hurst et al. (1967) found that both doses of amphetamine enhanced self-appraisal of performance, without improving actual performance, which corresponded with increases in risk taking behaviours. Similarly, Smith and Beecher (1960, 1964) also reported tendencies of an increase in positive self-appraisals of performance following the administration of 14mg/kg $d,l$-amphetamine. In contrast, in a later review of the effects of amphetamine on
driving, Hurst (1987) downplayed the increase of risk taking behaviours associated with amphetamine use in relation to traffic accidents. Although there are some contradictions in the reported effects of amphetamines on risk taking behaviour, these findings do provide some indication of effects on judgement, decision making, and risk taking behaviour that could negatively impact driving performance. As such they are consistent with the claims of the above-described epidemiological research, where risk taking behaviours were viewed as causally related to amphetamine-related road accidents (Logan, 1996; Logan et al., 1998). Thus, further research is warranted to help elucidate these inconsistencies and establish whether varying amphetamine doses increase risk taking behaviour.

Amphetamine has also been shown to impair performance on visual scanning tasks (Kennedy et al., 1990). Kennedy et al. (1990) investigated the effects of 10mg d-amphetamine on a range of cognitive processes, such as information processing, spatial processing, perceptual processing, and psychomotor performance, and found that d-amphetamine impaired performance only during a visual search task, whereas it improved performance on all other cognitive tasks. Further support for amphetamine induced decrements on tasks requiring use of the visual field has been reported using tasks that assess ‘tunnel vision’ (Mills et al., 2001).

‘Tunnel vision’, or perceptual narrowing, has been argued to occur with sympathetic arousal which results in a perceptual restriction to the focal point (Easterbrook, 1959). ‘Tunnelling’ has been shown to occur during high demand tasks and stress (Mills et al., 1999; Williams, 1988, 1995). For example, ‘tunnelling’ has been cited as the cause of accidents when police officers are engaged in high arousal pursuits (Mills et al., 1999). In addition, ‘tunnelling’ effects have 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).

In a recent study, Mills et al. (2001) explored the effects of 10mg d-amphetamine on ‘tunnel vision’. Mills et al. (2001) measured 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. The authors reported improved performance only on tasks where stimuli were presented
centrally, however, no improvements (or significant impairments) were observed when stimuli were presented in the peripheral positions. Based on these findings the authors concluded that $d$-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 $d$-amphetamine condition. These findings, in addition to the results of Kennedy et al. (1990), provide some suggestion for the negative effects of amphetamine on visual scanning ability, which in terms of driving would be particularly dangerous. If amphetamine does in fact induce ‘tunnelling’ this may provide a plausible explanation as to how amphetamine use is associated with road accidents, as ‘tunnelling’ would increase the risk of failing to attend to potential hazards that fall outside of the drivers’ attentional focus.

In addition to amphetamine-induced increases in risk taking behaviours and decrements in visual scanning, research has also shown amphetamine to have negative effects on prepulse inhibition and latent inhibition (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2003; Solomon et al., 1981; Weiner et al., 1988; Bakshi et al., 1995). These are measures of sensorimotor gating that reflect deficits in the ability to filter out irrelevant or intrusive stimuli which subsequently can cause an overload of information (Blumenthal et al., 1996; Swerdlow, 1996; Swerdlow & Geyer, 1998; refer to Section 5.4.2 for more detail). In terms of driving, a deficit in sensorimotor gating would decrease the driver’s ability to appropriately gather and organise information which, consequently, could increase the risk of failing to attend to relevant information and potential hazards, thus possibly resulting in a road crash.

In summary, the literature highlights the complex nature of the effects of amphetamine on human behaviour. The research indicates that at therapeutic doses amphetamine improves performance on cognitive processes, such as attention, psychomotor function and perceptual speed. However, for other aspects of functioning, such as risk taking, the ability to filter out irrelevant information, visual scanning proficiency, and efficient use of the visual field, low doses of amphetamine appears to impair performance. In terms of driving, the literature highlights that the effects of amphetamine on attention, psychomotor function and perceptual speed do not appear to be associated with the amphetamine-related driving fatalities. However, there is some evidence to suggest that amphetamine-induced
impairments in risk taking behaviours, filtering out of irrelevant information, visual scanning ability, and perceptual narrowing, may be associated with amphetamine-related driving impairments. However, further research is needed to explore this issue before causation can be inferred. In addition, further research needs to assess the acute effects of amphetamine on simulated driving performance. Although driving simulator studies have limitations in terms of how accurately they reflect real life driving ability, they can provide some valuable information as to the specific driving skills that may be impaired following the consumption of amphetamine. Furthermore, such investigations have the advantage of allowing controlled conditions to be easily included in the experimental design, which can control for differences in driving ability across participants. It is for these reasons that the effect of amphetamine on simulated driving performance, using a repeated-measures design, was employed in the present thesis.
Chapter 5. Amphetamines and Event Related Potentials

As was argued in the previous chapter (Chapter 4, Amphetamine and Driving-Related Cognitive Performance), acute amphetamine use improves attention, psychomotor functions and perceptual speed, therefore, these cognitive processes do not appear likely to be associated with reported amphetamine-related driving impairments. However, there was some evidence to suggest that acute amphetamine use causes increases in risk taking behaviours, disruptions in filtering out irrelevant information, impairs visual scanning ability, and induces perceptual narrowing, all of which are functions that may negatively impact driving ability. However, it was concluded that further research was required to clarify this issue.

Although the literature has generally indicated amphetamine to enhance cognitive functioning, it may also be likely that amphetamine-induced driving impairments result from decrements in functioning that are too subtle to be detected with standard cognitive measures. Employing more sensitive techniques, such as derivations of the electroencephalogram (EEG), enables a more sensitive analysis of the possible underlying impairments, as such methods assess the subtle effects of amphetamine on cognitive processes that can not be easily detected with standard cognitive tasks. Thus, to help determine how amphetamine use may be associated with impaired driving, this chapter will review research that has employed these more sensitive experimental techniques to examine the acute effects of amphetamine on cognitive functions related to driving. Specifically, studies that have used derivations of the electroencephalogram (EEG) will be discussed.

5.1 What is the Electroencephalogram (EEG)?
EEG (and its counterpart magnetoencephalogram) is a neurophysiological tool that non-invasively measures human brain electrical (and magnetic) activity. Compared to other brain imaging techniques, EEG provides the greatest temporal resolution available at present. This measurement of brain electrical activity involves placing electrodes on to multiple areas of the scalp. These electrodes detect and record patterns of electrical voltage fluctuations that are naturally produced by the brain. EEG recordings allow researchers to follow electrical voltage fluctuations across the surface of the brain and over time. An EEG
can reveal what gross mental state a person is in (i.e. asleep, awake, anaesthetized), and is often used to assess brain damage, epilepsy, and other neurological problems. EEGs are also often used to examine how efficiently the brain processes information in response to various visual, auditory, somatosensory, and olfactory stimuli. EEG derivatives, referred to as 'Event Related Potentials' (ERPs), are a useful tool for examining the effects of drugs on human information processing, as the high level of sensitivity may expose effects that are masked when using standard cognitive measures. For instance, a simple visual discrimination task requires a number of sub-abilities (visual acuity, attention/discrimination, motor response), and while impairment in one ability may be masked by another, the ERP can index these abilities separately. An example of how this may be particularly important in assessing the effect of amphetamine on driving performance might be if decision making was impaired but motor response improved with amphetamine, then the net result may be no change in the overt behaviour response.

5.2 What are Event-Related Potentials (ERPs)?
ERPs are very small electrical voltage changes that occur in the central nervous system in connection with a particular neural event. ERPs are a series of positive and negative voltage deflections that are time-locked to an ‘event’ (refer to Figure 5.1 for illustration). This event may be a sensory stimulus (such as a visual flash or an auditory sound), a cognitive event (such as recognition of a specified target stimulus), or the omission of a stimulus (such as an increased time gap between stimuli). To elicit ERPs, stimuli are generally presented in a visual, auditory or somatosensory modality. Although ERPs are very low in voltage relative to the high background electrical noise, the small signals can be discerned from this noise following the averaging of a number of responses to such events. ERP components are assessed in a number of different ways, however, the principle indices are amplitude and latency. The amplitude of the ERP components provides a measure of the intensity of neuronal activity, whereas the latency provides a measure of the speed of cognitive processing.
Figure 5.1 Example of a Positive and Negative ERP Component. The y-axis represents the amplitude of the ERP response (the intensity of neuronal activity). Thus, a small peak indicates minimal neuronal activity, whereas a large peak indicates considerable neuronal activity (as depicted with the two highlighted negative peaks in the above figure). Negative ERPs have a negative amplitude peak, whereas positive ERPs have a positive amplitude peak. The x-axis represents the latency of the peak. Thus, at what time relative to the ‘event’ was the ERP component evoked, where ‘0 ms’ represents the ‘event’. Therefore, the time prior to 0 ms (negative numbers) represents the time prior to the event occurring, and the time after 0 ms (positive numbers) represents the time following the occurrence of an event. Thus, as depicted in the figure above, the large negative ERP component occurred approximately 170 ms following stimulus onset and had amplitude of approximately -100µv, and the positive ERP component occurred approximately 380 ms following stimulus onset and had amplitude of approximately 100µv.

ERPs possess a number of characteristics which make them a powerful technique for investigating higher order mental functions (Kubová et al., 2002). Firstly, the high temporal resolution allows for the millisecond measurement of the time course of brain activity, which enables, for example, a means of determining which aspects of behavioural dysfunction are consequent or antecedent to other processing (Rugg et al., 1987). Secondly, as ERPs can be recorded simultaneously from electrodes located at multiple regions of the scalp, it is possible to explore different ERP effects occurring concurrently, and thus infer the existence of parallel processes underlying selective processing (Rugg et al., 1987). Finally, ERPs can be elicited from any stimulus event, irrespective of whether the task requires a behavioural response, therefore greatly enhancing the sensory-cognitive domain that can be assessed.
5.2.1 Defining the Components

Although there are a number of ERP components, only those relevant to the present thesis will be discussed. These are; the P100 component elicited with visual stimuli, the startle reflex and prepulse inhibition of the startle reflex elicited with auditory stimuli, the N200 component elicited with visual and auditory stimuli, the Mismatch Negativity (MMN) component elicited with auditory stimuli, and the P300 component elicited with visual and auditory stimuli.

5.2.1.1 Visual P100 Component

The P100 wave is a small positive component that generally peaks about 70-100 ms after visual stimulation (Mangun & Hillyard, 1991), and has maximal amplitude over visual cortical areas that reflects early activation of the primary visual cortex (Mangun & Hillyard, 1991). Research has demonstrated that the P100 component is related to spatial attentive processes (Mangun & Hillyard, 1991), where it has been shown that the amplitude of this ERP component is modulated by visual attention (Hillyard & Munte, 1984; Mangun & Hillyard, 1988), thus reflecting possible processing modulations in the prestriate visual cortex.

5.2.1.2 Pre-pulse Inhibition of the Acoustic Startle Reflex

Occurring 30 to 40 ms following stimulus onset, the startle response is reflected in a sudden increase in tension in the facial muscle surrounding the eyes (orbicularis oculi) (Lang, 1995), and is quantified by the amplitude and latency of this eyeblink response (the most consistent and reliable behavioural measure of the startle reflex response in humans) to a startling rare sensory stimulus (Lang, 1995). The startle response is 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, 1979). A major advantage of the startle reflex model is that it may be presented across multiple modalities (Davis, 1980). However, for the purpose of the present thesis only startle responses elicited with auditory stimuli will be discussed.

The startle reflex response can be inhibited when the startling stimulus is preceded by a weak sensory stimulus (prepulse) 30-500 ms earlier (Graham, 1975). This is referred to as prepulse inhibition of the startle reflex (PPI). This inhibitory mechanism represents an operational measure of 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 prepulse (Graham, 1975). It is thought that sensorimotor gating reflects an individual’s ability to ‘screen out’ irrelevant or intrusive sensory stimuli, thus preventing an overload of information (Blumenthal et al., 1996; Swerdlow, 1996; Swerdlow & Geyer, 1998). The period of a reduced response following the weaker prepulse is postulated to ‘protect’ information contained in the weak stimulus so that it can be adequately processed, without interference from the subsequent startling stimulus (Blumenthal et al., 1996; Swerdlow et al., 1999). Thus, this process aids in regulating environmental inputs and selectively allocating attentional resources to relevant stimuli.

5.2.1.3 N200 Component

The N200 is a negative-going waveform that can be evoked across all sensory modalities. However, in terms of the present thesis, only the N200 elicited with visual and auditory stimuli will be discussed. The N200 typically has a frontal-central peak and is evoked approximately 200 ms following the presentation of a specific visual or auditory stimulus. The N200 is an attention-dependant component that reflects stimulus discrimination and classification processes (Näätänen, 1992). The N200 is elicited with a conventional oddball paradigm, involving the random occurrence of an infrequent (oddball) target stimulus presented among frequently (standard) occurring stimuli. The participant is required to attentively discriminate the rare stimulus (the oddball/target) from the frequent stimulus (standard) by noting the occurrence of the target, typically by pressing a response button. N200 amplitude is thought to be related to the active processing of the stimulus, perhaps relating to a comparison process between the incoming stimulus and a mnemonic representation of the target stimulus. N200 amplitude is influenced by attention and task difficulty (Näätänen, 1992), whereas N200 latency is thought to reflect stimulus discrimination and evaluation time (Ritter et al., 1979; Näätänen & Picton, 1986).

5.2.1.4 Mismatch Negativity (MMN)

The MMN is a large negative voltage fluctuation that is maximal over frontal-central areas of the scalp and peaks between 100 and 250 ms following the deviant auditory stimulus (Näätänen, 1995; Näätänen & Alho, 1995), thus overlapping the N100 and P200 components. The MMN is an early ERP component that provides a sensitive index of the perceptual detection of change in auditory stimulation (Näätänen, 1992; Näätänen et al.,
The response is generally elicited with a standard auditory oddball paradigm following the occurrence of a deviant auditory stimulus occurring infrequently in a sequence of rapidly presented, repetitive, homogeneous, standard auditory stimuli. It can be evoked by any discriminable change in sound, such as tonal frequency or intensity, duration, interstimulus interval or location. However, unlike the N200 waveform, the MMN can be elicited in the absence of attention, therefore indicating that it is an automatic, pre-attentive auditory process (Näätänen, 1990).

The MMN wave is generated by a ‘mismatch’ process between the auditory input from a deviant stimulus with the auditory memory of the standard stimulus. According to Näätänen’s (1992) model, the MMN reflects a short-term sensory memory comparison process, and can only be elicited if the sensory memory of the standard stimulus is retained when the deviant stimulus is presented. Thus, rapid repetitions of the standard stimulus prevent the degrading in memory and ensure that the memory is still active when the deviant stimulus is delivered.

5.2.1.5 P300 Component

The P300 is arguably the most prominent and extensively researched ERP component. The P300 is a large (10-20 µV) parietal-maximum positive wave, typically observed approximately 350-450 ms post stimulus onset for visual stimuli, and 300-350 ms post stimulus onset for auditory stimuli (Picton, 1992; Polich & Kok, 1995; Comerchero & Polich, 1999). The P300 provides an index of general cognitive efficiency (Donchin & Coles, 1988). In particular, the P300 is considered to be an index of working memory (Donchin et al., 1986; Donchin & Coles, 1988), whereby its amplitude reflects the allocation of attentional resources and its peak latency reflects stimulus evaluation time or the speed of processing (Johnson, 1986; Donchin & Coles, 1988). The P300 is elicited using a simple discrimination task, dubbed the ‘oddball paradigm’, where two stimuli are presented in random order, one of which occurs less frequently than the other (i.e. the oddball). The participant is required to attentively discriminate the rare stimulus (the oddball/target) from the frequent one (standard) by noting the occurrence of only the target stimulus, typically by pressing a response button (Picton, 1992).

The P300 is typically viewed as an endogenous ERP as it is not directly affected by the physical characteristics of the stimulus presented (Donchin et al., 1978; Polich, 1998,
1999). Therefore, any rare but relevant stimulus (i.e. target stimuli that require a response) presented in any sensory modality (e.g. visual, auditory, somatosensory, etc) can elicit a P300 (Hruby & Marsalek, 2003). The literature indicates that there are no sensory modality effects on P300 scalp topography (Polich et al., 1996; Polich & Heine, 1996; Ramero & Polich, 1996; Katayama & Polich, 1999), although the amplitude and latency of the P300 wave can differ across modalities, even when task difficulty levels are similar (Polich et al., 1997; Katayama & Polich, 1999). For instance, the amplitude is smaller and the latency is shorter with responses to auditory stimuli compared to responses to visual stimuli (Pfefferbaum et al., 1984; Naumann et al., 1992; Polich & Heine, 1996; Ramero & Polich, 1996; Katayama & Polich, 1999).

It has consistently been demonstrated that stimulus type and task response conditions can modulate the P300 component (Courchesne et al., 1975; Squires et al., 1975; Courchesne, 1978; Courchesne et al., 1978; Pfefferbaum et al., 1980; Pfefferbaum & Ford, 1988; Katayama and Polich, 1996ab, 1999), whereby particularly alerting or novel stimuli (nontarget) produce an earlier frontal-central positive peak, referred to as the ‘P3a’ (Squires et al., 1975), whereas the infrequent-target stimuli (i.e. the oddball) elicit the later parietal maximum P300 peak or ‘P3b’. However, for the purpose of the present thesis only the standard P300 (P3b) will be discussed, as the P3a was not examined in the present thesis.

5.3 Amphetamine, Driving and Visual Processing

Driving a car is a complex task which involves all sensory modalities, however, vision comprises the major sensory input (Owsley and McGwin, 1999). Thus, it is logical to assume that a dysfunction within the visual system will affect driving performance and subsequently increase the risk of a road crash (Burg, 1967, 1968; Anstey et al., 2005). Visual evoked potentials are frequently used to obtain insight into the organisation of the visual system and visual attention, both of which are crucial to driving. Therefore, as driving is primarily a visual task, it is important to investigate whether amphetamine affects aspects of visual processing which, if found, may help elucidate how amphetamine use is associated with amphetamine-related driving fatalities. The present thesis focused on two fundamental aspects of visual processing: the visual system pathways, specifically the magnocellular and the parvocellular pathways; and aspects of the visual field, specifically relating to the central and the peripheral visual field.
5.3.1 Amphetamine, Driving and the Magnocellular and Parvocellular Visual Pathways

The visual system is organised into two main parallel systems, the magnocellular pathway and the parvocellular pathway (Butler et al., 2005; Farrag et al., 2002). These two functional entities are subserved by different types of neuronal cells and have different representations and pathways within the visual system. Both the magnocellular and parvocellular pathways begin in the retina, and project via the lateral geniculate nucleus (LGN), to the primary visual cortex (striate cortex, V1) (Livingstone et al., 1991). From the primary visual cortex, magnocellular information is conveyed predominantly to the parietal-occipital cortex (the ‘where’ pathway), and parvocellular information is conveyed predominantly to the temporal-occipital cortex (the ‘what’ pathway) (Pitzalis et al., 2005). Although some crossover does occur between the pathways, the two visual systems are largely segregated and independent (Livingstone et al., 1991).

The magnocellular system is responsible for the processing of transient visual stimuli (Samar et al., 2002; Livingstone et al., 1991). It transfers low contrast visual information rapidly to the cortex and is sensitive in detecting motion and coarse detail (Samar et al., 2002; Livingstone et al., 1991; Schechter et al., 2005). The magnocellular pathway is involved in visual attention (Samar et al., 2002; Steinman et al., 1997; Butler et al., 2005; Schechter et al., 2005) and processing of overall stimulus organisation (Samar et al., 2002; Butler et al., 2005). As magnocells receive information from larger regions of the visual field (peripheral processing), this visual system is particularly insensitive to high spatial frequencies (Brannan et al., 1998; Butler et al., 2005).

In contrast, the parvocellular pathway is a sustained system with slower processing speed (Brannan et al., 1998). The parvocellular system transfers high contrast visual information to the cortex and is sensitive in processing pattern and fine-grained stimulus information, as well as identifying colour and objects (Brannan et al., 1998; Butler et al., 2005; Farrag et al., 2002). As parvocellular neurons receive input from smaller regions of the visual field (central processing), this visual system is more sensitive to high spatial frequencies (Brannan et al., 1998; Butler et al., 2005).

The effect of amphetamine, or other similar dopamine agonists, on the magnocellular and parvocellular visual systems has not, to the author’s knowledge, previously been explored.
In light of this, research examining visual system functioning in patients with schizophrenia will briefly be discussed, as the acute effects of amphetamine have been extensively used to model schizophrenic deficits in early processing and attentional dysfunctions, therefore suggesting some similarities in cognitive functioning between amphetamine effects and schizophrenic symptoms. Although direct associations cannot be made between these two types of research, reviewing the schizophrenia research may shed some light as to how amphetamine may affect early visual system processing.

Previous clinical studies have consistently shown significant dysfunctions in early-stage visual processing in schizophrenia (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006). Specifically, the literature highlights that the early P100 component is impaired in schizophrenia (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006). Furthermore, this reduction in P100 has been shown to be most pronounced in the magnocellular system (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006), therefore, suggesting a preferential magnocellular impairment in schizophrenia.

As reductions to the P100 component during early visual processing, particularly within the magnocellular visual system, have been implicated in attentional dysfunctions (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006), and low doses of amphetamine have been shown to improve attention (Kelly et al., 1991; Koelega 1993; Comer et al., 1996; Ward et al., 1997; McKetin et al., 1999; Wachtel & de Wit, 1999; de Wit et al., 2002; Cami et al., 2000; Johnson et al., 2000), it seems reasonable to assume that the P100 component would be enhanced with amphetamine on measures of early visual processing, with particular improvements noted within the magnocellular system. However, research needs to be conducted to investigate this hypothesis.
In terms of driving, although, to the author’s knowledge, there has been no research that has explored the direct involvement of the visual system pathways in driving ability, there is some indirect evidence to suggest an association between the two. Herkes and Conlon (2002) conducted a study to determine whether the increase in mature-age related road fatalities was associated with a possible age-related decline in the magnocellular processing subsystem. The authors found a significant difference in performance between mature and young drivers on tasks measuring magnocellular performance, whereas, no difference in performance was found between the two driver groups on tasks measuring parvocellular processing. Herkes and Conlon (2002) discussed these findings as having negative implications for mature-aged drivers. Consistent with these findings, Steinman et al., (1994) reported age-related deficits in magnocellular functioning, and concluded that these deficits are a primary cause for visual attention deficits in the elderly, also having implications in daily functioning, such as driving. These results, therefore, provide some suggestion that the visual system pathways, particularly the magnocellular pathway, may be implicated in driving ability. Therefore, the effects of amphetamine on the visual system should be examined, as dysfunctions to the visual pathways could subsequently be associated with the amphetamine-related driving fatalities.

In summary, as a result of the lack of literature examining the acute effects of amphetamine on the magnocellular and parvocellular pathways, few conclusions can be made with reference to amphetamine and early visual processing. Although only speculative, previous schizophrenia research provides some evidence to suggest that acute amphetamine may enhance early visual processing, however, research needs to be conducted to explore this issue further. In terms of driving, as there is some evidence to suggest that the visual system pathways, specifically the magnocellular system, may be implicated in driving ability, research needs to be conducted that examines the acute effects of amphetamine on the magnocellular and parvocellular visual systems in order to help elucidate how amphetamine use may be associated with amphetamine-related road fatalities.

5.3.2 Amphetamine, Driving and the Visual Field

The visual field refers to the total visual area around the point of fixation in which information can be perceived and processed (Mackworth, 1965). Specifically, central visual field refers to the area that is in the fovea or the fixation point, and peripheral visual
field refers to the area outside the fixation point where information can still be perceived. The technique most often employed to measure central and peripheral visual field consists of presenting a fixation stimulus in the fovea while asking participants to identify and subsequently respond to a target presented in either the central or peripheral area of the visual field. The quantity and quality of perceived visual information is dependant on the size of the visual field, thus restriction of the visual field can have negative consequences to the analysis of the environment. Previous studies have demonstrated that the visual field is not fixed, as it can vary with individual subject characteristics, such as age (Ball et al., 1988). Furthermore, characteristics of visual field tests can also affect the size of the visual field. For example, central task complexity, peripheral task complexity, and priority given to the central task over the peripheral task, can all decrease the visual field (Ikeda & Takeuchi, 1975; Holmes et al., 1977; Williams, 1988).

ERP research examining the effects of amphetamine on the visual field is scarce, however, previous behavioural research has addressed this aspect. Mills et al. (2001) demonstrated that \(d\)-amphetamine improved performance on tasks where stimuli were presented centrally, with little or no changes observed when stimuli were presented in peripheral positions (Mills et al., 2001). Mills et al. (2001) argued that this represented the ‘tunnel vision’ effect, which has been reported to result from sympathetic arousal, in which perceived cues are restricted to the focal point (Easterbrook, 1959). It has been argued that mild arousal, such as that experienced following amphetamine consumption, benefits performance only when stimuli are presented centrally, while simultaneously impairing performance to stimuli presented in the periphery (Easterbrook, 1959; Mills et al., 2001). Thus, these results suggest that amphetamine may impair peripheral visual field processing.

It has been argued that any deterioration of the visual field can have significant consequences for many everyday activities, such as driving (Rogé et al., 2002). Previous research has shown that when the peripheral visual field is artificially impaired while driving, a decrease in the ability to estimate vehicle speed, to detect road signs and to avoid obstacles is observed (Osaka, 1988; Troutbeck & Wood, 1994; Wood & Troubeck, 1993). Furthermore, previous studies have demonstrated that when subjects are required to simultaneously complete a central task while driving, the ability to drive and to perceive decreases in the speed of vehicles in front, deteriorates (Summala et al., 1996; Summala et
Further substantiation for the role of the peripheral visual field in driving was highlighted in a study addressing visual parameters deemed to be most important for safe vehicle maneuvering (such as, overtaking, lane changing, collision avoidance, height clearance). The peripheral visual field was reported to be the most important factor for safe driving maneuvers (Szlyk et al., 1991).

A number of other studies have demonstrated the importance of the peripheral visual field in driving. Johnson and Keltner (1983) reported on the incidence of visual field loss in 10,000 participants. The authors observed that participants with binocular peripheral visual field loss had a driving accident rate that was twice as high as participants with a normal visual field. Other research has also shown that constriction of the binocular peripheral visual field significantly impairs driving performance (Szlyk et al., 1992; Wood & Troutbeck, 1992, 1993, 1994; Owsley, Ball et al., 1998; Owsley, McGwin et al., 1998; Sims et al., 2000).

In summary, the above studies highlight the need for research to be conducted addressing the effects of amphetamine on the visual field. The limited amphetamine research indicates that amphetamine may produce decrements to the peripheral visual field as deficits have previously been reported on tasks assessing ‘tunnel vision’. Following this, there is a considerable body of literature that emphasizes the significant role that the peripheral visual field has on driving performance. Thus, examining the effects of acute amphetamine on aspects of the visual field may help determine how amphetamine use may be associated with amphetamine-related road fatalities, as decrements to the peripheral visual field may be related with amphetamine-related driving impairments.

5.4 Amphetamine, Driving and Auditory Processing

Driving a car involves all sensory modalities, and although the visual modality is arguably the most important during driving, efficient auditory processing is also an important component to safe driving (Anstey et al., 2005). As it has not been previously established how amphetamine use may be associated with amphetamine-related road fatalities, it is important to investigate all aspects of human functioning relevant to driving, including auditory processing. Therefore, the present thesis focused on aspects of auditory processing including, the startle reflex and prepulse inhibition of the startle response, mismatch negativity (MMN), and the P300 response.
5.4.1 Amphetamine, Driving and Mismatch Negativity (MMN)

MMN has received considerable attention as a measure for clinical research, as it provides an objective index of auditory discrimination, sensory memory, and involuntary attention, that is elicited independent of the direction of attention (Näätänen, 2000). The most prominent MMN findings are in the assessment of cognitive brain development and dysfunction in newborns (Ceponiene et al., 2002a, Cheour et al., 2002) and infants (Cheour-Lunthanen et al., 1996, Kushnarenko et al., 2002), normal aging (Ceponiene et al., 2002b), Alzheimer’s disease (Pekkonen, 2000; Pekkonen et al., 1996, 2001), schizophrenia (Shelley et al., 1991; Catts et al., 1995; Javitt et al., 1993, 1995; Umbricht et al., 1998; Light & Braff, 2005; Umbricht & Krljes, 2005), and as an index of auditory dysfunction in dyslexia (Baldeweg et al., 1999; Kujala et al., 2000).

Although this pre-attentive information processing component has been employed in a wide variety of theoretical, empirical, and clinical applications, in regards to amphetamine use there has been no research that has explored the effects of this drug on the MMN response. In light of this, the effects of other dopamine agonists on MMN will be discussed because the enhancement of dopamine function is a key consequence of amphetamine intoxication.

In a recent study, Hansenne et al. (2003) assessed the relationship between both noradrenergic and dopaminergic systems and MMN in healthy adults. Specifically, dopaminergic activities were examined following the administration of an acute dose of apomorphine. The authors found that the direct dopamine agonist, apomorphine, did not effect MMN amplitude or latency. Hansenne et al. (2003) argued that based on these results dopaminergic activities do not appear to modulate MMN, however, the authors concluded that given the complexity of the central neurotransmitter system, the results can not be considered definitive and further research was required.

Winsberg et al. (1997) investigated the effects of methylphenidate (a central nervous system stimulant with similar properties to that of amphetamine) on several ERP indices in children with Attention Deficit Hyperactivity Disorder (ADHD). Among other findings, the authors failed to observe any effects of methylphenidate on the MMN component in children with ADHD. Based on the absence of a drug-induced change in MMN and the lack of differences between the control group and the ADHD group in MMN response,
Winsberg et al. (1997) concluded that MMN is not affected by methylphenidate. Interestingly, in a previous pilot study, using a subset of the sample employed in the Winsberg et al. (1997) study, Winsberg et al. (1993) reported differences in MMN between the ADHD group and the control group, and found the MMN response to normalise with methylphenidate treatment. However, as these results were not replicated in the later, extended investigation, these findings should be considered with caution.

Although there have been few studies that have explored the effects of dopamine modulation on the MMN response, the limited reports suggest that amphetamine should also have no effect on MMN due to its similar effect in dopamine activity. However, it is also possible that amphetamine may produce different MMN effects to that of methylphenidate due to its influence on other neurotransmitters, such as norepinephrine and serotonin. Furthermore, it should be noted that previous research has demonstrated that the COMT gene (which is related to dopamine function) is related to MMN, thus suggesting that dopamine modulation may in fact affect MMN (Baker et al., 2005). These inconsistencies, thus, highlight that further research is required to specifically assess the acute effects of amphetamine on MMN in order to understand the effect amphetamine has on this pre-attentive component.

In terms of driving, assessing the effects of amphetamine on the MMN response can provide useful information as to how efficiently a driver can automatically attend to key changes in the traffic environment. Involuntary attention shifting is an important function that helps drivers attend to unexpected and potentially harmful changes in the traffic environment. However, this involuntary shift in attention needs to be controlled when concentrating on goal-directed functioning, such as operating a motor vehicle. Impaired control of involuntary attention shifting can cause pronounced distractibility and an inability to modify responses to changing external stimuli. For instance, while driving a car, many sounds are continually perceived from the environment but not attended to, such as children playing on the street, passing motor vehicles, and rain. However, some sudden changes in auditory stimulation, such as a car horn, need to be immediately and automatically detected irrespective of where attention is currently located. This shift in attention, as a result of the perceptual detection of change, is required to avoid negative traffic consequences.
Although previous dopamine research suggests that amphetamine should have no effect on MMN due to its similar dopamine enhancing effects, it is possible that amphetamine may produce different effects as a result of its influence on other neurotransmitter activity, namely norepinephrine and serotonin. Thus, as the effects of amphetamine on MMN have not previously been examined, it cannot be dismissed that amphetamine-related driving impairments are not associated with possible amphetamine-induced modulations to the MMN response. Therefore, research needs to be conducted to examine the acute effects of amphetamine on MMN which, in turn, may provide some insight as to how amphetamine use may be associated with amphetamine-related driving fatalities.

In summary, literature pertaining to the effects of amphetamine on the MMN response in humans is non-existent. However, the limited dopamine agonist research provides some evidence to suggest that amphetamine may not modulate MMN. However, as amphetamine also exerts its influences on other neurotransmitters, it is possible that amphetamine will affect MMN differently to that of other dopamine agonists. Therefore, research is required that specifically examines the acute effects of amphetamine on the MMN response. Furthermore, as MMN reflects processes that are important to driving, assessing the acute effects of amphetamine on this component may help clarify how amphetamine use is associated with amphetamine-related fatalities.

5.4.2 Amphetamine, Driving and Prepulse Inhibition of the Acoustic Startle Reflex

Prepulse inhibition (PPI) of the startle reflex helps regulate environmental inputs and selectively allocates attentional resources to relevant stimuli. However, a breakdown in this normal ‘gating’ process has been argued to contribute to the sensory, motor and/or cognitive dysfunctions manifested in several neuropsychiatric disorders (Swerdlow et al., 1992a), such as, schizophrenia (Braff et al., 1978, 1992, 1999, 2001; Cadenhead et al., 1993, 2000; Grillon et al., 1992; Dawson et al., 1993; Bolino et al., 1994; Kumari et al., 1999, 2000), Tourette Syndrome (Castellanos et al., 1996), Huntington’s Disease (Swerdlow et al., 1995), and Obsessive Compulsive Disorder (OCD) (Swerdlow et al., 1993), as intrusive overwhelming stimuli are not filtered out properly.

The PPI of the startle reflex has been shown to be modulated pharmacologically (Mansbach et al., 1988; Swerdlow et al., 1991, 1992b, 1994, 2003; Bakshi et al., 1995; Wan et al., 1995) with experimental animals and human subjects. Animal research has
consistently shown that the PPI is disrupted in rats after the administration of drugs that facilitate dopaminergic transmission including the direct dopamine agonist apomorphine (Swerdlow et al., 1986, 1991, 1994; Mansbach et al., 1988), and the indirect dopamine agonist d-amphetamine (Mansbach et al., 1988; Swerdlow et al., 1994, 2003; Bakshi et al., 1995; Wan et al., 1995); and non-selective dopamine receptor antagonists have been shown to reverse these disruptive effects (Mansbach et al., 1988; Swerdlow et al., 1991, 1994).

The disruptive effects of dopamine agonists, specifically d-amphetamine, on PPI have also been demonstrated in healthy humans, however, these findings have not been consistent (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2003). Kumari and colleagues (1998) assessed the acute effects of 5mg d-amphetamine and 5mg haloperidol on habituation and PPI of the acoustic startle reflex response. Sixty participants were randomly assigned to one of three drug conditions (placebo, d-amphetamine, or haloperidol) and were tested twice; once prior to drug administration and once at 150 min after drug administration. The authors found that PPI did not differ significantly between the placebo and d-amphetamine groups, however, only a low dose of amphetamine (5 mg) was administered. Further analyses revealed that in a subgroup of smoking participants (n=6), PPI was significantly reduced following the administration of d-amphetamine compared to the same participants performance prior to drug administration. The authors concluded that 5mg d-amphetamine disrupted PPI in smoking participants, but had no effect in non-smoking participants, suggesting that smoking cigarettes may have an influence on the dopaminergic system. These results should, however, be interpreted with caution as it has been argued that low doses of amphetamine, such as those administered in the study by Kumari et al. (1998), are unlikely to produce decrements in performance (Logan, 2002). Furthermore, previous research has shown cigarette smoking to enhance PPI (Kumari et al., 1996), and it seems unlikely that such a low dose of amphetamine (5 mg) could reverse these effects. Thus, further research is warranted.

Disruptions to PPI in humans have, however, been reported following the administration of considerably higher doses of d-amphetamine. Hutchison and Swift (1999) investigated the effects of an oral dose of 20mg of d-amphetamine in healthy (non-smoking) humans on a variety of psychophysiological and subjective measures, including PPI. Using a within-subject design, 36 participants were assessed at 60, 90, and 120 minutes after the
consumption of \( d \)-amphetamine. The authors found that \( d \)-amphetamine reduced sensorimotor gating relative to the placebo condition only at 90 minutes following drug administration. Hutchison et al. (1999) subsequently reported that the Novelty Seeking subscale of the Tridimensional Personality Questionnaire (TPQ), which is argued to be directly associated with dopamine activation (Cloninger, 1987), moderated the effects of \( d \)-amphetamine on PPI, whereby participants high in novelty seeking attributes showed a greater amphetamine-induced attenuation of PPI (Hutchison et al., 1999).

In contrast, Swerdlow et al., (2002a) found no effect of 20 mg amphetamine on PPI over a period of 30-165 min after drug ingestion, using a between-subject design. However, only a small sample size was used \((n = 6)\), and the task employed only measured a single-prepulse interval \((100\text{ms})\). Therefore, the authors conducted a further study that addressed these limitations (Swerdlow et al., 2003). Specifically, using a between-subject design, 15 participants were administered placebo and 15 participants were administered 20 mg \( d \)-amphetamine (Swerdlow et al., 2003). Although, amphetamine was not found to disrupt PPI compared to the placebo condition, an amphetamine-reduced PPI effect was evident when post-drug PPI was compared to each participants’ pre-test baseline (pre-drug administration test) level of PPI (Swerdlow et al., 2003). However, unlike in Hutchison and Swift’s study (1999) that reported a disrupted PPI at 90 minutes post drug consumption, Swerdlow et al. (2003) reported that amphetamine reduced PPI at 25-40 minutes post drug administration, and not at 55-75 or 150-165 minutes. Furthermore, in contrast to Hutchison et al.’s (1999) findings, Swerdlow et al. (2003) failed to observe any significant association between the effects of amphetamine on PPI and personality markers associated with dopamine activation, which is consistent with previous reports using a drug free population (Swerdlow et al. 2002b).

Recently, Alessi et al., (2003) investigated whether individual differences in the level of motor activity (high versus low level) in a novel environment, predicted specific behavioural and physiological effects following 5 mg, 10 mg, or 20 mg \( d \)-amphetamine in healthy adults. The authors found that \( d \)-amphetamine did not affect the PPI response at 150 min after drug administration. The authors considered several factors that may have contributed to the lack of a \( d \)-amphetamine disrupted PPI effect, such as, time of task administration, task type, sample size, and gender differences. However, consistent with the findings by Hutchison et al. (1999), Alessi et al. (2003) found a negative correlation
between sensation seeking and PPI, with higher sensation-seeking personality scores associated with smaller PPI, following the administration of 10 mg and 20 mg d-amphetamine.

Although animal research has consistently shown amphetamine to disrupt PPI (Mansbach et al., 1988; Swerdlow et al., 1994, 2003; Bakshi et al., 1995; Wan et al., 1995), previous work with healthy humans have produced inconsistent findings. Furthermore, those studies that have reported PPI attenuation following amphetamine consumption in healthy humans were only for specific subgroups, distinguished by participants smoking history (Kumari et al., 1998), personality features (Hutchison et al., 1999), or when a within-subject analyses was employed (where post-drug PPI levels were compared to baseline PPI levels) (Swerdlow et al., 2003). The discrepancy in results may be attributed to several factors, such as, considerable differences in the time frame that PPI was assessed following amphetamine administration, stimulus characteristics such as prepulse intervals, response ranges, and other design features. Therefore, future research should employ similar study designs in order to reduce the amount of variance between the different studies.

In terms of driving, assessing the effects of amphetamine on PPI can provide useful information as to how efficiently the driver filters out irrelevant information. Operating a motor vehicle is a dynamic task which requires consistent attention to a substantial amount of visual and auditory information. In order to cope with the abundance of incoming stimuli, the driver must efficiently attend to relevant information, while ignoring irrelevant information, to prevent an overload of information. Thus, efficient information processing allows the driver to regulate environmental inputs and selectively allocate attention to relevant stimuli. Therefore, a disruption to the PPI response may be dangerous when driving, as a decrease in the drivers’ ability to filter out irrelevant or intrusive information appropriately, may result in an overload of information. This overload of information would increase the drivers’ risk of failing to attend to relevant information and potential hazards in the traffic. As there is some evidence to suggest that amphetamine may disrupt PPI, amphetamine-related driving impairments may be associated with amphetamine-induced dysfunctions in PPI. However, as the literature is inconsistent, further research is needed to explore the acute effects of amphetamine on the PPI response, in order to further understand how amphetamine use may be associated with amphetamine-related driving fatalities.
In summary, the limited research examining the effects of amphetamine on PPI in healthy humans is inconsistent, indicating that further research is needed to clarify this issue. Furthermore, those studies that have reported PPI attenuation following amphetamine consumption in healthy humans have only done so for specific subgroups, distinguished by participants smoking history (Kumari et al., 1998), personality features (Hutchison et al., 1999), or when a within-subject analyses was employed (where post-drug PPI levels were compared to baseline PPI levels) (Swerdlow et al., 2003). However, as there is some evidence to suggest that amphetamine may disrupt PPI, and as PPI reflects processes that are important to driving, it is important that further research be conducted that examines the acute effects of amphetamine on PPI. This may help clarify how amphetamine use is associated with amphetamine-related driving fatalities.

5.4.3 Amphetamine, Driving and the P300 Component

The P300, reflecting a number of basic cognitive processes (Donchin & Coles, 1988; Johnson, 1988; Picton, 1992; Polich, 1993), has been employed in a wide variety of theoretical, empirical, and clinical applications (Polich et al., 1997). Since its discovery by Sutton and colleagues (Sutton et al., 1965), studies have demonstrated that P300 amplitude and latency can be used as sensitive indices of the nature and speed of cognitive processing (Sutton et al., 1965; Polich, 1998; 1999). Therefore, it is a useful measure for assessing the acute effects of drugs, such as amphetamine, on human functioning.

The limited research that has explored the effects of amphetamine on the P300 component has produced inconsistent results (Halliday et al., 1994; McKetin et al., 1999). Halliday et al. (1994) found that a 10mg oral dose of d-amphetamine had no effect on P300 latency when measured from the average, yet d-amphetamine was found to speed reaction time performance. However, when P300 latency estimates were based on single-trial epochs, which is argued to be a more drug sensitive method (Brandeis et al., 1992), d-amphetamine was found to speed the P300. The authors concluded that the speeding of the P300 observed following the administration of d-amphetamine, reflected the noradrenergic effects of the drug, whereas the considerably greater speeding of reaction time following the administration of d-amphetamine, reflected the dopaminergic effects. Although these results provide some evidence to suggest that amphetamine speeds cognitive processing, further research is necessary, as traditionally the P300 is assessed using the averaging
technique, rather than with single-trial epochs, which was found to produce no significant results.

More recently, McKetin et al. (1999) assessed the effects of 10 mg and 20 mg \(d\)-amphetamine on selective attention using an auditory oddball paradigm. Similarly, the authors observed a speeding of reaction time without a commensurate speeding of P300 latency. In addition, McKetin et al. (1999) observed that \(d\)-amphetamine produced an increase in P300 amplitude at the vertex (Cz electrode) following the administration of 20 mg \(d\)-amphetamine. However, this effect was not found for the parietal electrodes, such as Pz. This increase in P300 amplitude reported at the vertex was found to be correlated with an increased accuracy in performance and a decrease in reaction time. Based on these results, the authors concluded that amphetamine improved the detection of relevant target stimuli. However, these findings should be interpreted with caution as \(d\)-amphetamine was only found to affect P300 amplitude at the vertex, specifically at the Cz electrode, whereas it has been well-established that the P300 is maximal at parietal scalp sites (Picton, 1992; Polich & Kok, 1995), particularly at the Pz electrode.

These studies, thus, provide some evidence to suggest that amphetamine may modulate the P300. However, as the findings are inconsistent across the two studies, and vary in the type of analysis employed, further research is warranted. In light of the limited and inconsistent literature examining the effects of amphetamine on the P300, the effects of other indirect dopamine agonists on the P300 will be discussed in an attempt to further understand the effects of amphetamine on this ERP component. The majority of this research has examined the effects of methylphenidate (a central nervous system stimulant) on account of its relevance in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Although, it has generally been shown that acute doses of methylphenidate have no effect on the P300 component (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Fitzpatrick et al., 1988), there have also been several studies that have shown the P300 to be modulated with methylphenidate (Coons et al., 1981; Strauss et al., 1984; Brumaghim et al., Study 2, 1987; Cooper et al., 2005). These studies will be briefly discussed.

Cooper et al. (2005) examined the effects of an acute dose of 5 mg, 15 mg and 45 mg of methylphenidate on behavioural and ERP measures during a working memory task.
Cooper et al. (2005) found a significant linear reduction in reaction time, omission errors and P300 latency, with a corresponding increase in P300 amplitude, with increased methylphenidate dose. The authors concluded that the relationship between these measures supported for an increase in performance following the administration of methylphenidate. Similarly, Brumaghim et al. (1987) examined the impact of 0.3mg/kg (maximum 25 mg) methylphenidate on the P300 wave, during a memory scanning task, in two separate studies. In both experiments the results yielded a significant decrease in error rates and reaction time, with no change in P300 amplitude, following the administration of methylphenidate. However, in contrast to Study 1, which revealed no significant effects on P300 latency, in Study 2 the authors found a significant reduction in P300 latency following the administration of methylphenidate. The authors discussed the discrepancy in results as being attributed to procedural differences between the two experiments, such as stimulus characteristics. Finally, in two studies assessing vigilance performance in healthy adults, 20 mg methylphenidate was found to increase P300 amplitude only when a substantial number of errors were made on the tasks or when a performance decrement was observed over time during the placebo conditions (Coons et al., 1981; Strauss et al., 1984). Although these experiments provide some evidence that methylphenidate modulates the P300, the results are inconsistent, and thus, little can be inferred as to the effects of amphetamine on the P300. The inconsistencies in results may be attributed to a number of factors, such as, task differences or study design differences, which indicate that further research is necessary to determine how amphetamine influences the nature and speed of cognitive processing as measured with the P300.

The present review of the literature highlights the inconsistency pertaining to the effects of amphetamine and other stimulants on P300 latency and amplitude. However, it has generally been shown that d-amphetamine and methylphenidate speed reaction time without a commensurate speeding of P300 latency (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Halliday et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999). It has, therefore, been argued that this may occur because these stimulants act on neurotransmitter systems, specifically dopamine, that mediate response processing (denoted by the decreases in reaction time), rather than stimulus evaluation (denoted by the lack of change in P300 latency) (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Halliday et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999).
This suggests that d-amphetamine and methylphenidate appear to affect information processing after the processes indexed by P300 are complete (as can be inferred from decreases in reaction time with no changes in latency). However, it should be noted that although stimulants typically do not affect P300 latency, accuracy has been shown to be improved by these drugs, suggesting that the quality of evaluation is enhanced (Coons et al., 1981; Strauss et al., 1984; Brumaghim et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999; Cooper et al., 2005).

In relation to driving, assessing the P300 can provide useful information regarding how efficiently a driver processes information from the environment. Operating a motor vehicle requires the constant ‘updating of working memory’ as new information is integrated within the current schema of the traffic environment. This reflects the basic information processing mechanisms of attention allocation and immediate memory. Research has shown that speed of information processing and efficient allocation of attention is associated with safe driving whereby, deficits in either process can increase crash risk (for a review see Anstey et al., 2005). The speed at which information is processed is an important aspect to responding appropriately to road situations, and successful negotiations of difficult or dangerous traffic conditions. Information processing speed also influences decision-making, as often there are only brief time periods during which drivers must make an appropriate decision and response. Assessing the P300 response in the context of driving performance can provide important information as to how and when information processing is affected following the consumption of amphetamine. This may thus provide insight as to how amphetamine use may be associated with amphetamine-related driving fatalities.

In summary, the limited research addressing the effects of d-amphetamine and other indirect dopamine agonists, specifically methylphenidate, on P300 amplitude and latency is ambiguous, and highlights the need for further research. Previous research has, however, shown decreases in reaction time without a commensurate effect on P300 latency, thus suggesting stimulant-related improvements in response processing rather than stimulus evaluation. However, few studies have found this effect with amphetamine. Thus, although amphetamine acts on similar neurotransmitters as methylphenidate, its influences on other neurotransmitters may produce different results. Therefore, further research is required that specifically examines the acute effects of amphetamine on the P300. In addition, as the
P300 reflects processes that are important to driving, assessing the acute effects of amphetamine on this component may help clarify how amphetamine use is associated with amphetamine-related driving fatalities.
Chapter 6. Detection of Drug Impaired Drivers

Although it has not been previously established that amphetamine use ‘causes’ road crashes, the epidemiological literature (refer to Chapter 3 Amphetamine and Driving) does indicate that there has been an overall increase in the number of drivers that drive while intoxicated with amphetamine, and that there is some association with amphetamine use and road fatalities. This has raised public and government concern, therefore, law enforcement strategies aimed at reducing the percentage of drivers that drive while intoxicated with amphetamine have been introduced. The present chapter will review the literature that supports the introduction of the legislation authorising Victorian police officers to administer the Standardised Field Sobriety Tests (SFSTs) to drivers, to detect driving impairment associated with the consumption of a drug other than alcohol. This will provide some indication of whether or not this is a valid method for detecting amphetamine intoxication.

6.1 Methods of Drug Detection

There are several different methods for determining the presence of a drug other than alcohol, such as, analysis of blood, urine, sweat, hair and saliva specimens, and performance on impairment tests (Samyn et al., 2002; Samyn & van Haeren, 2000). That there are these different methods highlights the division between testing for the presence of a drug in a driver’s specimen (the ‘drug presence approach’), and testing for driver impairment with respect to behaviour and physiology (the ‘impairment approach’).

The ‘drug presence’ approach relies on drug detection devices that are able to detect the presence of drugs other than alcohol in blood, urine, sweat, hair and saliva. A number of drug detection devices are available, however, many of them do not have adequate evaluation data that demonstrate their reliability or validity in routine use, with the exception of blood analysis. Furthermore, many devices are not appropriate or cost-effective for routine roadside drug testing (for example blood or urine tests). Recently, much attention has focused on the use of saliva drug detection devices, as these are the preferred method for use on the roadside because they are non-invasive, fast and simple to administer. However, further research is still required to adequately evaluate them. Irrespective of what method is used, the major limitation with the ‘drug presence’ approach
is that there is no clear relationship between a level of a drug in a specimen and an
associated level of impairment. Therefore, this approach can only be used to indicate drug
presence and not driving impairment. In contrast, the ‘impairment approach’ directly
addresses this issue as it identifies those drivers who are impaired with respect to
behaviour and physiology, irrespective of the cause. This latter approach consists of
standardised performance tests assessing attention, balance, and motor coordination, which
have been shown to be reliable impairment detection methods for alcohol and, in some
programs, for drugs other than alcohol.

6.2 Testing for Drugs Using Blood and Saliva Specimens

Although blood sample methods are not appropriate roadside testing tools, this is the most
reliable approach for detecting and quantifying the presence of drugs as a cause of
intoxication. Gas chromatography-mass spectrometry (GC/MS) is the most widely
employed method for confirmatory analysis and screening, since it provides a high level of
sensitivity and specificity (Kramer & Maurer, 1998; Moeller & Kramer, 2002). This is a
combined method utilizing the separation properties of gas chromatography with the
identification and quantification ability of the mass spectrometer (Kramer & Maurer,
1998). This method can confirm the presence of a range of drugs in blood simultaneously.

There are several saliva drug testing devices that are currently available. However, the
devices are not currently in widespread use within law enforcement agencies, as many of
the devices have limited validation data (Buxton et al., 2001). Moreover, the limited
research that has been conducted has involved spiking saliva samples with a specific
amount of a drug and using these spiked samples to test the efficiency of various saliva
drug testing devices to detect the presence of drugs. However, these spiked samples do not
provide appropriate validation data, as drugs are metabolised differently in humans than in
spiked samples, thus the results can be quite different. In addition, there are no standard
analytical cut-off values for specific drug classes (used to determine positive and negative
results) available for saliva drug tests. These cut-off values are generally based on the
sensitivity of the assay and the pharmacological relevance of the drug.

However, there are many advantages in using saliva to test for drugs. Saliva contains the
parent drug (which refers to the identifiable psychoactive compound of a substance)
similar to blood which depicts recent use, thus providing a good indication of current
intoxication. In addition, the level of drug in saliva is correlated to the level of drug in blood, reportedly with a ratio of 1:2 (Skopp & Pötsch, 1999), although this can vary across drugs. Furthermore, saliva tests are non-invasive, fast and simple to administer on the roadside.

### 6.3 Testing for Drugs Using Performance Tests

Although currently there are several alternative methods for determining drug use, many countries continue to employ performance tests in drug-detection programs, because existing national and state laws prevent police officers from obtaining specimens from drivers. Several impairment approaches have been adopted in the US, UK and Australia. Although these behavioural impairment tests vary, they all share the principle that certain physiological and/or psychomotor behaviours will be affected by drug consumption and that these effects can be compared to the normative data for unimpaired (drug-free) individuals. The Standardised Field Sobriety Tests (SFSTs; US), the Drug Evaluation and Classification Program (DECP; US), the roadside Field Impairment Testing process (FIT; UK), and the Performance Impairment Tests (PIT; Australia), are the most common test batteries being implemented to test drivers for impairment. As the SFSTs (referred to in Australia as PIT) are implemented in Victorian police procedures for identifying drug-impaired drivers, this procedure will be the focus of this chapter. However, little research has been conducted using the SFSTs alone in identifying drug-related impairment, therefore, research employing the DECP will be discussed, as this program includes the administration of the SFSTs in its ‘12-step’ procedure.

### 6.4 What are the Standardised Field Sobriety Tests?

The Standardised Field Sobriety Tests (SFSTs), referred to in Australia as Performance Impairment Tests (PIT), were developed by the Southern California Research Institute and pioneered in the USA for the detection and assessment of driving impairment caused by alcohol. The SFSTs are designed to assess psychomotor and cognitive functioning, and also include a divided attention component. The divided attention component is intended to assess the ability to sustain attention, follow simple instructions and divide attention between multiple tasks. This divided attention component is purported to be particularly relevant to driving, which also requires multiple tasking. The SFSTs are comprised of three tests; the Horizontal Gaze Nystagmus (HGN) test, the Walk and Turn (WAT) test, and the One Leg Stand (OLS) test (Papafotiou et al., 2005), which are rigidly administered without
any deviation in instruction or assessment. These tests were selected from many sobriety
tests as the most reliable, accurate and practical tests for detecting alcohol intoxication
(Burns & Moskowitz, 1977).

The tests have been demonstrated to be a sensitive measure of identifying alcohol
intoxication (Tharp et al., 1981; Compton, 1985; Burns & Anderson, 1995; Stuster &
Burns, 1998), with several studies indicating that performance on the SFSTs provides an
accurate indicator of impairment associated with alcohol consumption (Tharp et al., 1981;
Compton, 1985; Burns, 1987; Burns & Anderson, 1995; Stuster & Burns, 1998). In a large
scale project, Tharp et al. (1981) investigated the efficiency of the SFSTs in identifying
alcohol intoxication in a laboratory setting, and demonstrated that the SFSTs accurately
classified 81% of subjects as either above or below the Blood Alcohol Concentration
(BAC) criterion level of 0.10%. A limitation of the study by Tharp et al. (1981) was that
the test administrators were not adequately trained in administering the SFSTs. Thus, in a
later study, Burns and Anderson (1995) addressed these issues and examined real data
collected from experienced police officers using the SFSTs. The authors found that the
police officers correctly classified 86% of drivers with a BAC reading of above or below
the criterion level (0.05%). Drivers over the limit were correctly identified in 93% of cases,
and drivers below the limit were correctly identified in 64% of cases. The SFSTs have also
been shown to be efficient (94%) in detecting BAC levels between 0.04 and 0.08% (Stuster
& Burns, 1998).

Although the SFSTs were designed specifically for the detection of alcohol-intoxicated
drivers, the tests have been implemented within several drug impaired driver detection
programs to identify the presence of drugs other than alcohol in drivers. However, few
studies have examined the efficiency of the SFSTs alone in detecting drug-intoxicated
drivers. One study that has investigated the efficiency of the SFSTs alone, to detect recent
cannabis use, was recently conducted by Papafotiou et al. (2005). In a double blind,
placebo-controlled trial, 40 participants were administered placebo, low dose cannabis
(1.74% THC), and high dose cannabis (2.93% THC). The authors reported that the SFSTs
correctly identified the presence of cannabis in 23% of the low dose cases and 46% of the
high dose cases. Furthermore, the authors reported that impairment on the One Leg Stand
(OLS) test was the most sensitive test in detecting the presence of cannabis.
There has been no other research, to the author’s knowledge, that evaluates the efficiency of the SFSTs alone in identifying drug-related impairment. However, the SFSTs have been implemented within several drug impaired driver detection programs to identify the presence of drug/s other than alcohol in drivers. One such program is the Drug Evaluation and Classification Program (DECP). This program is a twelve-step procedure that includes the administration of the SFSTs in addition to other tests and observations related to drug intoxication. The Los Angeles Police Department (LAPD) developed the DECP in response to the steady incline in drug abuse and drug-related road crashes and fatalities. The 12-step procedure was designed to enable trained police officers to identify drivers that are impaired by a drug and recognise which drug category is attributed to the impairment observed (seven drug categories are included in the DECP) (Page, 1995).

The DECP is based on the premise that certain categories of drugs produce particular patterns of signs or symptoms which can be identified (Page, 1995). The DRE adheres to a systematic and standardised procedure that must be completed in a specific order (Page, 1995). The twelve steps include: BAC; interview; preliminary examination (health related questions, pupil size and eye tracking ability, pulse); eye examinations (horizontal gaze nystagmus, vertical gaze nystagmus and convergence); divided attention tests (the Romberg Balance Test, the Walk and Turn test, the One Leg Stand test, and the Finger to Nose test); vital signs examination (pulse, blood pressure, temperature); darkroom examinations of pupil size (nasal and oral cavities are also assessed); muscle tone; examination of injection sites; statements and interrogation; opinion; and toxicology (obtaining a specimen).

Research has demonstrated that trained DREs can accurately identify individuals that are impaired by a drug and can determine which drug category is producing this impairment. The John Hopkins Study (Bigelow et al., 1984) and the 173 Case Study (Compton, 1986) are the two most renowned studies investigating the efficiency of the DECP. The John Hopkins Study (Bigelow et al., 1984) was a controlled clinical trial where 80 participants were administered either d-amphetamine (15 or 30mg), marijuana, diazepam, secobarbital or placebo. The authors found the DRE’s to be 92% accurate in identifying drug intoxication and the class of drug associated with the impairment. However, this percentage was only relevant to the 55% of cases where the DRE’s opinion was ‘intoxicated’.
The 173 Case Study (Compton, 1986) was a field study which involved drivers who were arrested for suspicion of driving under the influence of drugs other than alcohol. Results of 173 blood analyses were compared with the DRE evaluations. The findings indicated that in 94% of cases where a drug other than alcohol was identified, the DRE also reported it. However, the drug classifications were complicated by the fact that over 70% of the apprehended drivers had consumed multiple drugs. The drug classifications that were at least partially correct were noted in 87% of cases (where all drugs were identified in 49% of cases and at least one of the drugs was identified in 38% of cases). In only 13% of cases the DRE’s decision was not supported by the blood analysis. A limitation of Compton’s (1986) field study was that suspects classified as ‘not impaired’ were released and no data was available to confirm that the DRE’s decision was correct, thus contributing to the high percentage of correct classifications. A further limitation was that the study did not include an accurate representation of the CNS stimulant class of drugs, as the only stimulant detected in blood samples was cocaine.

Adler and Burns (1994) addressed some of the limitations of the 173 Case Study (Compton, 1986) by including the blood analyses of drivers that were released following a DRE opinion of ‘not impaired’. The study involved the analysis of 500 Drug Influence Evaluation records and the analysis of a blood specimen. The results revealed that in 83.5% of cases the DRE’s decision on whether a driver was drug impaired or not impaired was supported by the laboratory blood analysis. The authors concluded that the DRE program is a valid method for identifying and classifying drug impaired drivers.

In two controlled laboratory studies, Heishman et al. (1996; 1998) evaluated the validity of the DECP and also explored which individual variables of the program best predict drug intake. In an initial randomised, double blind, placebo-controlled study, Heishman et al. (1996) found that when 17-28 variables were used, the DECP accurately predicted the presence or absence of ethanol, cocaine or marijuana. However, the authors also reported that the DRE’s opinion on the specific drug causing the impairment was not as accurate. In this case, the DRE’s evaluation was consistent with toxicology reports in only 44% of the cases.

In a further study, Heishman et al. (1998) conducted a laboratory validation of the DECP in predicting whether participants were administered d-amphetamine (12.5 or 25mg),
alprazolam, codeine, or marijuana. The authors found that the DECP was optimal in predicting the use of \(d\)-amphetamine, alprazolam, codeine, or marijuana when 2-7 variables were assessed. Furthermore, the DRE’s opinion on impairment, irrespective of drug, was consistent with toxicology reports in 76% of the cases, whereas the specific drug class predicted was consistent with toxicology reports in only 32% of the cases. The DRE classified the majority of subjects dosed with \(d\)-amphetamine as not impaired, where in only 4% of cases the DRE correctly identified the presence of \(d\)-amphetamine. Furthermore, the DRE’s reported subjects to be dosed with other drugs more often than with \(d\)-amphetamine. The authors concluded that overall, using the DECP appears to be an efficient procedure in identifying recent drug use, however, reported some difficulty in discriminating between the various drugs.

Finally, in a recent double blind study, Shinar et al. (2000) evaluated the ability of police officers to detect drug-related impairments and identify the type of drug responsible for the impairment using the DECP. The drugs investigated in this study were amphetamine, marijuana, alprazolam, codeine, and placebo. The results indicated that the sensitivity (the ability of the test to detect the presence of a drug) was 72% and the specificity (the ability of the test to determine the specific drug class) was 43%. Of the 51 cases where amphetamine was administered, the DRE’s decision was unimpaired in 41% of cases, and in only 8% of cases correct classifications were made. The authors reported that the DRE’s identification of amphetamine-related impairment was no better than chance, and concluded that \(d\)-amphetamine in particular was the most difficult drug to identify.

In summary, the research clearly indicates that overall, the DECP is accurate in identifying drug impairment, however, the sensitivity of this program in recognising the specific drug class responsible for the impairment is questionable, particularly for the stimulant class of drugs. However, in contrast to the extensive research conducted on the DECP, the SFSTs alone have not been rigorously assessed for detecting drug-related impairment. Furthermore, since the DECP employs the SFSTs in conjunction with other behavioural and physiological tests, these validation studies do not provide an accurate assessment of the effectiveness of the SFSTs alone in identifying impairment associated with drugs other than alcohol.
While the SFSTs were designed specifically for the detection and assessment of alcohol intoxication (Burns & Moskowitz, 1977), they are currently implemented in Victoria (Australia) Police ‘drugged-driver detection’ procedures to identify drug-impaired drivers. It is, therefore, essential that rigorous research be conducted to evaluate the sensitivity of the SFSTs alone in identifying behaviours associated with drugs other than alcohol, in particular with amphetamine.
Chapter 7.

Experiment 1: The Effect of d-amphetamine on Simulated Driving Performance, Driving-Related Cognitive Functions, and the SFSTs

7.1 Introduction

As was argued in Chapter 1 (Introduction) and Chapter 3 (Amphetamine and Driving), it is important to examine the acute effects of various amphetamines on driving performance in order to help determine how amphetamine use is associated with amphetamine-related road fatalities. Assessing on-road driving performance, while intoxicated with amphetamines, is not viable in Victoria (Australia) due to legal restrictions. Simulated driving studies are, thus, an important type of experimental paradigm for examining the effects of amphetamine on driving performance as they can, to some extent, reflect ‘real life’ driving ability in a controlled environment (Moskowitz, 1985). However, there are few studies that have assessed the effects of an acute dose of amphetamine on simulated driving performance. For these reasons, the present experiment investigated the effects of a single acute therapeutic dose of d-amphetamine on simulated driving performance.

Although research using simulated driving tasks can provide useful information on the effect of amphetamines on driving performance, these tests are not able to establish whether there are specific amphetamine-induced deficits in cognitive functioning that contribute to the amphetamine-related driving impairments (refer to Chapter 4 for details). Therefore, the present experiment also administered a range of cognitive tasks that assessed cognitive processes important to safe driving that may not be easily observable with a driving simulator task, such as attention, psychomotor performance, perceptual speed, visual scanning ability, and movement estimation (Hurst, 1987; Lamers et al., 2003; Anstey et al., 2005). Specifically, the present experiment administered: the Digit Span Test as a measure of working memory and efficiency of attention; Digit Vigilance to assess sustained attention; a Movement Estimation Task to assess estimation of movement speed and ‘time to contact’; Digit Symbol Substitution Test and a Tracking Task as measures of psychomotor performance; the Trail-Making Test to assess visual scanning ability; and Inspection Time to assess perceptual speed. These tests were selected as they specifically
measure cognitive functions that have been reported to be important in safe driving (Hurst, 1987; Lamers et al., 2003; Anstey et al., 2005).

Additionally, in response to the increasing number of ‘drug other than alcohol’ related road accidents, a second aim of the present experiment was to investigate the efficiency of the SFSTs to identify any impairment following a single acute therapeutic dose of d-amphetamine in drivers. As was discussed in Chapter 1 (Introduction) and Chapter 6 (Section 6.4 What are the Standardised Field Sobriety Tests in Detection of Drug Impaired Drivers), while the SFSTs were designed specifically for the detection and assessment of alcohol intoxication (Burns & Moskowitz, 1977), they are currently implemented in Victorian (Australia) police ‘drugged-driver detection’ procedures to identify drug-impaired drivers. However, limited research has been conducted that assess the sensitivity of the SFSTs to identify impairment associated with amphetamine. Therefore, the present experiment examined the acute effects of a single therapeutic dose of d-amphetamine on SFSTs performance. Although it is unlikely that performance on the SFSTs will be impaired following a single therapeutic dose of d-amphetamine (as the tests were designed to detect impairment associated with considerably higher amphetamine concentrations than those administered in the present study), the results of this experiment will provide valuable information as to the usefulness of this drug-impairment test following a single therapeutic dose of d-amphetamine.

The present experiment assessed the acute effects of d-amphetamine on simulated driving performance, driving-related cognitive processes, and performance on the SFSTs, using a repeated-measures, counter-balanced, double blind, placebo-controlled design. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg d-amphetamine, separated by a one week wash-out period, to reduce residual effects of the drug from the first session. The present chapter will describe the materials and methodologies employed, the results, and provide a discussion of the results.
7.2 Materials and Methods

7.2.1 Participants

7.2.1.1 Selection Criteria
All participants were screened with an interview and medical examination conducted by a medical practitioner to ensure that they had no history of substance abuse, had no pre-existing physical or neurological conditions, no history of psychiatric, cardiac, endocrine, gastrointestinal, or bleeding disorders, that they were not pregnant or lactating, not taking any prescription medication (excluding the contraceptive pill), and that they were not regular illicit stimulant users (i.e. they used less than once a month). However, for ethical reasons only participants who had previously experimented with any illicit stimulants were permitted to participate. Participants were required to have a valid, full drivers license (no probationary or learner drivers) to ensure that they had at least 3 years of driving experience.

7.2.1.2 Psychological and Physical Health
All participants completed a medical examination which involved a questionnaire followed by a brief medical examination conducted by a registered medical practitioner. The self-administered questionnaire consisted of questions related to medical history, such as, allergies, medications, health problems, operations, diet, alcohol consumption, and pregnancy (females only) (see Appendix A for complete patient medical questionnaire). A medical practitioner briefly interviewed participants on their medical and drug history, and obtained several physical and physiological measures, such as, weight, height, heart rate, and pulse rate (see Appendix B for medical examination sheet). The medical practitioner formed an opinion as to whether the participant was fit to participate based on this medical examination, and they were excluded from the experiment at this point if they were not fit to participate.

7.2.1.3 Sample Characteristics
Twenty healthy illicit stimulant users (10 males; 10 females), aged between 21 and 32 years (mean = 25.4 years, SD = 3.3 years), with an average male weight of 82.1kg (SD = 10.6), and an average female weight of 62.2kg (SD = 10.4) were recruited through advertisements. All participants had a minimum of 11 years education. All participants were consumers of caffeine, with an average daily intake of 1.3 cups of coffee (range 0-4).
Of the 20 participants, 11 were self-assessed smokers, averaging 5.8 cigarettes a day (range 0-20).

Participants were provided with an information sheet outlining details of the research project (see Appendix C for information sheet), and all participants gave written informed consent (see Appendix D for consent form). Participants were informed that they were free to withdraw from the study at any time. The Swinburne University of Technology Human Research Ethics Committee approved the research.

7.2.2 Drug
Dexamphetamine Tablets (Sigma Pharmaceuticals Pty Ltd, Victoria, Australia) contain the dextro isomer of the compound \( d,l \)-amphetamine sulphate, a sympathomimetic amine of the amphetamine group (as described in Section 2.1.1.1). Dexamphetamine sulphate (5mg Dexamphetamine Tablets) was prepared by mixing 0.42mg/kg dose of dexamphetamine tablets with flour, which was encapsulated in three soft gelatine capsules to render them visually indistinguishable from the placebo capsules, which contained only flour. As was argued in Section 1.3 (Project Aims: Introduction), in order to simulate as close to real-life amphetamine-induced effects as is ethically viable, oral doses of 0.42mg/kg \( d \)-amphetamine was administered, as it is one of the highest approved (by Research Ethics Committees) doses administered to humans for controlled experimental research purposes. It must be highlighted that although the results of the present study will not be directly representative of behaviours typically observed with recreational amphetamine abusers (as amphetamine concentrations are generally significantly higher in the real-world population of amphetamine-impaired drivers than those administered in the present study), the results will provide some useful indications as to how a single therapeutic dose of \( d \)-amphetamine affects performance, which subsequently, if impairments are observed, can provide important information of possible impairments associated with considerably higher doses.

7.2.3 Experimental Design
A repeated-measures, counter-balanced, double blind, placebo-controlled design was employed. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \( d \)-amphetamine, separated by a one week wash-out period, to reduce residual effects of the drug from the first session. All participants consented to refrain from consuming alcohol for at least 24 hours prior to each testing session and illicit drugs for at least 7 days prior to
each testing session. Recent drug use prior to the experimental sessions was monitored with blood samples (obtained during the experimental sessions) which were screened for the seven major drug classes (opiates, amphetamines, benzodiazepines, cannabinoid, barbiturates, cocaine and methadone). All participants were screened for recent use of drugs other than amphetamines, as no baseline measures were obtained (refer to Chapter 12 Limitations for discussion on this limitation).

7.2.4 Materials

7.2.4.1 Questionnaires

7.2.4.1.1 Demographics

Demographic details regarding age, gender, marital status, education, employment status, work hours, and health was obtained with a brief questionnaire (see Appendix E for complete questionnaire).

7.2.4.1.2 Drug Use History Questionnaire

The drug use history questionnaire was a self-administered questionnaire that consisted of questions relating to current and past drug use patterns across various drug types, such as, tobacco, alcohol, caffeine, cannabis, ecstasy, cocaine, amphetamine, heroin, and inhalants (see Appendix F for complete questionnaire).

7.2.4.1.3 Profile of Mood Scale (POMS; McNair, Lorr and Droppleman, 1992)

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 (note that the reported Kronbach alpha values are an average of males and females combined; tension-anxiety K-R20 = .91, depression-dejection K-R20 = .95, anger-hostility K-R20 = .92, vigour-activity K-R20 = .88, fatigue-inertia K-R20 = .94, and confusion-bewilderment K-R20 = .86) (McNair et al., 1992).

The POMS was administered at the beginning of the two experimental sessions (prior to drug consumption) to establish whether there were baseline differences in mood between the placebo and d-amphetamine sessions, as differences in mood at the start of the two sessions may affect subsequent cognitive performance (see Appendix G for POMS). For
example, administering the POMS prior to drug consumption controlled for the misinterpretation of changes to cognitive performance attributed to pre-existing mood rather than the administration of the drug itself. If a significant difference in the Total Mood Disturbance score was found at the beginning of the two experimental sessions, the possibility of differences in mood due to carry-over drug effects was investigated. If differences in mood were found to be attributed to carry-over drug effects, the session that \textit{d}-amphetamine was administered (‘session order’) was used as a between subject factor for all cognitive analyses. Although there is no evidence to suggest that a therapeutic dose of \textit{d}-amphetamine may produce psychological carry-over effects 7 days after consuming the drug, there is also no evidence to suggest that psychological carry-over effects will not occur 7 days after \textit{d}-amphetamine administration. Therefore, the POMS was administered to control for this unknown possibility of residual psychological \textit{d}-amphetamine carry-over effects.

7.2.4.2 Snellen Eye Chart

The Snellen Eye Chart is a standard measure of visual acuity. The chart has a series of letters arranged in lines. The bottom of the chart typically begins with a line of very small letters that increase in size with each line, with the largest letter found at the top of the chart. Standard operating procedures were employed whereby participants viewed the Snellen chart at a distance of 3 metres and read aloud the letters in each line in descending order. As visual acuity was assessed separately for each eye, one eye was covered at a time, thus, the test was administered twice in each experimental session. This test was scored such that the number of letters identified correctly was the indication of visual acuity (i.e. higher scores indicated better vision). This test was administered to clarify whether any amphetamine related changes in driving performance were associated with gross changes in visual acuity.

7.2.4.3 Driving Simulator

The driving simulator was the CyberCAR™ LITE driver training and evaluation simulator (Thoroughbred Technologies Pty. Ltd.). The steering wheel, a ‘Force Feedback’ with integrated horn, indicators, headlights, ignition, automatic gears and hand brake, was affixed to a bench. Brake and accelerator pedals were placed underneath the bench. Participants could adjust the pedal and seat position to suit their height. The simulator task was projected onto a 175cm x 120cm white screen (distance from steering wheel was
Participants observed a two-dimensional computer-generated driving scene, as they would through a vehicle windscreen. The simulated dashboard, which was also projected onto the white screen, included a speedometer, rear-view mirror, and side mirrors. The tasks administered employed a simulated conventional on-road light motor vehicle with automatic transmission. The CyberCAR™ LITE simulator is predominantly used in industry, government and education agencies for training of both novice and experienced drivers (Papafotiou et al., 2005a). Previous studies that have employed the CyberCAR™ LITE simulator have shown this driving simulator to be sensitive to the effects of drugs on driving ability (Papafotiou et al., 2005a; Stough et al., 2005).

The driving simulator program consisted of two modules: the ‘Basic Driving Module’ and the ‘Driving Module’. The Basic Driving Module comprised of two tasks that were used to assess basic steering ability and basic speed control. This module was administered for training, to familiarise participants with the driving simulator and to ensure that they felt confident with the steering, accelerator and brake pedal. The Driving Module consisted of four tasks - ‘freeway traffic driving’ and ‘city traffic driving’, in both day and night conditions. Each task took approximately five minutes to complete. The computer program recorded each driver’s performance continuously on a range of variables, in terms of vehicle management and conformance to the pre-programmed set of driver and vehicle standard operating procedures. Following previous research in our laboratory (Papafotiou et al., 2005a), a subset of 33 relevant variables was analysed, where each reflected an error that can occur during the driving tasks. In accordance with the CyberCAR™ LITE driving simulator manual (Thoroughbred Technologies Pty. Ltd.), each variable score was multiplied by that variable’s ‘loading factor’, a number which represents the severity of the error, and subsequently all adjusted variable scores were summed to give an overall driving performance score. Table 7.1 summarises the 33 relevant driving variables and the respective loading factors. Driving simulator variable scores were summed separately for the day and night time driving conditions.
Table 7.1 Driving Simulator Variables and Corresponding Loading Factors

<table>
<thead>
<tr>
<th>Driving Simulator Variables</th>
<th>Loading Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dangerous Action Skid</td>
<td>1</td>
</tr>
<tr>
<td>Collision</td>
<td>10</td>
</tr>
<tr>
<td>Straddled the solid line</td>
<td>2</td>
</tr>
<tr>
<td>Exceeded speed limit</td>
<td>2</td>
</tr>
<tr>
<td>No signal when moving off</td>
<td>5</td>
</tr>
<tr>
<td>No signal cancel when moving off</td>
<td>4</td>
</tr>
<tr>
<td>Waited too long before moving off</td>
<td>1</td>
</tr>
<tr>
<td>Wide/Cut</td>
<td>4</td>
</tr>
<tr>
<td>Wandering</td>
<td>2</td>
</tr>
<tr>
<td>Straddled barrier line</td>
<td>2</td>
</tr>
<tr>
<td>No signal when changing lane</td>
<td>5</td>
</tr>
<tr>
<td>No signal cancel when changing lane</td>
<td>4</td>
</tr>
<tr>
<td>No signal when entering freeway</td>
<td>5</td>
</tr>
<tr>
<td>No signal cancel when entering freeway</td>
<td>4</td>
</tr>
<tr>
<td>Incorrect signalling at intersection</td>
<td>5</td>
</tr>
<tr>
<td>No signal cancel at intersection</td>
<td>4</td>
</tr>
<tr>
<td>No signal when overtaking (left)</td>
<td>5</td>
</tr>
<tr>
<td>No signal when overtaking (right)</td>
<td>5</td>
</tr>
<tr>
<td>No signal cancel when overtaking (left)</td>
<td>4</td>
</tr>
<tr>
<td>No signal cancel when overtaking (right)</td>
<td>4</td>
</tr>
<tr>
<td>Wheels not straight on approaching intersection</td>
<td>3</td>
</tr>
<tr>
<td>Driving too fast</td>
<td>5</td>
</tr>
<tr>
<td>Driving too slow</td>
<td>1</td>
</tr>
<tr>
<td>Inappropriate Braking</td>
<td>2</td>
</tr>
<tr>
<td>No safe following distance</td>
<td>5</td>
</tr>
<tr>
<td>Not sufficient clear space when stopping</td>
<td>2</td>
</tr>
<tr>
<td>Needless/Unnecessary stop</td>
<td>1</td>
</tr>
<tr>
<td>Released brake incorrectly when stopping</td>
<td>2</td>
</tr>
<tr>
<td>Did not stop at red traffic light</td>
<td>10</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred</td>
<td>x 3.6 to calculate KPH</td>
</tr>
<tr>
<td>Reaction time (emergency stop)</td>
<td>x 10 ms</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop</td>
<td>in metres</td>
</tr>
<tr>
<td>Collision when emergency situation occurred</td>
<td>10</td>
</tr>
</tbody>
</table>

7.2.4.4 Neuropsychological Measures

A battery of auditory and visual neuropsychological tests were selected to assess aspects of attentional processing (Digit Span, Digit Vigilance, Digit Symbol Substitution Test, Movement Estimation), psychomotor function (Digit Symbol Substitution Test, Tracking Task, Trail Making) and perceptual speed (Inspection Time), associated with neural functions related to driving, as well as to assess CNS functions influenced by amphetamines. The battery consisted of a combination of pen and paper tests and computerised tasks. All tests were conducted in accordance to the standard procedures. The tests are described below.
7.2.4.4.1 **Digit Span (Wechsler, 1997)**

Digit Span (DS) is a measure that loads heavily on working memory and efficiency of attention (i.e. freedom from distractibility). Standard administration procedures were employed (Wechsler, 1997) which involved the immediate verbal recall of a series of numbers (ranging from two to eight digits in length). DS consists of two tasks: DS forwards and DS backwards. DS forwards requires the immediate verbal recall of a series of numbers in the exact order as presented, whereas DS backwards requires the immediate recall in reverse order. The series of digits for both forwards and backwards become progressively longer as the participant correctly recalls the series. The digit span for DS forwards and backwards was recorded. Brief practice trials were given immediately prior to administration of the tasks to ensure that the instructions were clearly understood. Digit Span, a subtest of the WAIS-III, has exhibited good test-retest reliability, with coefficients ranging from 0.70-0.89 according to age group (Wechsler, 1997). Alternate forms of the test were used for the two drug conditions to minimise order and learning effects.

7.2.4.4.2 **Digit Vigilance**

Digit Vigilance, a measure of sustained attention, is a subtest of the Cognitive Drug Research (CDR®) battery, which is a computerised cognitive assessment system comprised of tests that are sensitive to the effects of psychopharmacological substances (Wesnes *et al.*, 1989). Although initially designed to assess the ability to focus and sustain attention, Digit Vigilance also provides a measure of simple reaction time. Standard procedures were employed in which participants were required to respond as quickly as possible to a randomly selected target digit (displayed throughout the task on the right side of the screen), every time it appeared in the centre of the screen. Numbers were presented at the rate of 2.5 digits per second for 5 minutes. Three measures of vigilance were computed; accuracy, reaction time and number of false alarms.

7.2.4.4.3 **Movement Estimation Task**

The Movement Estimation Task is a computerised attention task that assesses the estimation of movement speed and ‘time to contact’. The task is an adaptation of the Object Movement Estimation under Divided Attention (OMEDA) task (Read *et al.*, 2000). Research has shown detrimental effects in estimation of ‘time to contact’ with age (Read *et al.*, 2000), chronic cannabis use (Ward *et al.*, 2000), and acute 3,4-methylenedioxymethamphetamine (MDMA) use (Lamers *et al.*, 2003), each of which are
relevant to traffic safety. The present task consisted of two tasks of differing levels of difficulty. The first task required the estimation of ‘time to contact’ of a moving object to a fixed point. The second, more difficult task, involved the estimation of ‘time to contact’ of a moving object to a second moving object. For the first task, participants were instructed to fixate on a small black cross located in the centre of the computer screen. From one corner, a yellow shaded circle (target) travelled at a constant speed towards the cross. Before the target reached the cross it disappeared. The time at which the target disappeared varied across trials as a function of occlusion size (4, 8, and 14cm diameter). The speed at which the target travelled also varied across trials (10cm per sec, 5cm per sec, or 2.5cm per sec). For the more difficult version of the task, two circles (targets) were employed, and disappeared at one of the three occlusions and travelled at one of the three speeds. For both tasks participants were instructed to respond by pressing a response button when they estimated ‘time of contact’. ‘Time to contact’ error was defined as the mean difference between estimated and actual ‘time to contact’. The number of trials in the first task was 27 and the number of trials in the second, more difficult task, was 54. Practice trials were given immediately prior to administration of the tasks and participants received feedback as to how accurate their estimation of ‘time to contact’ was. The total duration of this task was 15 minutes.

7.2.4.4.4 Digit Symbol Substitution Test (Wechsler, 1997)

The Digit Symbol Substitution Test (DSST) is a pencil and paper test that measures attention, motor performance, response speed, and visuomotor coordination. This test consists of nine predetermined symbols that are individually matched with numbers one to nine. In accordance with the standard administration procedures, participants were required to substitute these numbers for the appropriately paired symbols as quickly as possible. The measure of performance is the number of correctly substituted symbols within 90 seconds. A practice trial was given immediately prior to administration of the task to ensure that the task requirements were clearly understood. Test-retest reliability of the DSST, a subtest of the WAIS-III, has produced relatively high correlation coefficients, ranging from 0.82-0.88 (Wechsler, 1981; Matarazzo & Herman, 1984; Youngjohn et al., 1992). Alternative forms were used for the two drug conditions to minimise order and learning effects.
7.2.4.4.5 Tracking Task (Baddeley et al., 1986)

The Tracking Task measures visual-motor coordination. This computerised task had two difficulty levels. The first level required the participant to follow a moving stimulus (2x2cm white square) that randomly changes directions. The participant was instructed to keep the cursor directly on the moving square, and if they failed to do this it changed colour. Initially the square moved slowly, and then the speed gradually increased to a speed whereby the participant was unable to maintain the cursor on the stimulus for more than 60% of the time. The stimulus remained at this speed for the remainder of the task. The second level was more difficult as it was a divided attention task which required participants to complete the visual-motor task (Tracking Task) and an auditory short term memory task (DS Forward) simultaneously. The number of digits presented in the DS was consistent across trials, where the difficulty level was adjusted according to the participants’ previous performance on the DS Forward test. Participants were instructed to verbally recall a series of numbers in the exact order as presented, while simultaneously tracking a moving square presented on the computer monitor with the cursor. Participants were instructed to complete both tasks as accurately as possible. Only the tracking task results were used. Performance on the two tracking tasks was determined by the number of errors and the total time spent in error. A practice trial was given immediately prior to administration of the task.

7.2.4.4.6 The Trail-Making Test

The Trail-Making Test measures visual-conceptual and visual-motor tracking (Giovagnoli et al., 1996). It is a pencil and paper test consisting of two parts: Trail A and Trail B. Trail A required the participant to draw a continuous line connecting 25-circled digits that are randomly situated on a single page, in ascending order (1-25). Trail B is similar to Trail A except that the participant is required to connect numbers and letters in ascending order, but alternating between number and letter (eg. 1 – A – 2 – B – 3 - C etc.). In accordance with standard administration procedures, participants were instructed to complete the tests as quickly as possible, without removing the pencil from the page. Errors during task completion require immediate correction and performance is measured as the speed at which the task is correctly completed. Practice trials were given immediately prior to administration of the tasks to verify that the instructions were clearly understood. Reliability coefficients for the Trail-Making Task have varied considerably, with most
above 0.60, several in the 0.90s, and more in the 0.80s (Spreen & Strauss, 1991). Alternate forms of the Trail Making Test were used for the two drug conditions.

7.2.4.4.7 Inspection Time (Deary & Stough, 1996)

Inspection Time (IT) is a measure of perceptual speed. This task assesses the presentation time that a subject requires to discriminate between two possible stimuli. The task consists of a stimulus with two vertical parallel lines joined at the top by a horizontal line. There are two versions of the stimulus; either the left line is shorter than the right or the right line is shorter than the left (as illustrated in Figure 7.1). Stimuli were flashed on a computer screen and the participant was instructed to press a key corresponding to the side of the symbol that was shorter. Each stimulus presentation was followed by the presentation of a backward visual mask. This prevented further processing of the stimulus in iconic memory. The speed of stimulus presentation was varied according to the accuracy of the participants’ responses. The length of presentation of the backward visual mask was also varied to determine the optimal visual encoding time. The objective was to respond as accurately, rather than as quickly, as possible. The duration of stimulus presentation is varied until an 80% accuracy level is obtained by the participant, and the stimulus presentation duration at when this occurs, is taken as the measure of IT. Practice trials were given immediately prior to administration of the task.

![Figure 7.1 Inspection Time Task Stimuli. There are two versions of the stimulus; either the left line is shorter than the right (as can be seen in the stimuli to the left) or the right line is shorter than the left (as can be seen in the stimuli to the right)](image)

7.2.4.5 The Standardised Field Sobriety Tests (SFSTs)

The SFSTs are comprised of three tests. Each test must be administered in a precise and systematic manner to all individuals, and specific signs must be observed in order for a participant to be classified as impaired using the test. The SFSTs can only be administered by a trained individual. Members of the Victorian police, Inspector Martin Boorman and
Sergeant Vic Little, trained the investigator (Beata Silber) in the administration of the SFSTs. The investigator was required to conduct the SFSTs under the supervisions of Dr Katherine Papafotiou, a trained SFSTs administrator. Supervision continued until Dr Katherine Papafotiou was satisfied with the investigators procedural skills.

### 7.2.4.5.1 Horizontal and Vertical Gaze Nystagmus (HGN and VGN) Test

This test assesses nystagmus, which is the involuntary jerking of the eyes. Nystagmus is a natural and normal phenomenon which can be magnified with certain drugs and alcohol. Participants were required to focus on a pen located 30 to 36 centimetres in front of their nose, with the pen moving horizontally and vertically. The specific instructions given by the investigator were as follows:

“"I am going to check your eyes. Keep your head still and follow the tip of my pen with your eyes only. Keep focusing on the tip until I tell you to stop. Do you understand?” If the participant answered “no” the instructions were repeated and any questions were clarified, if the participant responded “yes” the experimenter began the test. The stimulus travelled smoothly across the participants’ entire field of vision, and then was moved smoothly vertically in front of the subjects face to the highest and lowest point in their visual field. The investigator discontinued the test if the participant was feeling dizzy or demonstrated poor balance. See Figure 7.2 and 7.3.

Specifically, the signs recorded were as follows (left and right eye were recorded separately):

1. Lack of smooth pursuit (Left: Yes/No, Right: Yes/No)
2. Nystagmus at maximum deviation (Left: Yes/No, Right: Yes/No)
3. Nystagmus onset before 45 degrees (Left: Yes/No, Right: Yes/No)
4. Vertical Gaze Nystagmus (Left: Yes/No, Right: Yes/No)

If a total of four signs or more were observed, out of a maximum of eight, the participant was classified as impaired on the test.
As can be seen in Figures 7.2 and 7.3, the participant was required to keep eyes focused on the tip of a pen that moved horizontally (Figure 7.2) and vertically (Figure 7.3) in front of the participants nose.

An additional sign, head movements and/or jerks (HMJ), was also recorded. Previous research has reported that head movements were observed in the highest percentage of participants in both low and high THC (delta-9 tetrahydrocannabinol) conditions compared to any other sign recorded (Papafotiou et al., 2005b). For this reason, this sign was recorded in the present study to investigate its pertinency to amphetamine intoxication. HMJ was recorded as a sign if the participant was not able to keep their head stationary two or more times, while following a moving stimulus with their eyes.

7.2.4.5.2 Walk and Turn (WAT) Test
This test required the participant to take nine heel-to-toe steps along a straight line, turn in a prescribed manner, and take nine heel-to-toe steps back along the line. This test assessed a variety of aspects including divided attention, balance, and coordinating body movements. The specific instructions given were as follows:

“Place your left foot on the line (experimenter demonstrates). Place your right foot on the line in front of your left foot with the heel of your right against the toe of your left (correct stance demonstrated by examiner). Place your arms by your side and keep this position
until I tell you to begin the test. Do you understand?” If the participant answered “no” the instructions were repeated and any questions were clarified, if the participant responded “yes” the experimenter continued with the instructions.

“When I tell you to start, take nine heel-to-toe steps up the line like this (correct steps demonstrated), turn taking a series of small steps like this (correct turning procedure demonstrated), and take nine heel-to-toe steps back up the line (demonstrate). While you are walking, keep your arms by your side, watch your feet and count your steps out loud. Once you start walking do not stop until you have finished the test. Do you understand?” If the participant responded “no” the experimenter asked “which part of the test did you not understand?” and the instructions were repeated and clarified. If the participants responded “yes” the experimenter continued with the instructions. “Begin and count your first step as one”. The investigator discontinued the test if the participant was feeling dizzy or was likely to fall over. See Figure 7.4.

![Figure 7.4 WAT](image)

Figure 7.4 WAT. Participants were required to take nine heel-to-toe steps along a marked straight line, turn in a prescribed manner, and take nine heel-to-toe steps back along the line.

The investigator observed the participant at all times during the test. The specific behaviours that were recorded were as follows:

1. Cannot keep balance while listening to the instructions of the test
2. Starts the test before the instructions are complete
3. Stops walking during the test
4. Does not touch heel-to-toe while walking
5. Steps off the line
6. Uses arms to maintain balance
7. Improper turn (not as demonstrated during instruction phase)
8. Takes incorrect number of steps (more or less than 9 in either direction)

Each sign observed was recorded only once irrespective of the number of times the error occurred. Therefore, the maximum number of signs that could be recorded was 8. If two or more signs were observed, the participant was classified as impaired on the test. If the participant failed to complete the test, all 8 signs of the WAT test were recorded.

7.2.4.5.3 One Leg Stand (OLS) Test
This task required the subject to stand on one leg, with the other leg extended to the front and held approximately 15 cm above the ground. The participant was required to maintain this stance while counting out loud for 30 seconds by thousands. The specific instructions given were as follows:

“Stand with your feet together and your arms by your side like this (experimenter demonstrates). Do not start the test until I tell you to do so. Do you understand so far?” If the participant responded “no” the instructions were repeated and clarified. If the participants responded “yes” the experimenter continued with the instructions.

“When I tell you to start, raise one leg, either leg, approximately 15cm off the ground, toes pointed and arms by your side (position demonstrated). While holding this position count out loud for thirty seconds in the following manner: 1001, 1002, 1003, and so on. Keep your arms by your side at all times, keep watching your raised foot and keep both legs straight. Do you understand?” If the participant responded “no” the experimenter asked “which part of the test did you not understand?” and the instructions were repeated and clarified. If the participant responded “yes” the experimenter continued, “Go ahead and perform the test.” The experimenter discontinued the test after 30 seconds had elapsed. The participant then repeated the test alternating legs. The investigator discontinued the test if the participant could not safely complete the test. See Figure 7.5.
Figure 7.5 OLS. Participants were required to stand on one leg, with the other leg extended to the front, and held approximately 15 cm above the ground with toes pointed towards the ground, and arms by their side. The participant was required to maintain this stance while counting out loud for 30 seconds by thousands. This was subsequently repeated with the second leg.

The investigator observed the participant at all times during the test. The specific behaviours recorded were as follows:

1. Sways while balancing on one leg
2. Uses arms to maintain balance
3. Hops during test to maintain balance
4. Puts raised foot down

Each sign observed was recorded only once irrespective of the number of times the error occurred. Therefore, the maximum number of signs that could be recorded was 4. If two or more signs were observed, the participant was classified as impaired on the test. If the participant failed to complete the test, all 4 signs of the OLS test were recorded.

7.2.4.5.4 Overall Performance on the SFSTs
Overall performance on the SFSTs was calculated by summing the performance of the three tests (HGN, WAT, and OLS). In accordance with Victoria Police (Australia) implementation training procedures, if the participant was identified as impaired on two or
more of the tests, the participant was subsequently classified as impaired on the SFSTs (see Appendix H for SFSTs scoring sheet).

7.2.4.6 Blood and Saliva Samples
Three blood and three saliva samples were taken from each participant by a registered nurse during each experimental session. As d-amphetamine has a peak blood concentration between two and four hours (Kupietz, et al., 1985; Angrist, et al., 1987; Brauer et al., 1996), the first blood and saliva sample was obtained 120 minutes after administration of the drug, the second sample 170 minutes after administration of the drug, and the third sample 240 minutes after the administration of the drug. 10ml samples of blood were obtained using a syringe by venipuncture from the antecubital vein. 1ml samples of saliva were obtained using Cozart Rapiscan (Biomediq DPC Pty Ltd) saliva collection kits. The saliva collection method involves placing a cotton swab collector into the mouth. An indicator colour (blue) appears at the end of the swab once the swab absorbs 1ml of saliva. The swab containing saliva is then placed into a test tube containing 2 mL of assay buffer. The swab is then compressed using a small plunger (to separate the saliva from the swab). Blood and saliva samples were immediately stored in a –20ºC freezer and subsequently transported to a –70ºC freezer after 5-7 days. Blood samples were screened for the seven major drug classes (opiates, amphetamines, benzodiazepines, cannabinoid, barbiturates, cocaine and methadone) using ELISA/EMIT screens. Subsequently, blood and saliva samples were analysed for specific amphetamine levels using the Gas Chromatography Mass Spectroscopy method (Moeller & Kraemer, 2002). This method has been documented to be the most accurate technique for testing specific drug levels in blood and saliva. Thus, all participants were screened for recent use of drugs other than amphetamines.

7.2.5 Procedure
In a preliminary session, on a separate day in which no drug was administered, participants read an information sheet (see Appendix C for information sheet), and signed an informed consent form (see Appendix D for consent form), completed the demographics questionnaire (see Appendix E for complete questionnaire), the drug use history questionnaire (see Appendix F for complete questionnaire), completed a medical examination (see Appendix A and B for complete medical questionnaires), and completed the four simulated driving tasks described in Section 7.2.4.3 for practice. For all
experimental sessions the experimenter and participant were blind to the treatment condition. A medical practitioner was on-call and a registered nurse was on-site throughout all experimental sessions.

Participants were asked to eat a normal breakfast or lunch before arrival, and to refrain from consuming any products containing caffeine (e.g. coffee, tea, coca cola, chocolate), for at least 4 hours prior to each experimental sessions. In addition, participants were not permitted cigarettes throughout experimental sessions. Testing times were kept constant for participants across sessions so that differences in time of day would not confound the results.

At the beginning of each experimental session the POMS was completed. The POMS was administered prior to drug consumption to establish whether there were any baseline differences in mood between the placebo and d-amphetamine sessions, as differences in mood at the start of the two sessions may have affected subsequent cognitive performance. Participants then completed the city-traffic simulated driving task (to re-familiarise themselves with the driving simulator). The research nurse then administered the drug/placebo orally.

The first blood and saliva sample was obtained 120 minutes after the administration of the drug, followed by the Snellen Eye Test, the driving simulator task, and the SFSTs. A second blood and saliva sample was obtained 170 min after drug administration. The battery of neuropsychological tests was subsequently administered. Task order was only partially counterbalanced across participants with block 1 (consisting of the Digit Span and Tracking Task) and block 4 (consisting of the Dual Task: Digit Span combined with the Tracking Task) always presented first and last respectively, and the order of block 2 (consisting of the Movement Estimation and Trail Making) and block 3 (consisting of the Digit Vigilance, Inspection Time, and Digit Symbol Substitution) counterbalanced with half the participants completing block 2 followed by block 3, and the second half completing block 3 followed by block 2. Alternate forms of the Digit Span, Trail Making and Digit Symbol Substitution tests were used for the two drug sessions. Upon completion of the cognitive tests, the third and final blood and saliva sample was obtained 240 minutes following drug consumption. Participants were provided with a taxi voucher for transport home, and were escorted safely to a taxi by the experimenter. The only reported adverse
reaction to \textit{d}-amphetamine consumption was difficulty with falling asleep and/or disturbed sleep on the night following that session. Table 7.2 illustrates the testing protocol adhered to during the two experimental sessions. Note that the protocol was the same during both experimental sessions.

\begin{center}
\textbf{Table 7.2 Testing Protocol}
\end{center}

\begin{center}
\begin{tabular}{l l}
\hline
Elapsed Time (min) & Event \\
0 & POMS \\
5 & Practice City Traffic Driving Task \\
10 & Treatment Administered Orally \\
130 & 1st Blood and Saliva Sample \\
145 & Snellen Eye Test \\
150 & Driving Simulator Task \\
175 & Standardised Field Sobriety Tests \\
185 & 2nd Blood and Saliva Sample \\
200 & Neuropsychological Tests \\
240 & 3rd Blood and Saliva Sample \\
255 & End of Session (Taxi) \\
\hline
\end{tabular}
\end{center}

\textbf{7.2.6 Statistical Analyses}

\textbf{7.2.6.1 Driving Performance}

\textbf{7.2.6.1.1 Main Analyses}

In order to determine whether acute \textit{d}-amphetamine use affects simulated driving performance, a 2x2 repeated-measures analyses of variance (ANOVA) was conducted where the independent variables were drug condition (placebo/\textit{d}-amphetamine) and driving task scenario (day/night), and the dependant variable was overall simulated driving performance score. Driving task scenario (day and night) was included as a factor to determine whether \textit{d}-amphetamine affected simulated driving performance differently for day and night time driving scenarios. Outliers were removed from the analysis where appropriate (greater than three standard deviations from the mean). A Bonferroni Adjustment was made to correct for Type 1 error by dividing the alpha by the total number of tests (i.e. 1). All reported \textit{p}-values are corrected \textit{p}-values.

\textbf{7.2.6.1.2 Exploratory Analyses}

In order to determine how acute \textit{d}-amphetamine use affects specific driving behaviours, a Wilcoxon Signed-Rank Test was performed for each individual driving variable (therefore
a total of 33 analyses were conducted), where the independent variable was the drug condition (placebo/d-amphetamine) and the dependent variable was performance on individual driving variables. For these analyses day and night time driving scenario scores were combined as visibility conditions were not found to significantly differ for the drug conditions (see Results Section 7.3.3.1 for details). Non-parametric tests were employed as the data for the individual driving variables could not be normally distributed. No correction for multiple comparisons was made as these analyses were exploratory.

In order to determine whether d-amphetamine affected visual acuity, two Paired Samples t-tests were performed, with an independent variable of drug condition (placebo/d-amphetamine), and a dependant variable of Snellen Eye Test performance. If the results revealed that d-amphetamine affected visual acuity, a Spearman’s Rho measure of association was performed to determine whether any d-amphetamine related changes in simulated driving performance was associated with changes in visual acuity.

7.2.6.2 POMS

In order to determine whether there were baseline differences in mood at the start of the testing sessions (prior to drug administration) between the placebo and d-amphetamine experimental sessions, a Wilcoxon Signed-Rank Test was conducted with an independent variable of drug condition (placebo/d-amphetamine) and a dependent variable of the POMS Total Mood Disturbance Score (a composite of the tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment dimensions). This non-parametric test was employed as the data for the Total Mood Disturbance Score was not normally distributed.

7.2.6.3 Neuropsychological Measures

7.2.6.3.1 Main Analyses

To examine the effect of d-amphetamine on driving-related cognitive processes, the present thesis performed separate repeated-measures analyses of variance tests (ANOVAs) for each of the seven cognitive tasks, with ‘session order’ as a between subject factor. The between subject factor was employed as significant differences were found on the POMS Total Mood Disturbance Score between the two testing sessions, suggesting possible carry-over effects of the drug (see Section 7.3.4 for full description).
To determine the effect of $d$-amphetamine on performance on the DSST, three Digit Vigilance indices (accuracy, reaction time and number of false alarms), and Inspection Time, five one-way ANOVAs were performed, with an independent variable of drug condition (placebo/$d$-amphetamine), and a dependent variable of the performance score for DSST, DV Accuracy, DV Reaction time, DV Number of False Alarms, and Inspection Time. In order to assess the effect of $d$-amphetamine on Digit Span (Forward/Backward), number of errors made on the Tracking Task (Easy/Difficult), total time spent in error on the Tracking Task (Easy/Difficult), and Trail-Making performance (Trail A/Trail B), four 2x2 ANOVAs were conducted, where the independent variables were drug condition (placebo/$d$-amphetamine) and task level (Digit Span Test - Forward/Backward; number of errors made on the Tracking Task - Easy/Difficult; total time spent in error on the Tracking Task - Easy/Difficult; Trail-Making Test - Trail A/Trail B), and the dependent variable was the performance score on the Digit Span Test, number of errors made on the Tracking Task, total time spent in error on the Tracking Task, and the Trail-Making Test. Finally, to determine the effect of $d$-amphetamine on movement estimation, a 2x2x3x3 ANOVA was performed, with an independent variable of drug condition (placebo/$d$-amphetamine), task type (Easy/Difficult), Occlusion Size (Small/Medium/Large), Speed (Slow/Medium/Fast), and a dependent variable of task performance. Outliers were removed from the analysis where appropriate (greater than three standard deviations from the mean).

If an interaction was found between ‘session order’ and drug ($p < .05$) for any of the cognitive tasks, paired t-test comparisons were performed to explore the effects of $d$-amphetamine on cognitive performance separately for each of the two session order groups (i.e. $d$-amphetamine administered in first session and $d$-amphetamine administered in second session), with an independent variable of drug condition (placebo/$d$-amphetamine) and a dependent variable of cognitive performance. For each significant interaction (or main effect where degrees of freedom were greater than 1), a Bonferroni adjustment was employed to correct for Type 1 error by dividing the alpha by the number of post hoc comparisons. All $p$-values reported are corrected $p$-values.

7.2.6.3.2 Exploratory Analyses

To examine the relationship between individual amphetamine levels in blood (determined by the average blood levels obtained at 170 min and at 240 min after drug administration; as neuropsychological measures were completed during this time bracket) and changes in
cognitive performance (determined as a difference score, where the placebo performance score was subtracted from the \(d\)-amphetamine performance score for each individual across all tasks), a series of 14 Spearman’s Rho measures of association were performed. Alpha was reduced to 0.01 to reduce Type I error. All \(p\)-values reported are corrected \(p\)-values.

7.2.6.4 Standardised Field Sobriety Tests (SFSTs)
A series of difference in proportions tests based on paired data were performed to establish whether using the SFSTs accurately identified impairment associated with the consumption of single therapeutic acute dose of \(d\)-amphetamine (Newcombe, 1998; Method 10). This analysis was selected as the dependent variable (classification of impairment) was categorical (present/not present) and a repeated-measures design was employed in the present thesis. Therefore, a difference in proportions test was the most appropriate analysis to perform in order to determine the effects of \(d\)-amphetamine on SFSTs performance. For these tests, the independent variable was the drug condition (placebo/\(d\)-amphetamine) and the classification of impairment (present/not present) for overall SFSTs performance and each individual sobriety test score (HGN, WAT and OLS test) were the dependent variables. This test uses a \(z\)-statistic that tests the hypothesis that the number of participant scores that change as a function of experimental condition in one direction (i.e. not impaired in placebo but impaired in \(d\)-amphetamine), and the number of participant scores that change in the opposite direction (i.e. impaired in placebo but not impaired in \(d\)-amphetamine) is equal to zero in the population. The corresponding \(z\)-statistic is then used to calculate 95% confidence intervals around the point-estimate (i.e. the numerical difference between the proportions).

7.3 Results

7.3.1 Demographic Characteristics of Participants
Demographic characteristics of the participants are summarised in Table 7.3.
### Table 7.3 Demographics and Recreational Drug Use for Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.4</td>
<td>3.2</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.1</td>
<td>1.8</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Current amphetamine use (per year)</td>
<td>4.2</td>
<td>8.8</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Amphetamine use when consumed most (per year)</td>
<td>7.4</td>
<td>12</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using amphetamine (years)</td>
<td>5.3</td>
<td>5.7</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Current ecstasy use (per year)</td>
<td>15.2</td>
<td>17.4</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Ecstasy use when consumed most (per year)</td>
<td>0.5</td>
<td>0.8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Period of time using ecstasy (years)</td>
<td>13.2</td>
<td>17.7</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Current marijuana use (per year)</td>
<td>72.8</td>
<td>117.9</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Marijuana use when consumed most (per year)</td>
<td>0.5</td>
<td>0.8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Period of time using marijuana (years)</td>
<td>0.5</td>
<td>0.8</td>
<td>0</td>
<td>5+</td>
</tr>
<tr>
<td>Alcohol per week (units)</td>
<td>8.9</td>
<td>10.3</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

*Note that N=20 and that 'drug use' refers to number of occasions the specific drug was consumed in a year.*

As depicted in Table 7.3, on average, participants consumed amphetamine, ecstasy, and cocaine, less than once a month in the preceding year, while marijuana was on average consumed approximately once a month over the preceding year (13 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 slightly more than once a month (approximately 15 times). During the period when participants consumed marijuana most frequently, participants on average reported to have used marijuana around 1-2 times a week during that year (approximately 73 times).

#### 7.3.2 Level of \(d\)-amphetamine in Blood and Saliva

Figure 7.6 summarises the mean level of \(d\)-amphetamine detected in blood and saliva at three time points following drug administration: 120, 170 and 240 minutes after drug administration.
As depicted in Figure 7.6 the mean level of $d$-amphetamine detected in blood and saliva at 120 minutes after drug administration was 83ng/ml (SD=25.0) and 236ng/ml (SD=181.5) respectively, at 170 minutes after drug administration was 98ng/ml (SD=20.3) and 242ng/ml (SD=130.9) respectively, and at 240 minutes after drug administration was 96ng/ml (SD=15.4) and 260ng/ml (SD=126.5) respectively. For the raw data of blood and saliva concentrations for each subject across the three time points, refer to Appendix I.

### 7.3.3 Simulated Driving Performance

#### 7.3.3.1 Main Analyses

A significant reduction in simulated driving performance was observed in the $d$-amphetamine condition (mean = 217.1, Std Error = 11.0) relative to the placebo condition (mean = 195.0, Std Error = 12.9), irrespective of the driving task scenario (day/night), $F(1, 18) = 4.7$, $p < .05$. The difference in simulated driving performance between the placebo and $d$-amphetamine conditions was not different for the day time and night time driving scenarios, $F(1, 18) = 0.73$, $p = .40$. Moreover, there was no significant difference in simulated driving performance for the day and night time driving task scenarios, $F(1, 18) = 1.16$, $p = .30$. 

![Figure 7.6 Level of $d$-amphetamine in Blood and Saliva](image-url)
7.3.3.2 Exploratory Analyses

7.3.3.2.1 Effect of d-amphetamine on Individual Driving Variable Performance

Table 7.4 summarises the means and standard deviations for the individual driving simulator variables for the placebo and d-amphetamine drug conditions. Note that performance for the day and night time driving scenarios were combined for each individual driving variable, as no significant differences were found between day and night time driving performance (refer to Section 7.3.3.1 for results).

As can be seen in Table 7.4, there was a tendency towards decreased signalling adherence in the d-amphetamine condition, such as at intersections ($T = 13.50, p < .05$) and when entering a freeway ($T = 10, p = .05$). Additionally, during the d-amphetamine condition participants drove too fast significantly more often than during the placebo condition ($T = 0, p < .05$). Participants dosed with d-amphetamine were also found to travel significantly slower on the freeway at the time when an emergency situation occurred compared to placebo ($T = 52, p = .05$). Finally, the stopping distance between the vehicle and another object was shorter (trend level) in the d-amphetamine condition, when an emergency situation occurred on the freeway ($T = 32, p = .06$).

7.3.3.2.2 Effect of d-amphetamine on Visual Acuity and its Relation to Driving Ability

Visual acuity in the left eye significantly decreased in the d-amphetamine condition compared to the placebo condition, $t (18) = 2.28, p = 0.04$, however, d-amphetamine was not found to affect visual acuity in the right eye, $t (18) = 0.62, p = 0.55$. This poorer visual acuity noted in the left eye during the d-amphetamine condition was not found to be associated with the decrease in simulated driving performance observed in the d-amphetamine condition, $r (19) = -0.17, p = 0.50$. 
### Table 7.4 Driving Simulator Variable Results for Placebo and d-amphetamine Conditions

<table>
<thead>
<tr>
<th>Driving Simulator Variables</th>
<th>Placebo Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>T</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision</td>
<td>5.0 (7.6)</td>
<td>6.5 (8.8)</td>
<td>39</td>
<td>.64</td>
</tr>
<tr>
<td>Dangerous action skid</td>
<td>0.1 (0.3)</td>
<td>0.1 (0.2)</td>
<td>2</td>
<td>.56</td>
</tr>
<tr>
<td>No signal cancel when entering freeway</td>
<td>1.2 (1.9)</td>
<td>2.6 (3.3)</td>
<td>10</td>
<td>.05</td>
</tr>
<tr>
<td>No signal when entering freeway</td>
<td>2.8 (3.8)</td>
<td>2.8 (4.4)</td>
<td>13.5</td>
<td>.93</td>
</tr>
<tr>
<td>Incorrect signalling at intersection</td>
<td>4.0 (5.0)</td>
<td>7.0 (5.0)</td>
<td>13.5</td>
<td>.02</td>
</tr>
<tr>
<td>No signal cancel at intersection</td>
<td>0.0 (0.0)</td>
<td>0.2 (0.9)</td>
<td>0</td>
<td>.32</td>
</tr>
<tr>
<td>Wheels not straight on approaching intersection</td>
<td>1.1 (1.5)</td>
<td>0.9 (1.4)</td>
<td>30</td>
<td>.76</td>
</tr>
<tr>
<td>No signal when changing lane</td>
<td>28.8 (27.3)</td>
<td>37.0 (14.4)</td>
<td>49</td>
<td>.11</td>
</tr>
<tr>
<td>No signal cancel when changing lane</td>
<td>21.4 (10.5)</td>
<td>21.6 (10.7)</td>
<td>91.5</td>
<td>.89</td>
</tr>
<tr>
<td>No signal when moving off</td>
<td>40.5 (14.7)</td>
<td>43.0 (11.6)</td>
<td>48.5</td>
<td>.51</td>
</tr>
<tr>
<td>No signal cancel when moving off</td>
<td>9.4 (5.7)</td>
<td>9.4 (7.3)</td>
<td>37.5</td>
<td>.90</td>
</tr>
<tr>
<td>Waited too long before moving off</td>
<td>0.7 (1.0)</td>
<td>0.7 (1.0)</td>
<td>44.5</td>
<td>.94</td>
</tr>
<tr>
<td>No signal cancel when overtaking (left)</td>
<td>2.2 (3.6)</td>
<td>2.4 (5.1)</td>
<td>17.5</td>
<td>.94</td>
</tr>
<tr>
<td>No signal cancel when overtaking (right)</td>
<td>4.7 (4.9)</td>
<td>3.0 (4.1)</td>
<td>24</td>
<td>.23</td>
</tr>
<tr>
<td>No signal when overtaking (left)</td>
<td>2.8 (3.4)</td>
<td>0.8 (2.5)</td>
<td>9</td>
<td>.05</td>
</tr>
<tr>
<td>No signal when overtaking (right)</td>
<td>3.3 (5.9)</td>
<td>2.5 (4.1)</td>
<td>27.5</td>
<td>.62</td>
</tr>
<tr>
<td>Speed Control Brake Inappropriate</td>
<td>6.0 (4.8)</td>
<td>7.2 (6.0)</td>
<td>58</td>
<td>.61</td>
</tr>
<tr>
<td>Driving too fast</td>
<td>0.5 (1.5)</td>
<td>2.3 (3.8)</td>
<td>0</td>
<td>.04</td>
</tr>
<tr>
<td>No safe following distance</td>
<td>34.0 (19.4)</td>
<td>35.0 (18.2)</td>
<td>68.5</td>
<td>.70</td>
</tr>
<tr>
<td>Driving too slow</td>
<td>3.2 (1.0)</td>
<td>3.4 (1.6)</td>
<td>74</td>
<td>.89</td>
</tr>
<tr>
<td>Straddled barrier line</td>
<td>1.9 (5.4)</td>
<td>0.4 (1.1)</td>
<td>7</td>
<td>.23</td>
</tr>
<tr>
<td>Steering Wandering</td>
<td>5.7 (4.1)</td>
<td>5.5 (4.1)</td>
<td>58.5</td>
<td>.93</td>
</tr>
<tr>
<td>Steering Wide/cut</td>
<td>2.4 (3.3)</td>
<td>1.4 (2.4)</td>
<td>22</td>
<td>.29</td>
</tr>
<tr>
<td>Released brake inappropriately when stopping</td>
<td>0.0 (0)</td>
<td>0.2 (0.6)</td>
<td>0</td>
<td>.16</td>
</tr>
<tr>
<td>Not sufficient clear space when stopping</td>
<td>0.6 (1.5)</td>
<td>0.2 (0.6)</td>
<td>6</td>
<td>.32</td>
</tr>
<tr>
<td>Unnecessary/needless stopping</td>
<td>1.3 (1.0)</td>
<td>1.7 (1.0)</td>
<td>30</td>
<td>.27</td>
</tr>
<tr>
<td>Did not stop at red traffic light</td>
<td>1.5 (3.7)</td>
<td>3.5 (5.9)</td>
<td>7</td>
<td>.21</td>
</tr>
<tr>
<td>Straddled the solid line</td>
<td>1.1 (2.2)</td>
<td>0.7 (2.3)</td>
<td>9</td>
<td>.38</td>
</tr>
<tr>
<td>Exceeded speed limit</td>
<td>6.8 (5.4)</td>
<td>7.1 (9.1)</td>
<td>68.5</td>
<td>.45</td>
</tr>
<tr>
<td>Advanced situation collision</td>
<td>2.5 (5.5)</td>
<td>2.5 (5.5)</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (freeway)</td>
<td>105.6 (7.1)</td>
<td>101.8 (8.2)</td>
<td>52</td>
<td>.05</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (city)</td>
<td>32.5 (13.4)</td>
<td>33.2 (9.3)</td>
<td>103</td>
<td>.94</td>
</tr>
<tr>
<td>Reaction time (emergency stop)</td>
<td>17.1 (3.0)</td>
<td>18.0 (3.6)</td>
<td>76</td>
<td>.45</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (freeway)</td>
<td>93.2 (22.5)</td>
<td>84.6 (17.1)</td>
<td>32</td>
<td>.06</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (city)</td>
<td>25.0 (11.7)</td>
<td>29.9 (12.3)</td>
<td>3</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Note that alpha is .05*
7.3.4 POMS

Prior to drug administration, participants in the placebo condition reported more negative moods than prior to the \(d\)-amphetamine condition (\(T = 29.50, p < .02\)). The mood dimensions that loaded most strongly on this Total Mood Disturbance Score were ‘vigour-activity’ (\(T = 33.50, p < .05\)), ‘depression-dejection’ (\(T = 30, p < .05\)), ‘confusion-bewilderment’ (\(T = 37, p < .05\)), and fatigue-inertia (\(T = 43, p = .06\)).

To further explore why these differences were evident ‘prior’ to any drug administration, the data were divided into two groups, according to whether \(d\)-amphetamine was administered in the first or second experimental session. Wilcoxon’s signed-rank tests showed that those who received \(d\)-amphetamine in their first session reported more negative moods prior to their subsequent placebo session (\(T = 6, p < .05\)), whereas those who received placebo in their first session scored similarly on the POMS prior to their subsequent \(d\)-amphetamine session (\(T = 10, p = .14\)). This suggests that there may have been residual psychological effects of \(d\)-amphetamine that may have affected performance during the subsequent placebo condition, and so to account for any session-order effects, the session that \(d\)-amphetamine was administered (first or second) was employed as a between subject factor in all cognitive statistical analyses.

7.3.5 Neuropsychological Measures

7.3.5.1 Main Analyses

Details of the results for all main effects and interactions for the cognitive tasks, including means and standard errors, are presented in Table 7.5. Results for all post hoc tests are given in the text below, and all \(p\)-values reported are corrected \(p\)-values. The number of outliers excluded from analyses can be determined by the degrees of freedom reported in Table 7.5.
### Table 7.5 Overview of Main Effects of \(d\)-amphetamine on Cognitive and Psychomotor Performance

<table>
<thead>
<tr>
<th>Test</th>
<th>Factor</th>
<th>Mean (Std. Error)</th>
<th>d.f.</th>
<th>(F)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span</td>
<td>(T) x (Ses) (Forward)</td>
<td>placebo</td>
<td>1,17</td>
<td>2.06</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>(d)-amphetamine</td>
<td>1,17</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>(T) x Task (Backward)</td>
<td>placebo</td>
<td>1,17</td>
<td>1.05</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>(d)-amphetamine</td>
<td>5.5 (0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>(T) x (Ses)</td>
<td>73.8 (3.1)</td>
<td>1,18</td>
<td>5.54</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>67.3 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(d)-amphetamine</td>
<td>63.0 (3.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.4 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV / Accuracy</td>
<td>(T) x (Ses)</td>
<td>98.5 (0.5)</td>
<td>1,18</td>
<td>0.93</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>97.9 (0.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV / Reaction Time</td>
<td>(T) x (Ses)</td>
<td>396.8 (5.0)</td>
<td>1,18</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>384.5 (6.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV / False Alarms</td>
<td>(T) x (Ses)</td>
<td>1.3 (0.5)</td>
<td>1,18</td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>0.7 (0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Track/No. of errors</td>
<td>(T) x (Ses) (Tracking Only)</td>
<td>32.2 (3.0)</td>
<td>1,15</td>
<td>4.29</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>28.8 (2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task (Dual Tracking)</td>
<td>29.0 (3.7)</td>
<td>1,15</td>
<td>1.76</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>28.2 (2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Track/Time in error</td>
<td>(T) x (Ses) (Tracking Only)</td>
<td>2990.7 (706.4)</td>
<td>1,13</td>
<td>4.47</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>3368.8 (584.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Dual Tracking)</td>
<td>3236.7 (845.0)</td>
<td>1,13</td>
<td>1.68</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>3429.5 (505.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement Est.</td>
<td>(T) x (Ses) (Easy Task)</td>
<td>-0.16 (0.06)</td>
<td>1,18</td>
<td>13.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>0.04 (0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Difficult Task)</td>
<td>-0.13 (0.09)</td>
<td>1,18</td>
<td>6.09</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>0.17 (0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Small Occlusion)</td>
<td>-0.00 (0.09)</td>
<td>1,18</td>
<td>0.69</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>-0.24 (0.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Occl x (Ses) (Medium Occlusion)</td>
<td>-0.19 (0.06)</td>
<td>1,18</td>
<td>5.13</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>-0.10 (0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Occl x (Ses) (Large Occlusion)</td>
<td>-0.01 (0.04)</td>
<td>1,18</td>
<td>4.21</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>-0.04 (0.14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Occl x (Ses) (Slow Speed)</td>
<td>-0.02 (0.06)</td>
<td>1,18</td>
<td>6.02</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>-0.08 (0.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Speed x (Ses) (Fast Speed)</td>
<td>-0.24 (0.07)</td>
<td>1,18</td>
<td>3.69</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>(T) x Speed x (Ses)</td>
<td>-0.09 (0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspection Time</td>
<td>(T) x (Ses)</td>
<td>67.3 (3.9)</td>
<td>1,18</td>
<td>7.76</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>68.9 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>68.6 (3.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>59.6 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-Making A &amp; B</td>
<td>(T) x (Ses)</td>
<td>3431.2 (352.9)</td>
<td>1,18</td>
<td>4.36</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>3800.0 (389.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>4269.8 (352.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>4027.1 (389.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Trail A)</td>
<td>2087.8 (203.7)</td>
<td>1,18</td>
<td>0.16</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>2176.6 (251.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>2654.5 (203.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>2606.3 (251.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Trail B)</td>
<td>4774.6 (580.9)</td>
<td>1,18</td>
<td>1.00</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(T)</td>
<td>5423.3 (591.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses)</td>
<td>5885.1 (580.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(T) x Task x (Ses) (Fast Speed)</td>
<td>5447.9 (591.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note that 1/ F tests are reported for both main effects and interactions, where main effects refer to drug effects on overall task performance and interactions refer to the interaction of drug effects with specific aspects of the task. 2/ Where there is a significant interaction between drug and session order, the means and standard errors are presented separately for subjects who consumed d-amphetamine in their first session and subjects who consumed d-amphetamine in their second session (however, where the interaction was not significant, the means for both sessions combined (first and second) are displayed in the ‘1st Session’ column). 3/ Tests in brackets represent the subsets of the preceding test. 4/ ‘DV’ = Digit Vigilance, ‘T’ = Treatment Main Effect, ‘Ses’ = Session Order, ‘Occl’ = Occlusion.

As illustrated in Table 7.5, in the Digit Vigilance task there was a trend-level reduction in reaction time in the d-amphetamine condition (p=.06). Although an overall main effect of drug was not found for the Movement Estimation Task, a significant interaction was observed between session order and drug (p<.01). Post hoc tests revealed that when d-amphetamine was administered in the first session, participants in the d-amphetamine condition misjudged ‘time to contact’ significantly less relative to placebo [t(9) = 4.17, p < .01]. It should be noted that during the placebo condition participants underestimated ‘time to contact’, whereas in the d-amphetamine condition participants overestimated ‘time to contact’. No significant effects were observed when d-amphetamine was administered in the second session [t(9) = 1.69, p = .50]. In addition, a significant interaction was found between session order and task (p=.04). Paired t-test analyses revealed that during the easy task, when d-amphetamine was administered in the first session, participants in the d-amphetamine condition overestimated ‘time to contact’, whereas they underestimated ‘time to contact’ in the placebo condition [t(9) = 3.47, p < .05]. No further significant differences were found. A trend-level interaction was also noted for session order and occlusion (p=.06). Post hoc tests showed that when d-amphetamine was administered in the first session, participants in the d-amphetamine condition misjudged ‘time to contact’ significantly less relative to placebo, for the small [t(9) = 4.18, p < .01], medium [t(9) = 3.40, p < .05], and large [t(9) = 3.62, p < .05] occlusions. However, it should be noted that in the d-amphetamine condition, participants overestimated ‘time to contact’, whereas in the placebo condition participants underestimated ‘time to contact’, and this effect increased as a function of occlusion size. No significant effects were observed when d-amphetamine was consumed in the second session. Finally, there was a significant
interaction of session order with speed ($p=.03$). A series of post hoc tests showed that when $d$-amphetamine was consumed in the first session, participants in the $d$-amphetamine condition overestimated ‘time to contact’ significantly more for the slow speed [$t(9) = 5.01$, $p < .01$], and underestimated significantly less for the fast speed [$t(9) = 3.28$, $p < .05$], compared to placebo. When $d$-amphetamine was consumed in the second session, participants in the $d$-amphetamine condition underestimated ‘time to contact’ more, at a trend level, relative to placebo [$t(9) = 2.98$, $p = .08$].

In order to normalise the data, square root transformations were performed on Trail-Making A and B data. Although an overall main effect of drug was not found, there was a significant interaction of session order with drug ($p=.05$). However, post hoc tests revealed no significant differences between drug conditions for either of the two groups ($d$-amphetamine consumed in first session [$t(9) = 1.56$, $p = .31$]; $d$-amphetamine consumed in second session [$t(9) = 1.21$, $p = .52$]). Similarly, for the DSST, a significant interaction was found for session order and drug ($p=.03$), however, paired sample t-tests yielded no significant differences between drug conditions for either of the two groups ($d$-amphetamine consumed in first session [$t(9) = 1.70$, $p = .12$]; $d$-amphetamine consumed in second session [$t(9) = 1.69$, $p = .13$]).

Although no main effect for drug was found on the total time spent in error on the Tracking tasks, a significant interaction was noted between session order and drug ($p=.05$). Post hoc tests indicated that when $d$-amphetamine was administered in the second session, there was a trend-level decrease in time spent in error in the $d$-amphetamine condition relative to placebo [$t(8) = 2.36$, $p = .09$]. No significant drug effects were found when $d$-amphetamine was administered in the first session [$t(5) = 0.74$, $p = .99$]. Finally, $d$-amphetamine improved Inspection Time performance at a trend level ($p=.07$). In addition, an interaction was found with session order ($p=.01$), with post hoc tests indicating that when $d$-amphetamine was consumed in the second session, $d$-amphetamine significantly improved inspection time performance compared to placebo [$t(9) = 3.54$, $p < .01$]. This difference in performance between drug conditions was not observed when $d$-amphetamine was consumed in the first session [$t(9) = 0.58$, $p = .58$].
7.3.5.2 Exploratory Analyses
No significant associations were found between the level of \(d\)-amphetamine in the blood and cognitive performance.

7.3.6 Effect of \(d\)-amphetamine on the Standardised Field Sobriety Test (SFSTs) Performance

7.3.6.1 Horizontal Gaze Nystagmus (HGN) Test
The percentage of individuals exhibiting each of the signs recorded during the HGN test for both the placebo and \(d\)-amphetamine conditions are illustrated in Figure 7.7. Additionally, the percentage of individuals classified as impaired on the HGN test with and without the inclusion of HMJ in the scoring procedure (Overall HGN incl HMJ and Overall HGN respectively) is also depicted in Figure 7.7.

![Figure 7.7 Percentage of Individuals Exhibiting Each Sign of the HGN Test across Drug Conditions](image)

As illustrated in Figure 7.7 many signs were not observed during the administration of the HGN test in the \(d\)-amphetamine condition. HMJ was observed more frequently than any other HGN sign in the \(d\)-amphetamine condition, however, this difference was not found to be statistically significant (\(d\)-amphetamine 7/20 impaired; placebo 2/20 impaired), \(p > 0.05\), 95\% CI = -0.49 to 0.04. In terms of overall HGN performance, \(d\)-amphetamine did not significantly impair performance on the HGN test (\(d\)-amphetamine 0/20 impaired; placebo 0/20 impaired), \(p > 0.05\), 95\% CI = -0.17 to 0.17. Including HMJ in the HGN
scoring procedure did not change the percentage of individuals classified as impaired using the HGN test.

7.3.6.2 Walk and Turn (WAT) Test

The percentage of individuals exhibiting each of the signs recorded during the WAT test for both the placebo and \(d\)-amphetamine conditions are illustrated in Figure 7.8. In addition, the percentage of individuals classified as impaired on the WAT test (Overall WAT) is depicted in Figure 7.8.

![Figure 7.8 Percentage of Individuals Exhibiting Each Sign of the WAT Test across Drug Conditions](image)

As can be seen in Figure 7.8, many of the WAT signs were not observed during the \(d\)-amphetamine condition. However, those signs that were observed were noted similarly for the placebo and the \(d\)-amphetamine conditions. Improper Turn (IT) occurred most frequently across both the placebo and \(d\)-amphetamine conditions. Overall, \(d\)-amphetamine was not found to significantly impair performance on the WAT test (\(d\)-amphetamine 2/20 impaired; placebo 2/20 impaired), \(p > 0.05\), 95% CI = -0.20 to 0.20.

7.3.6.3 One Leg Stand (OLS) Test

The percentage of individuals exhibiting each of the signs recorded during the OLS test for both the placebo and \(d\)-amphetamine conditions are shown in Figure 7.9. In addition, the
percentage of individuals classified as impaired on the OLS test (Overall OLS) is illustrated in Figure 7.9.

As can be seen in Figure 7.9, a higher percentage of individuals made errors on the OLS test during the placebo condition relative to the \(d\)-amphetamine condition. Furthermore, a higher percentage of individuals were classified as impaired on overall OLS performance in the placebo condition compared to the \(d\)-amphetamine condition, however, this difference was not significant, \((d\)-amphetamine 1/20 impaired; placebo 2/20 impaired\), \(p > 0.05\), 95% CI = -0.13 to 0.24.

**7.3.6.4 Overall SFSTs Performance**

The percentage of individuals classified as impaired using the SFSTs is depicted in Figure 7.10. In addition, Figure 7.10 illustrates whether including HMJ in the HGN test scoring procedure increased the percentage of individuals classified as impaired on overall SFSTs performance.
As can be seen in Figure 7.10, one participant was classified as impaired using the SFSTs in the $d$-amphetamine condition. However, this was not found to be statistically significant ($d$-amphetamine 1/20 impaired; placebo 0/20 impaired), $p > 0.05$, 95% CI = -0.24 to 0.17. 
Including HMJ in the HGN test scoring procedure did not alter the percentage of individuals classified as impaired using the SFSTs. Table 7.6 summarises the accuracy of the SFSTs in identifying the presence of $d$-amphetamine.

### Table 7.6 Number of Participants Classified as Impaired or Not Impaired Using the SFSTs Following the Administration of $d$-amphetamine

<table>
<thead>
<tr>
<th></th>
<th>Impaired</th>
<th>Not Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGN</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>WAT</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>OLS</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Overall SFSTs</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>HMJ</td>
<td>7</td>
<td>13</td>
</tr>
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</table>

#### 7.4 Discussion

##### 7.4.1 Effect of $d$-amphetamine on Simulated Driving Performance

The present experiment found that the administration of 0.42mg/kg $d$-amphetamine significantly impaired simulated driving performance irrespective of the driving task scenario (day/night). Contributing to this decrement in simulated driving performance, drivers with low-level $d$-amphetamine drove too fast for the driving conditions more frequently than in the placebo condition. The results also indicated that $d$-amphetamine
affected signalling adherence; and the stopping distance between the vehicle and another object was shorter in the \textit{d}-amphetamine condition when an emergency situation occurred on the freeway, at a trend-level. Interestingly, drivers in the \textit{d}-amphetamine condition travelled significantly slower on the freeway at the time when an emergency situation occurred.

As the driving simulator task was completed within the 2-3 hour post-drug administration period, and as \textit{d}-amphetamine blood concentrations are relatively constant during this period (Kupietz \textit{et al.}, 1985; Brauer \textit{et al.}, 1996), it is reasonable to conclude that the observed reduction in driving skills corresponded to mean blood and saliva \textit{d}-amphetamine concentrations of approximately 90 ng/ml and 240 ng/ml respectively. It should be noted that the present cognitive findings (refer to Section 7.4.2) did not indicate significant associations between \textit{d}-amphetamine blood concentrations and cognitive performance. It is also worth pointing out that the considerable variations in saliva concentrations in comparison to blood concentrations, are most likely attributed to the fact that ion tapping in the more acidic saliva matrix resulted in higher saliva concentrations. It is also worth mentioning that although blood concentrations peaked 170 min after the drug was consumed, whereas saliva concentrations were still increasing at 240 min, the blood concentrations remained relatively stable during this time.

Furthermore, poorer left eye visual acuity was found in the \textit{d}-amphetamine condition. It is not clear whether this is a real finding (or merely statistical noise), as the only literature on visual acuity that the author is aware of suggests that \textit{d}-amphetamine may improve visual acuity, and does so bilaterally (Adachi-Usami, 1990). Furthermore, it is not clear why this reduction was observed in only one eye following one acute therapeutic dose of \textit{d}-amphetamine. As these issues suggest limitations with this finding, and as this reduction in visual acuity was not statistically associated with the decrements in overall simulated driving performance, this will not be discussed any further.

Since there are limited studies examining the effects of amphetamine on simulated driving performance, it is difficult to directly relate the results of the present investigation to previous research. However, one study that examined the acute effects of methamphetamine on simulated driving performance reported improvements in driving ability following drug administration (Mitler \textit{et al.}, 1993). Although inconsistent with the
present findings, the enhancement was noted following a 10mg dose of methamphetamine in healthy adults, which was considerably lower than the average dose of 30mg d-amphetamine administered in the present study. Moreover, it has previously been argued that doses ranging from 5-10 mg of amphetamine are unlikely to produce decrements in performance (Logan, 2002). Therefore, although Mitler et al. (1993) reported improvements in driving performance following methamphetamine administration, the results did not indicate that the improvement in driving ability would be maintained at higher methamphetamine doses. However, the present results provide evidence that at higher doses, d-amphetamine produces some impairment to simulated driving performance.

The present results are consistent with the epidemiological driving literature in that they indicate an association between amphetamine consumption and driving impairment (Logan, 1996; Logan et al., 1998). In a study examining the records of drivers arrested or killed in traffic accidents while intoxicated with methamphetamine, Logan (1996) found that 57% of the drivers involved in an accident were responsible for the crash. The most typical driving behaviours associated with the road accidents were drifting out of the lane of travel, such as onto the shoulder, into stationary objects, or into oncoming traffic. Although these driving behaviours are not consistent with the present results, Logan (1996) argued that the lack of attention, which resulted in the manifestation of these adverse driving behaviours, was not typical of amphetamine use, and suggested that it may be attributed to the withdrawal-related fatigue following extended methamphetamine use. Thus, the inconsistency in driving behaviours noted in Logan’s (1996) study with the present findings, may be attributed to differences in the testing phase, as the present experiment examined only the acute effects of d-amphetamine on driving performance, rather than the withdrawal-related effects observed later following extended amphetamine use.

However, there were other driving behaviours that Logan (1996) reported to be associated with amphetamine-related road crashes that are consistent with the present results. These behaviours included erratic driving, speeding, and errors in judgement. Logan et al. (1998) reported similar findings in a later study with blood concentrations ranging from 50 to 2600 ng/ml. However, although that study included blood concentration levels that are consistent with the average levels reported in the present experiment, the low
concentrations in the study by Logan (1996) may be attributable to the withdrawal phase associated with amphetamine use rather than the acute effects that are reported in the present study. However, as argued by Logan (1996), amphetamine concentrations required to elicit adverse driving behaviours vary across individuals as a result of differences in patterns of drug use, drug tolerance, fatigue, and alcohol or other drug use. Therefore, even relatively low concentrations of methamphetamine may produce symptoms that will negatively impact driving ability in some individuals. This suggestion is supported with the present results.

Interestingly, the present study found that drivers in the d-amphetamine condition travelled significantly slower on the freeway at the time when an emergency situation occurred. This is not consistent with previous research that reports that drivers under the influence of amphetamines, specifically methamphetamine, tended to speed more (Logan, 1996). It is thus difficult to interpret the present finding. Although it can be argued that the present results indicate more cautious driving, it may also be possible that the speed reduction observed in the laboratory setting may act as a compensatory mechanism to permit drivers to attend to other aspects of driving, particularly as drivers were aware that their performance was being assessed. This is highlighted by the trend-level finding that the stopping distance between the vehicle and another object was shorter in the d-amphetamine condition when the emergency situation occurred on the freeway, suggesting that it took participants dosed with d-amphetamine longer to stop, albeit travelling at a slower speed.

The decrements in simulated driving performance observed in the present experiment following d-amphetamine consumption may be seen as inconsistent with the cognitive literature which indicates cognitive enhancement following acute amphetamine administration (Rapoport et al., 1980; Hurst, 1987; Kelly et al., 1991; Halliday et al., 1994; Fleming et al., 1995; Comer et al., 1996; Kumari et al., 1997; Servan-Shreiber et al., 1998; Wachtel and de Wit 1999; Cami, et al., 2000; de Wit et al., 2000; Johnson et al., 2000; Mattay et al., 2000; de Wit et al., 2002; Asghar et al., 2003; Barch and Carter, 2005). However, it is difficult to draw strong parallels between the simulated driving results and the cognitive research, as there are notable differences in task attributes that may explain the inconsistencies. For instance, operating a motor vehicle requires the simultaneous execution of several tasks involving a range of cognitive processes, such as, attention, motor coordination, decision making, and working memory. In contrast, cognitive tasks...
generally involve focused performance of one task only, thus all attention is directed to the specific neuropsychological function being assessed, such as reaction time or divided attention specifically. Therefore, although amphetamines appear to improve informational and attentional processes when a simple cognitive task is administered (Rapoport et al., 1980; Kelly et al., 1991; Koelega 1993; Halliday et al., 1994; Fleming et al., 1995; Comer et al., 1996; Johnson et al., 1996, 2000; Kumari et al., 1997; Ward et al., 1997; Servan-Shreiber et al., 1998; McKetin et al., 1999; Wachtel & de Wit, 1999; Cami et al., 2000; de Wit et al., 2002; Asghar et al., 2003; Fillmore et al., 2005), this may not be the case when the subject is required to execute many tasks simultaneously, as for example when driving.

A further explanation for the discrepancy between the research demonstrating cognitive enhancing effects of amphetamines and the present driving results is that the driving decrements observed in the present experiment may be attributed to ‘tunnel vision’ effects (perceptual narrowing). ‘Tunnel vision’ effects have previously been reported to occur following d-amphetamine administration (Mills et al., 2001), which results in perceived cues restricting to the focal point (Easterbrook, 1959). It is claimed that mild arousal benefits performance in tasks when stimuli are presented centrally, while simultaneously impairing abilities in the periphery (Easterbrook, 1959; Mills et al., 2001). Thus, tasks that require the subject to focus on only one area of the visual field, such as a simple cognitive task, are more likely to manifest improvement in performance following amphetamine administration. In contrast, tasks that require the subject to scan an entire visual field and identify targets in the close or far periphery, such as driving (Mills et al., 2001), are likely to become impaired following amphetamine consumption.

‘Tunnelling’ has previously been shown to occur during tasks with high demands and stress, such as driving (Mills et al., 1999; Williams, 1988, 1995). ‘Tunnelling’ can be dangerous while driving as it increases the risk of failing to attend to potential hazards that fall outside of the driver’s attentional focus, such as traffic lights. This phenomenon is consistent with previous reports that have shown drivers under the influence of methamphetamine fail to stop at stop signs, resulting in road accidents and fatalities (Logan, 1996). Although the present experiment did not find d-amphetamine to significantly decrease traffic light adherence, it is of interest to note that the means during the d-amphetamine condition indicated a tendency for drivers to fail to stop at red traffic lights more frequently when compared to the placebo condition. These findings, therefore,
are not inconsistent with the hypothesis that amphetamine-induced ‘tunnel vision’ effects may be contributing to adverse driving performance. However, further research is needed in order to corroborate this hypothesis.

Although overall driving performance was found to be significantly impaired with \(d\)-amphetamine, it is important to emphasise that only few specific driving behaviours were found to be significantly reduced with \(d\)-amphetamine. Moreover, the driving behaviours that were found to be impaired do not reflect the typical driving behaviours that are most commonly seen in \textit{real-life} amphetamine impaired drivers, such as drifting out of the lane of travel or crossing dividing lines, high speed collisions, or weaving (Logan, 1996).

It is also important to address the appropriateness of the loading factors that were assigned for each driving variable. The loading factors used in the present study were in accordance with the standard loading factors provided by the driving simulation software used in our research laboratory (CyberCAR™ LITE driving simulator manual; Thoroughbred Technologies Pty. Ltd.), and employed in other research (e.g. Papafotiou et al., 2005). However, the loadings assigned to some of the driving variables are questionable, and consequently may have produced some misleading results. For instance, according to the driving simulator analysis manual, signalling errors are assigned loading factors of 4 and 5, while straddling the solid line, exceeding the speed limit, and straddling the barrier line are assigned loading factors of 2. Yet, it is these latter driving behaviours that are most commonly reported in amphetamine impaired literature. Although there may be limitations, in order to avoid reducing the reliability and validity of the driving assessment, performance was analysed according to the driving simulation software manual. Therefore, although using the standard loading factors suggested possible driving decrements with \(d\)-amphetamine, this may be somewhat misleading as the significant reduction in driving performance noted in the \(d\)-amphetamine condition may have resulted, for example, from excessive signalling (due to the high loading). Therefore, caution should be applied to the above interpretation of the present results.

In conclusion, the results of the present experiment suggest that a single acute therapeutic dose of \(d\)-amphetamine decreases simulated driving performance in recreational stimulant users. Contributing to this overall reduction in simulated driving performance, drivers under the influence of \(d\)-amphetamine drove too fast for the traffic conditions more often
that in the placebo condition. The results also indicated that \textit{d}-amphetamine affected signalling adherence. Interestingly, drivers in the \textit{d}-amphetamine condition travelled significantly slower on the freeway at the time when an emergency situation occurred.

These results are consistent with the epidemiological driving research which indicates an association between amphetamine use and a reduction in driving ability. Although the present driving results are not consistent with the cognitive literature, which generally indicates an an acute therapeutic dose of \textit{d}-amphetamine improves performance, other more subtle factors may relate to these differences, such as particular aspects of cognitive functioning. Therefore, as the results of the present study provide some indication that a single acute therapeutic dose of \textit{d}-amphetamine decreases driving ability, the possible mechanisms attributed to this impairment need to be explored. This will now be discussed in Section 7.4.2.

### 7.4.2 Effect of \textit{d}-amphetamine on Driving-Related Cognitive Processes

The present experiment examined the acute effects of 0.42mg/kg \textit{d}-amphetamine on cognitive measures relevant to driving, including attention, psychomotor function, and perceptual speed. Although only trend-level findings, the present results, provide some indication of improvements in aspects of attention, psychomotor functioning and perceptual speed. Although only trend-level, these findings are consistent with previous \textit{d}-amphetamine cognitive research that have similarly shown an improvement in attention (de Wit \textit{et al.}, 2002; Wachtel & de Wit, 1999; Cami \textit{et al.}, 2000; Kelly \textit{et al.}, 1991; Ward \textit{et al.}, 1997; Comer \textit{et al.}, 1996), psychomotor performance (Comer \textit{et al.}, 1996; Kennedy \textit{et al.}, 1990), and perceptual speed (Kennedy \textit{et al.}, 1990; Fillmore \textit{et al.}, 2005; Asghar \textit{et al.}, 2003; Kumari \textit{et al.}, 1997; Halliday \textit{et al.}, 1994; Fleming \textit{et al.}, 1995; Rapoport \textit{et al.}, 1980), with doses ranging from 5mg to 30mg of amphetamines.

In terms of the Digit Vigilance task, although only a trend level finding, response speed was faster in the \textit{d}-amphetamine condition compared to the placebo condition, which is consistent with previous research (Kelly \textit{et al.}, 1991; Koelega 1993; Comer \textit{et al.}, 1996). This improvement in response speed was further substantiated with trend-level improvements in perceptual speed during the Inspection Time task following \textit{d}-amphetamine consumption. This is in accordance with the bulk of the literature that has consistently shown amphetamines to improve perceptual speed across a range of
amphetamine doses and task types (Rapoport et al., 1980; Callaway et al., 1994; Halliday et al., 1994; Fleming et al., 1995; Kumari et al., 1997; Ward et al., 1997; Servan-Shreiber et al., 1998; McKetin et al., 1999; Johnson et al., 2000; Asghar et al., 2003; Fillmore et al., 2005). In addition, consistent with previous reports, the present findings indicated that d-amphetamine enhanced psychomotor ability (at a trend-level), specifically relating to tracking performance (de Wit et al., 2002; Wachtel & de Wit, 1999; Cami et al., 2000; Kelly et al., 1991; Ward et al., 1997; Comer et al., 1996). However, as these were only trend-level findings, the present results need to be addressed with caution.

The present experiment revealed that for the movement estimation task, the difference between estimated ‘time to contact’ and actual ‘time to contact’ was smaller in the d-amphetamine condition compared to the placebo condition (when d-amphetamine was administered in the first session). However, it is important to note that although the difference between the estimated ‘time to contact’ and the actual ‘time to contact’ was smaller in the d-amphetamine condition relative to placebo, in the d-amphetamine condition participants overestimated ‘time to contact’, while in the placebo condition participants underestimated ‘time to contact’. This apparent improvement of performance may also be attributed to participants being more impatient and hasty in their decisions, responding earlier than under normal conditions (placebo), which in turn may lead to greater risk taking behaviour. A difficulty with interpreting these results is that the present experiment also revealed that those participants who received d-amphetamine in the first session reported more negative moods prior to the subsequent placebo session. Although it may be possible that these participants may have been experiencing residual psychological effects of previously administered d-amphetamine, which subsequently may have affected performance during the second session (placebo session), this is difficult to be sure of, and thus further research is warranted. Therefore, these findings need to be addressed with caution.

The movement estimation task was included in the present experiment to examine the influence of d-amphetamine on perceiving and predicting motion. In terms of real-life driving, the estimation of ‘time to contact’ would translate to one’s ability to judge whether another vehicle will collide with one’s own vehicle. The ability to judge vehicle contact depends on efficient estimation of actual motion and speed, and the capacity to predict when and where a collision will occur. Following from this, the present results indicate that
the overestimation of ‘time to contact’ observed with \(d\)-amphetamine would have compromising effects on traffic safety, as the ability to judge the incidence of a collision may be impaired. In contrast, the underestimation of ‘time to contact’ observed in the placebo condition can be seen as representative of safer and more cautious driving, as a larger gap would be available from the object in front.

Since no previous studies have examined the effects of amphetamines on movement estimation, it is difficult to compare the present results with other research. Recently, however, Lamers et al. (2003) examined the effects of an acute dose of MDMA (75 mg) on movement estimation performance. Although there are many affective and entactogenic activities that are quite different to amphetamines, MDMA does share some general central nervous system activation effects with amphetamines. Thus, in light of the limited amphetamine research, these MDMA findings will be discussed.

Consistent with the present results, Lamers et al. (2003) found MDMA affected ‘time to contact’ performance, although unlike the present findings, the authors reported impairments resulting from both the overestimation and underestimation of ‘time to contact’. Lamers et al. (2003) argued, however, that any drug-induced impairment in the ability to judge motion is unacceptable due to its negative implications to traffic safety. The results from the present experiment and the study by Lamers et al. (2003), thus suggests that stimulants affect the ability to perceive and predict motion, which, when applied to traffic safety, indicates that the ability to judge whether a vehicle will collide with one’s own will be affected. This impairment would lead to a greater risk of a traffic accident.

The present cognitive findings support the notion that \(d\)-amphetamine levels in the blood and \(d\)-amphetamine behavioural effects are generally dissociable in healthy subjects following a single therapeutic dose of \(d\)-amphetamine (Angrist et al., 1987; Brauer et al., 1996; Asghar et al., 2003), as no associations were found between blood amphetamine levels and cognitive performance. This is consistent with previous epidemiological research which has shown that methamphetamine concentrations required to evoke adverse driving behaviours can vary considerably across individuals (range 50 to 2600 ng/ml), as a result of differences in patterns of drug use, drug tolerance, fatigue, and alcohol or other drug use (Logan, 1996). Therefore, specific amphetamine levels in blood do not
necessarily indicate impairment, as there are many factors that can influence performance differently across individuals.

The Trail-Making task was included in the present study to assess possible visual scanning deficits which have previously been shown to occur following \textit{d}-amphetamine administration (Kennedy \textit{et al.}, 1990). The present results revealed that \textit{d}-amphetamine did not impair visual scanning ability, however, it should be noted, that the Trail-Making task, administered in the present study, was not as pure a measure of visual scanning as that employed by Kennedy \textit{et al.} (1990). Therefore, it is possible that a visual scanning deficit may have been obscured by the choice of task in the present study. The Trail-Making Test is argued to primarily measure visual-conceptual and visual-motor tracking performance (Giovagnoli \textit{et al.}, 1996). Although visual scanning is necessary to complete the task, the test does not specifically measure visual scanning ability, thus performance on the test may not adequately reflect visual scanning ability.

In addition, it is important to note that the present results indicated some possibilities of practice effects. As can be seen in Table 7.5, improvements in performance were generally observed during the second experimental session, irrespective of drug condition. It has been suggested that adequate practice sessions should be implemented when assessing cognitive constructs to avoid learning effects and possibly differential learning between treatment conditions. Therefore, there is the possibility, as only brief practices were given in the present experiment, of learning effects obscuring \textit{d}-amphetamine effects on the Trail-Making task.

Overall, the present cognitive results provide little indication as to how acute low-level \textit{d}-amphetamine use may be associated with a reduction in driving ability. It is possible that cognitive dysfunctions associated with amphetamine use are too subtle to be observed using standard cognitive measures, or that the dose administered in the present study was too low to elicit significant cognitive impairments. However, the present findings do provide one suggestion as to how driving ability may be negatively affected with \textit{d}-amphetamine. The results from the movement estimation task suggest that the overestimation of ‘time to contact’, following \textit{d}-amphetamine consumption, can be understood as a reduction in safe driving, possibly attributed to increases in risk taking behaviour. This possibility is consistent with previous research that have similarly shown
that stimulants, such as MDMA, impair perception of motion and ‘time to contact’, which may lead to reduced traffic safety (Lamers et al., 2003). In addition, the d-amphetamine-induced driving impairments observed in the present experiment, relating to speed control and the stopping distance during emergency situations, may have resulted from deficits in estimating movement and time of collision. However, further research is needed to support this hypothesis.

In summary, the results of the present experiment indicate that a single acute therapeutic dose of d-amphetamine appears to have only minimal (and enhancing) effects on aspects of attention, psychomotor functioning and perceptual speed. Although the findings also indicate that the ability to perceive and predict motion and ‘time to contact’, assessed using the movement estimation task, appears to improve with d-amphetamine compared to placebo, this has been argued to represent a reduction in safe driving, possibly attributable to increases in risk taking behaviours. Specifically, the smaller gap found between estimated and actual ‘time to contact’ following d-amphetamine consumption, indicates a reduction in safe driving as there is less time to respond appropriately if a sudden change occurs in the traffic environment. However, these results need to be addressed with caution, as this difference in performance between the d-amphetamine and placebo condition was observed only for participants who received d-amphetamine in the first session. The present findings also substantiate previous research indicating that low amphetamine levels in the blood and acute d-amphetamine behavioural effects are generally dissociable in healthy subjects.

In terms of driving, the present results shed little light as to how acute d-amphetamine use may impair driving performance. However, the overestimation in ‘time to contact’ observed with d-amphetamine, during the movement estimation task, indicates that amphetamine-related driving impairments may be associated with modulations in the ability to perceive motion and predict when a vehicle will collide with another. This is supported with the present driving simulator results, which indicated d-amphetamine to impair speed control and the stopping distance between the vehicle and another object. However, further research is necessary to clarify this issue. Alternatively, it may be that driving impairments associated with d-amphetamine result from deficits that are too subtle to be detected using standard cognitive measures, or that the dose administered in the present study was too low to elicit cognitive impairments.
7.4.3 Efficiency of the Standardised Field Sobriety Tests (SFSTs) in Detecting d-amphetamine Impairment

The present experiment found that 0.42mg/kg d-amphetamine did not significantly impair performance on the Standardised Field Sobriety Tests (SFSTs). Using these sobriety tests, impairment associated with d-amphetamine consumption was identified in only 5% of cases when blood and saliva d-amphetamine concentration levels were approximately 90ng/ml and 240ng/ml respectively.

It is difficult to relate the present findings to previous research, as the SFSTs in the present investigation were not administered in conjunction with other behavioural and physiological tests, as have been done in previous sobriety test research (i.e. the DEC Program; Bigelow et al., 1984; Compton, 1986). However, the extremely low percentage of participants identified as being intoxicated with d-amphetamine, is consistent with previous research that has highlighted the difficulty of detecting this stimulant drug class. For example, Heishman et al. (1998) reported that the majority of subjects dosed with d-amphetamine were classified as ‘not impaired’ by the Drug Recognition Examiners (DRE), and that in only 2% of cases where d-amphetamine was administered, was the classification correct. Furthermore, the DRE’s classified subjects as dosed with other drugs correctly more frequently than those where amphetamines was administered. Similarly, Shinar et al. (2000) also found stimulants, specifically d-amphetamine, to be the most difficult to identify, with only 7.8% of cases correctly classified.

The cognitive literature indicates that with therapeutic doses (ranging from 5mg to 30mg), d-amphetamine generally enhances neuropsychological functioning, such as attention and psychomotor performance (Kennedy et al., 1990; Kelly et al., 1991; Koelega 1993; Comer et al., 1996; Johnson et al., 1996, 2000; Ward et al., 1997; McKetin et al., 1999; Wachtel & de Wit, 1999; Cami et al., 2000; de Wit et al., 2002). The SFSTs were designed to assess these processes. Thus, following from the cognitive research it would be expected that a moderately low d-amphetamine dose (30mg) would not impair performance on the SFSTs, but possibly improve performance. This notion is consistent with the findings of the present experiment and previous research, which indicates improvements on the OLS test following the administration of d-amphetamine (Heishman et al., 1998). Furthermore, the SFSTs were designed to detect impairment associated with considerably higher amphetamine concentrations than administered in the present study. Thus, it is unlikely
that the single therapeutic \(d\)-amphetamine dose administered in the present study would elicit such impairment, and therefore, it is not surprising that the SFSTs did not detect impairment following this dose of \(d\)-amphetamine.

\(d\)-amphetamine was not found to significantly impair performance on the HGN test. In fact, many of the traditionally scored signs were not observed at all, suggesting that these signs are not typically induced following the consumption of low \(d\)-amphetamine doses. Although this test was designed to assess gross impairment, and the dose administered in the present study was unlikely to produce such impairments, these findings are consistent with the DRE instructor’s manual (1993) and other research, which report that stimulants do not affect performance on the Horizontal Gaze Nystagmus, Lack of Smooth Pursuit, Vertical Gaze Nystagmus, and Lack of Convergence tests (Kosnoski, et al., 1998; Adler and Burns, 1994).

Including the sign head movements and/or jerks (HMJ) in the HGN test scoring procedure, did not increase the percentage of impairment classifications. However, consistent with research by Papafotiou et al. (2005b) involving cannabis, HMJ was observed more frequently in the \(d\)-amphetamine condition than any other sign. Although this is an interesting observation, and one which merits further investigation, it should be noted that the HMJ sign was also present in 10% of subjects during the placebo condition, therefore making it a greater risk for false positives in a drug evaluation than many of the other signs. Furthermore, as the SFSTs were designed to detect gross drug-related impairment, and the dose administered in the present study was unlikely to produce such effects, the present SFST data needs to be addressed with some caution, particularly the HMJ data. However, since the SFST battery has not been appropriately validated for the detection of drugs other than alcohol, the findings of the present experiment provide valuable information regarding the relation between acute low level amphetamine consumption and the SFSTs. The results of the present experiment and previous cannabis research (Papafotiou et al., 2005b) suggest that law enforcement agencies employing, or considering employing these sobriety tests, may want to consider observing the HMJ sign. However, due to the scant evidence of any psychophysical impairment with this low drug dose, this makes assessment of the HMJ sign speculative, and thus, further research is necessary.
*d*-amphetamine did not impair performance on the WAT test. However, as has previously been argued, this finding is not surprising given the low *d*-amphetamine dose administered in the present study. Improper Turn (IT) was observed more frequently than any other WAT sign in both the placebo and *d*-amphetamine conditions. This is consistent with previous research, in which IT was observed similarly across both placebo and cannabis conditions (Papafotiou et al., 2005b). These results indicate that IT is likely to be observed irrespective of drug consumption, thus, it may not be appropriate to include this sign in the scoring procedure of impairment tests.

Finally, *d*-amphetamine did not impair performance on the OLS test. Although not significant, it is of interest to note that more errors were observed in the placebo condition than during the *d*-amphetamine condition. Heishman et al. (1998) found that a decrease in errors on the OLS test was the third best predictor for the presence of *d*-amphetamine. However, it is unlikely that improvements in OLS test performance would be observed at amphetamine concentrations encountered in apprehended and fatally injured drivers. As the tests were designed to assess impairment associated with considerably higher drug doses, interpretation of the present data needs to be addressed with caution. However, the present findings do suggest that the dose administered was too low to produce any impairing effects on the OLS test.

The SFSTs were implemented in Victoria Police procedures to detect driving impairment associated with the consumption of a drug/s other than alcohol. However, the findings from the present experiment indicate that these sobriety tests may not be effective in detecting driving impairment associated with low dose *d*-amphetamine. Specifically, the present experiment found that simulated driving performance was impaired 2-3 hours following 0.42mg/kg *d*-amphetamine consumption, however, a commensurate impairment in SFSTs performance was not observed at a similar time following *d*-amphetamine administration (refer to Table 7.2 for specific times that the driving simulator and the SFSTs were administered). Although the present results provide some evidence to suggest that the SFSTs may not be effective in identifying impairment associated with low dose *d*-amphetamine, it should be emphasised that the SFSTs were designed to detect gross impairment, and thus it is not surprising that the present study did not find the SFSTs to be accurate in detecting impairment associated with a single therapeutic dose of *d*-amphetamine. However, as a driving impairment was observed following a single
therapeutic dose of \textit{d-}amphetamine, further research is warranted as to the efficiency of the SFSTs to detect impairment associated with amphetamine consumption.

In conclusion, the results from the present experiment suggest that following the administration of 0.42mg/kg \textit{d-}amphetamine, performance on the SFSTs is not impaired. Using the SFSTs, impairment associated with low dose \textit{d-}amphetamine was identified in 5% of cases. These findings indicate that the SFSTs may not be efficient in identifying impairment associated with low dose levels of \textit{d-}amphetamine in drivers. Although this supports previous research that these sobriety tests may not be appropriate to test for the stimulant drug class, particularly at these dose levels (Heishman \textit{et al.}, 1998), it is important to note that these tests are employed by law enforcement agencies to detect impairment associated with high amphetamine concentrations. However, as a driving impairment was observed in the present experiment following the administration of a therapeutic dose of \textit{d-}amphetamine, further research is needed to assess the efficiency of these tests in detecting amphetamine-related impairment.

\subsection*{7.4.4 Summary of the Acute Effects of \textit{d-}amphetamine on Simulated Driving Performance, Driving-Related Cognitive Processes, and SFSTs Performance}

In summary, the results of the present experiment indicate that 0.42mg/kg \textit{d-}amphetamine impaired simulated driving performance, in recreational stimulant users 2-3 hours post-drug administration. Contributing to this overall reduction in simulated driving performance, drivers dosed with \textit{d-}amphetamine drove too fast for the driving conditions more frequently than in the placebo condition. Furthermore, \textit{d-}amphetamine affected signalling adherence. Interestingly, drivers in the \textit{d-}amphetamine condition travelled significantly slower on the freeway at the time when an emergency situation occurred.

The results from the driving-related cognitive measures provide limited suggestions as to how a single acute therapeutic dose of \textit{d-}amphetamine may impair driving performance. Although the present findings found that a low \textit{d-}amphetamine dose produced only trend-level improvements to aspects of attention, psychomotor functioning and perceptual speed, the present findings also provide some evidence to suggest that \textit{d-}amphetamine affects the ability to perceive and predict motion and ‘time to contact’, possibly attributed to increases in risk taking behaviours. Specifically, during the movement estimation task, the smaller difference found between estimated and actual ‘time to contact’ following \textit{d-}amphetamine
consumption, suggests a reduction in safe driving, as there is less time to respond appropriately if a sudden change occurs in the traffic environment.

Finally, the present study indicates that a single therapeutic dose of $d$-amphetamine does not impair performance on the SFSTs. Although this supports previous research that sobriety tests may not be appropriate to test for the stimulant class of drugs at these levels (Heishman et al., 1998), the SFSTs were designed to detect impairment associated with considerably higher amphetamine concentrations. However, as a driving impairment was observed following a single therapeutic dose of $d$-amphetamine, further research is warranted as to the efficiency of the SFSTs to detect impairment associated with amphetamine consumption.
Chapter 8.

Experiment 2: The Effect of d,l-methamphetamine on Simulated Driving Performance, Driving-Related Cognitive Functions, and the SFSTs

8.1 Introduction
As was argued in Chapter 1 (Introduction) and Chapter 3 (Amphetamine and Driving), it is important to examine the acute effects of various amphetamines on driving performance to determine how amphetamine use may be associated with amphetamine-related driving impairments. The results from Experiment 1 (Chapter 7) suggest that a single acute therapeutic dose of $d$-amphetamine impairs simulated driving performance. However, as the findings from Experiment 1 (Chapter 7) are the only available literature (with the exception of one other study that examined the acute effects of 10mg methamphetamine on driving performance (Milter et al., 1993; refer to Chapter 4 for details) that has addressed the effects of an acute dose of amphetamines on simulated driving performance, further research is necessary to confirm these findings.

It is important to assess amphetamines that are commonly used by drivers to allow for comparison to in situ driving. Methamphetamine is considered to be one of the most popular abused stimulants amongst drivers. Within the transport industry, particularly long-distance drivers, methamphetamine has long been used for its functional use of allowing longer and more sustained work performance. Methamphetamine exists in two isomeric forms, dextro ($d$-) and levo ($l$-) (Logan, 2002), with the $d$-isomer having greater central nervous system potency than the $l$-isomer (Hardman & Limbird, 1996). A racemic mixture of methamphetamine ($d,l$-) is less potent than the $d$-isomeric form and more potent than the $l$-isomeric form (Logan, 2002). The present experiment investigated the acute effects of $d,l$-methamphetamine on simulated driving performance. The results of this experiment will further clarify how amphetamine use may be associated with driving impairment (Experiment 3, presented in Chapter 9, will test for similar effects using the more potent form, $d$-methamphetamine).

Although research using simulated driving tasks can provide useful information on the effect of amphetamine consumption on driving performance, these tests are not able to
establish whether there are specific cognitive dysfunctions produced with amphetamines that may contribute to amphetamine-related driving impairments. The cognitive results from Experiment 1 (Chapter 7) provide limited data as to how acute amphetamine use may affect driving performance, with the only exception being the results from the movement estimation task. Although the findings of Experiment 1 indicated that the ability to perceive and predict motion and ‘time to contact’ improved with \( d \)-amphetamine compared to placebo, this was interpreted as a reduction in safe driving. Specifically, participants in the \( d \)-amphetamine condition tended to overestimate ‘time to contact’, and this, in terms of real traffic conditions, could result in collisions. These findings provide some suggestion of how a low acute dose of amphetamine may decrease driving performance. However, as there is limited research that has examined this, further research is necessary to clarify this issue.

Therefore, the present experiment employed the same cognitive tasks as were administered in Experiment 1 (Chapter 7), to further explore the acute effects of amphetamine consumption on cognitive processes that are deemed important to safe driving, such as, attention, psychomotor performance, perceptual speed, visual scanning ability, and movement estimation (Hurst, 1987; Lamers et al., 2003; Anstey et al., 2005). Specifically, the present experiment administered: the Digit Span Test as a measure of working memory and efficiency of attention; Digit Vigilance to assess sustained attention; a Movement Estimation Task to assess estimation of movement speed and ‘time to contact’; Digit Symbol Substitution Test and a Tracking Task as measures of psychomotor performance; the Trail-Making Test to assess visual scanning ability; and Inspection Time to assess perceptual speed. These tests were selected as they specifically measure cognitive functions that have been reported to be important to safe driving (Hurst, 1987; Lamers et al., 2003; Anstey et al., 2005).

Additionally, in response to the increasing number of ‘drug other than alcohol’ related road accidents, a second aim of the present experiment was to investigate the efficiency of the SFSTs to identify amphetamine-related impairment in drivers. The results from Experiment 1 (Chapter 7) indicated that the \( d \)-amphetamine dose seemed to be too low to elicit significant deficits in SFSTs performance, however, a driving impairment was observed following the same dose. Therefore, as this was the first study that investigated the efficiency of these sobriety tests (not in conjunction with other behavioural and
physiological tests) to detect impairment associated with amphetamine consumption in healthy, stimulant-using, non-fatigued adults, in a controlled laboratory setting, further research is warranted to determine the efficiency of the SFSTs to detect impairment associated with amphetamine consumption. Therefore, to extend the findings from Experiment 1 (Chapter 7), the present experiment examined the acute effects of \textit{d,l}-methamphetamine on SFSTs performance. The results of this experiment will contribute towards understanding how a therapeutic dose of \textit{d,l}-methamphetamine may affect performance on the SFSTs.

The present experiment assessed the acute effects of \textit{d,l}-methamphetamine on simulated driving performance, driving-related cognitive processes, and performance on the SFSTs, using a repeated-measures, counter-balanced, double blind, placebo-controlled design. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \textit{d,l}-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The present chapter will describe the materials and methodologies employed, the results, and provide a discussion of the results.

8.2 Materials and Methods

8.2.1 Participants

8.2.1.1 Selection Criteria
The selection criteria for the present experiment was the same as for Experiment 1 (Chapter 7). Refer to Section 7.2.1.1 for full description.

8.2.1.2 Psychological and Physical Health
Psychological and Physical Health was assessed with the same procedure as for Experiment 1 (Chapter 7). Refer to Section 7.2.1.2 for full description.

8.2.1.3 Sample Characteristics
Twenty healthy illicit stimulant users (10 males; 10 females), aged between 21 and 34 years (mean = 24.3 years, SD = 3.4 years), with an average male weight of 81.2kg (SD = 12.6), and an average female weight of 59.7kg (SD = 6.9) were recruited. All participants had a minimum of 11 years education, and a valid, full driver’s license. All participants were consumers of caffeine, with an average daily intake of 1.0 cups of coffee (range 0-2).
Of the 20 participants, 11 were self-assessed smokers, averaging 3.5 cigarettes a day (range 0-22). Note that the participants in the present experiment were different to the participants in Experiment 1.

Participants were provided with an information sheet outlining details of the research project (see Appendix C for information sheet), and all participants gave written informed consent (see Appendix D for consent form). Participants were informed that they were free to withdraw from the study at any time. The Swinburne University Human Research Ethics Committee approved the research.

8.2.2 Drug

d,l-methamphetamine (Lipomed, Arlesheim, Switzerland) was prepared by mixing d,l-methamphetamine with magnesium carbonate, which was encapsulated in soft gelatine capsules to render them visually indistinguishable from the placebo capsules, which contained only magnesium carbonate. Capsules contained either 2mg, 5mg or 10mg d,l-methamphetamine. Each participant was administered an oral dose of 0.42mg/kg d,l-methamphetamine. As was argued in Section 1.3 (Project Aims; Introduction), in order to simulate as close to real-life amphetamine-induced effects as is ethically viable, oral doses of 0.42mg/kg d,l-methamphetamine was administered, as it is one of the highest approved (by Research Ethics Committees) doses administered to humans for controlled experimental research purposes. It must be highlighted that although the results of the present study will not be directly representative of behaviours typically observed with recreational amphetamine abusers (as amphetamine concentrations are generally significantly higher in the real-world population of amphetamine-impaired drivers than those administered in the present study), the results will provide some useful indications as to how a single therapeutic dose of d,l-methamphetamine affects performance, which subsequently, if impairments are observed, can provide important information of possible impairments associated with considerably higher doses.

8.2.3 Experimental Design

A repeated-measures, counter-balanced, double blind, placebo-controlled design was employed. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg d,l-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The wash-out period was extended to two weeks in the
present experiment based on the results from Experiment 1 (Chapter 7), which indicated the possibility of d-amphetamine-related residual psychological effects and/or practice effects following only a 1 week wash-out period (refer to Section 7.3.4 for full details). Although there is no evidence, other than that described in Chapter 7, that residual psychological effects can occur 7 days after amphetamine administration, there is also no evidence to negate this possibility. Therefore, to control for this possibility a two-week washout period was introduced. All participants consented to refrain from consuming alcohol for at least 24 hours prior to each testing session and illicit drugs for at least 7 days prior to each testing session.

8.2.4 Materials
8.2.4.1 Questionnaires
Demographic details (see Appendix E for complete questionnaire) and drug use history (see Appendix F for complete questionnaire) was obtained using the same questionnaires as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.1.1 and 7.2.4.1.2, respectively, for full description. In addition, consistent with the methodology employed in Experiment 1 (Chapter 7), the Profile of Mood Scale (POMS) was administered at the beginning of the two experimental sessions (prior to drug consumption) to establish whether there were any baseline differences in mood between the placebo and d,l-methamphetamine sessions (see Appendix G for POMS). Refer to Section 7.2.4.1.3 for a full description of the POMS.

8.2.4.2 Snellen Eye Chart
Identical to the rational employed for Experiment 1 (Chapter 7), the Snellen Eye Chart was administered in the present experiment to clarify whether any methamphetamine related changes in driving performance were associated with gross changes in visual acuity. Consistent with Experiment 1 (Chapter 7), the Snellen Eye Chart was administered following standard operating procedures. Refer to Section 7.2.4.2 for full description.

8.2.4.3 Driving Simulator
The driving simulator task was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.3 for full description of the task.
8.2.4.4 Neuropsychological Measures

The same battery of neuropsychological tests were administered in the present experiment as those described for Experiment 1 (Chapter 7). These tests were selected to examine the effect of methamphetamine on cognitive functions related to driving, specifically aspects of attention (Digit Span, Digit Vigilance, Digit Symbol Substitution Test, Movement Estimation), psychomotor function (Digit Symbol Substitution Test, Tracking Task, Trail Making) and perceptual speed (Inspection Time). Refer to the following sections for a full description of each task: Digit Span 7.2.4.4.1, Digit Vigilance 7.2.4.4.2, Movement Estimation 7.2.4.4.3, Digit Symbol Substitution Test 7.2.4.4.4, Tracking Task 7.2.4.4.5, Trail-Making Test 7.2.4.4.6, and Inspection Time 7.2.4.4.7.

8.2.4.5 The Standardised Field Sobriety Tests (SFSTs)

The SFSTs were the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.5 for full description. For details relating to specific tests of the SFSTs refer to Section 7.2.4.5.1 for description of the Horizontal Gaze Nystagmus (HGN) test, Section 7.2.4.5.2 for the Walk and Turn (WAT) test, Section 7.2.4.5.3 for One Leg Stand (OLS) test, and Section 7.2.4.5.4 for Overall SFSTs performance.

8.2.4.6 Blood and Saliva Samples

Three blood and three saliva samples were taken from each participant by a registered nurse during each experimental session. Consistent with Experiment 1 (Chapter 7), the first blood and saliva sample was obtained 120 minutes after administration of the drug, the second sample 170 minutes after administration of the drug, and the third sample 240 minutes after the administration of the drug. Blood and saliva samples were obtained and analysed similarly as described for Experiment 1 (Chapter 7; refer to Section 7.2.4.6 for full details).

8.2.5 Procedure

The procedure was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.5 for full description of the procedure followed in the present experiment. Table 8.1 summarises the testing protocol adhered to during the two experimental sessions. Note that the protocol was the same during both experimental sessions.
### Table 8.1 Testing Protocol

<table>
<thead>
<tr>
<th>Elapsed Time (min)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>POMS</td>
</tr>
<tr>
<td>5</td>
<td>Practice City Traffic Driving Task</td>
</tr>
<tr>
<td>10</td>
<td>Treatment Administered Orally</td>
</tr>
<tr>
<td>130</td>
<td>1st Blood and Saliva Sample</td>
</tr>
<tr>
<td>145</td>
<td>Snellen Eye Test</td>
</tr>
<tr>
<td>150</td>
<td>Driving Simulator Task</td>
</tr>
<tr>
<td>175</td>
<td>Standardised Field Sobriety Tests</td>
</tr>
<tr>
<td>185</td>
<td>2nd Blood and Saliva Sample</td>
</tr>
<tr>
<td>200</td>
<td>Neuropsychological Tests</td>
</tr>
<tr>
<td>240</td>
<td>3rd Blood and Saliva Sample</td>
</tr>
<tr>
<td>255</td>
<td>End of Session (Taxi)</td>
</tr>
</tbody>
</table>

### 8.2.6 Statistical Analyses

All statistical analyses employed in the present experiment were the same as described for Experiment 1 (Chapter 7). Refer to the following sections for a full description of each of the analyses conducted: Simulated Driving Performance refer to Section 7.2.6.1, POMS refer to Section 7.2.6.2, Neuropsychological Measures refer to Section 7.2.6.3, and the Standardised Field Sobriety Tests refer to Section 7.2.6.4.

### 8.3 Results

It should be noted that data from one participant was omitted from all statistical analyses as high levels of amphetamines were found in the blood during the placebo session, due to participant-confirmed, self-administration of amphetamines prior to the experimental session. Therefore, for all $d,l$-methamphetamine statistical analyses $N=19$.

### 8.3.1 Demographic Characteristics of Participants

Demographic characteristics of the participants are summarised in Table 8.2.

As illustrated in Table 8.2, 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 1-2 times a 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 8.2 Demographics and Recreational Drug Use for Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.3</td>
<td>3.4</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.2</td>
<td>1.8</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Current amphetamine use (per year)</td>
<td>3.6</td>
<td>4</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Amphetamine use when consumed most (per year)</td>
<td>10</td>
<td>11.5</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using amphetamine (years)</td>
<td>0.5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current ecstasy use (per year)</td>
<td>8.9</td>
<td>7.1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Ecstasy use when consumed most (per year)</td>
<td>19.7*</td>
<td>14.6</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using ecstasy (years)</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current marijuana use (per year)</td>
<td>26.6</td>
<td>66.2</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Marijuana use when consumed most (per year)</td>
<td>100.4</td>
<td>134.6</td>
<td>1</td>
<td>300</td>
</tr>
<tr>
<td>Period of time using marijuana (years)</td>
<td>1</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cocaine use (per year)</td>
<td>1.5</td>
<td>2.6</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Period of time using cocaine (years)</td>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol per week (units)</td>
<td>8.8</td>
<td>6.2</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

Note that N=20, except where denoted by an ‘*’ (where N=19), and that ‘drug use’ refers to number of occasions the specific drug was consumed in a year.

8.3.2 Level of $d,l$-methamphetamine in Blood and Saliva

Figure 8.1 summarises the mean level of $d,l$-methamphetamine detected in blood and saliva at three time points following drug administration: 120, 170 and 240 minutes after drug administration.

Figure 8.1 Level of $d,l$-methamphetamine in Blood and Saliva
As illustrated in Figure 8.1, the mean level of $d,l$-methamphetamine detected in blood and saliva at 120 minutes after drug administration was 90ng/ml (SD=40.3) and 343ng/ml (SD=246.3) respectively, at 170 minutes after drug administration was 95ng/ml (SD=26.5) and 475ng/ml (SD=359.9) respectively, and at 240 minutes after drug administration was 105ng/ml (SD=28.0) and 568ng/ml (SD=417.2) respectively. For the raw data of blood and saliva concentrations for each subject across the three time points, refer to Appendix J.

### 8.3.3 Simulated Driving Performance

#### 8.3.3.1 Main Analyses

A trend-level reduction in simulated driving performance was observed during the $d,l$-methamphetamine condition (mean = 125.4, Std Error = 4.6), relative to the placebo condition (mean = 117.3, Std Error = 6.6), irrespective of the driving task scenario (day/night), $F(1, 16) = 3.05, p = .10$. The difference in simulated driving performance between the placebo and $d,l$-methamphetamine conditions was not different for the day time and night time driving scenarios, $F(1, 16) = 0.12, p = .73$. Moreover, there was no significant difference in simulated driving performance for the day and night time driving task scenarios, $F(1, 16) = 0.34, p = .57$.

#### 8.3.3.2 Exploratory Analyses

**8.3.3.2.1 Effect of $d,l$-methamphetamine on Individual Driving Variable Performance**

Table 8.3 summarises the means and standard deviations for the individual driving simulator variables for the placebo and $d,l$-methamphetamine drug conditions. Note that performance for the day and night time driving scenarios were combined for each individual driving variable, as no significant differences were found between day and night time driving performance (refer to Section 8.3.3.1 for results).

As can be seen in Table 8.3, there was a trend towards decreased braking ability observed during the $d,l$-methamphetamine condition, with drivers releasing the brakes inappropriately when stopping more often than during the placebo condition ($T = 0, p = .10$). Additionally, during the $d,l$-methamphetamine condition participants drove too fast for the traffic conditions more often than during the placebo condition (trend level) ($T = 3.50, p = .10$). Finally, drivers in the $d,l$-methamphetamine condition were found to travel slower on the freeway, at a trend level, at the time that an emergency situation occurred relative to the placebo condition ($T = 51, p = .08$).
8.3.3.2.2  Effect of $d,l$-methamphetamine on Visual Acuity and its Relation to Driving Ability

There were no significant differences in visual acuity between drug conditions for the left eye, $t(18) = -0.10$, $p = .92$, or the right eye, $t(18) = 0.71$, $p = .49$. No further analyses were conducted as $d,l$-methamphetamine did not affect visual acuity.

<table>
<thead>
<tr>
<th>Driving Simulator Variables</th>
<th>Placebo Mean (SD)</th>
<th>$d,l$-meth Mean (SD)</th>
<th>$T$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision</td>
<td>9.0 (8.8)</td>
<td>9.5 (7.1)</td>
<td>46.5</td>
<td>.68</td>
</tr>
<tr>
<td>Dangerous action skid</td>
<td>0.1 (0.3)</td>
<td>0.2 (0.5)</td>
<td>2</td>
<td>.56</td>
</tr>
<tr>
<td>No signal cancel when entering freeway</td>
<td>3.0 (3.5)</td>
<td>2.3 (3.4)</td>
<td>20</td>
<td>.41</td>
</tr>
<tr>
<td>No signal when entering freeway</td>
<td>3.4 (4.1)</td>
<td>2.9 (4.8)</td>
<td>18.5</td>
<td>.62</td>
</tr>
<tr>
<td>Incorrect signalling at intersection</td>
<td>5.8 (6.1)</td>
<td>7.9 (6.3)</td>
<td>30</td>
<td>.14</td>
</tr>
<tr>
<td>No signal cancel at intersection</td>
<td>0.0 (0)</td>
<td>0.0 (0.0)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Wheels not straight on approaching intersection</td>
<td>0.5 (1.1)</td>
<td>0.6 (1.6)</td>
<td>9</td>
<td>.74</td>
</tr>
<tr>
<td>No signal when changing lane</td>
<td>29.2 (14.8)</td>
<td>29.5 (15.2)</td>
<td>74</td>
<td>.91</td>
</tr>
<tr>
<td>No signal cancel when changing lane</td>
<td>21.7 (7.9)</td>
<td>20.8 (11.4)</td>
<td>68</td>
<td>.68</td>
</tr>
<tr>
<td>No signal when moving off</td>
<td>39.2 (20.0)</td>
<td>37.9 (15.8)</td>
<td>69.5</td>
<td>.74</td>
</tr>
<tr>
<td>No signal cancel when moving off</td>
<td>8.4 (7.8)</td>
<td>9.1 (6.5)</td>
<td>46.5</td>
<td>.70</td>
</tr>
<tr>
<td>Waited too long before moving off</td>
<td>0.7 (0.9)</td>
<td>0.6 (1.0)</td>
<td>28</td>
<td>.64</td>
</tr>
<tr>
<td>No signal cancel when overtaking (left)</td>
<td>4.2 (5.1)</td>
<td>5.5 (4.7)</td>
<td>21</td>
<td>.27</td>
</tr>
<tr>
<td>No signal cancel when overtaking (right)</td>
<td>8.2 (5.1)</td>
<td>7.6 (5.8)</td>
<td>39.5</td>
<td>.67</td>
</tr>
<tr>
<td>No signal when overtaking (left)</td>
<td>1.6 (2.9)</td>
<td>3.2 (8.0)</td>
<td>10</td>
<td>.49</td>
</tr>
<tr>
<td>No signal when overtaking (right)</td>
<td>2.9 (5.9)</td>
<td>5.0 (7.6)</td>
<td>22</td>
<td>.31</td>
</tr>
<tr>
<td>Speed Control Brake Inappropriate</td>
<td>6.5 (5.8)</td>
<td>8.4 (7.4)</td>
<td>49.5</td>
<td>.34</td>
</tr>
<tr>
<td>Driving too fast</td>
<td>0.3 (1.2)</td>
<td>1.3 (2.3)</td>
<td>3.5</td>
<td>.10</td>
</tr>
<tr>
<td>No safe following distance</td>
<td>55.8 (21.5)</td>
<td>58.7 (22.5)</td>
<td>81</td>
<td>.57</td>
</tr>
<tr>
<td>Driving too slow</td>
<td>3.2 (1.4)</td>
<td>3.1 (0.8)</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>Straddled barrier line</td>
<td>0.8 (1.7)</td>
<td>1.1 (2.0)</td>
<td>5</td>
<td>.48</td>
</tr>
<tr>
<td>Steering Wandering</td>
<td>4.1 (3.9)</td>
<td>5.0 (3.3)</td>
<td>63</td>
<td>.32</td>
</tr>
<tr>
<td>Steering Wide/cut</td>
<td>2.5 (3.8)</td>
<td>1.9 (3.1)</td>
<td>17.5</td>
<td>.54</td>
</tr>
<tr>
<td>Released brake inappropriately when stopping</td>
<td>0.2 (0.6)</td>
<td>0.6 (1.2)</td>
<td>0</td>
<td>.10</td>
</tr>
<tr>
<td>Not sufficient clear space when stopping</td>
<td>0.4 (0.8)</td>
<td>0.8 (2.0)</td>
<td>9</td>
<td>.38</td>
</tr>
<tr>
<td>Unnecessary/needless stopping</td>
<td>1.3 (1.1)</td>
<td>1.4 (1.5)</td>
<td>38</td>
<td>.93</td>
</tr>
<tr>
<td>Did not stop at red traffic light</td>
<td>1.6 (3.8)</td>
<td>3.7 (7.6)</td>
<td>6</td>
<td>.32</td>
</tr>
<tr>
<td>Straddled the solid line</td>
<td>0.2 (0.6)</td>
<td>0.6 (1.9)</td>
<td>1.5</td>
<td>.41</td>
</tr>
<tr>
<td>Exceeded speed limit</td>
<td>9.5 (8.7)</td>
<td>8.8 (9.0)</td>
<td>46</td>
<td>.24</td>
</tr>
<tr>
<td>Advanced situation collision</td>
<td>4.7 (6.1)</td>
<td>2.1 (4.2)</td>
<td>8</td>
<td>.13</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (freeway)</td>
<td>103.7 (8.4)</td>
<td>99.3 (10.7)</td>
<td>51</td>
<td>.08</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (city)</td>
<td>32.7 (13.5)</td>
<td>32.3 (11.3)</td>
<td>93</td>
<td>.94</td>
</tr>
<tr>
<td>Reaction time (emergency stop)</td>
<td>18.1 (3.0)</td>
<td>17.8 (2.6)</td>
<td>86</td>
<td>.72</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (freeway)</td>
<td>105.8 (31.3)</td>
<td>117.6 (92.4)</td>
<td>44</td>
<td>.92</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (city)</td>
<td>22.5 (11.3)</td>
<td>30.5 (17.0)</td>
<td>39</td>
<td>.13</td>
</tr>
</tbody>
</table>

Note that alpha is .05
8.3.4 POMS
There was no significant difference between the two experimental sessions (prior to drug consumption) on the Total Mood Disturbance Score ($T = 82.50, p = .90$).

8.3.5 Neuropsychological Measures
8.3.5.1 Main Analyses
Details of the results for all main effects and interactions for the cognitive tasks, including means and standard errors, are presented in Table 8.4. Results for all post hoc tests are given in the text below, and all $p$-values reported are corrected $p$-values. Note that although no significant difference in the Total Mood Disturbance POMS Score was found between the two experimental sessions (refer to Section 8.3.4), the session that $d,l$-methamphetamine was administered was included as a between subject factor for all cognitive analyses in order to reduce error variance (resulting from Type II error). This was done based on the possibility of practice and/or carry-over effects that were found in Experiment 1 (Chapter 7; refer to Section 7.3.5.1 for full details of $d$-amphetamine cognitive results).

As can be seen in Table 8.4, in the Digit Vigilance task there was a significant reduction in reaction time in the $d,l$-methamphetamine condition ($p=.04$). A significant overall improvement in DSST performance was observed in the $d,l$-methamphetamine condition relative to the placebo condition ($p=.03$). In addition, a significant interaction was found with session order ($p<.01$). Post hoc tests revealed that when $d,l$-methamphetamine was consumed in the second session, $d,l$-methamphetamine significantly improved DSST performance compared to placebo [$t(9) = 5.72, p < .01$]. However, this was not observed when $d,l$-methamphetamine was consumed in the first session [$t(8) = 1.59, p = .15$]. Although no main effect of drug was found on the Trail-Making tasks, there was an interaction of session order with drug ($p=.03$). However, post hoc tests yielded no significant differences in performance between drug conditions when $d,l$-methamphetamine was consumed in the first session [$t(8) = 1.88, p = .19$], or when $d,l$-methamphetamine was consumed in the second session [$t(9) = 1.47, p = .35$]. Finally, participants in the $d,l$-methamphetamine condition spent significantly less time in error on the Tracking tasks compared to the placebo condition ($p=.04$).
### Table 8.4 Overview of Main Effects of $d,l$-methamphetamine on Cognitive and Psychomotor Performance

<table>
<thead>
<tr>
<th>Test</th>
<th>Factor</th>
<th>$d,l$-methamphetamine 1st session</th>
<th>$d,l$-methamphetamine 2nd session</th>
<th>d.f.</th>
<th>$F$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>T</td>
<td>T</td>
<td>1,17</td>
<td>3.61</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(Forward)</td>
<td>6.7 (0.2)</td>
<td>6.5 (0.2)</td>
<td>1,17</td>
<td>1.86</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(Backward)</td>
<td>7.7 (0.1)</td>
<td>7.5 (0.2)</td>
<td>1,17</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>T x Task</td>
<td>5.8 (0.3)</td>
<td>5.5 (0.4)</td>
<td>1,17</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.0 (2.4)</td>
<td>67.4 (3.2)</td>
<td>1,17</td>
<td>23.71</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>66.8 (7.8)</td>
<td>69.5 (9.5)</td>
<td>1,17</td>
<td>5.61</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>97.6 (0.6)</td>
<td>97.7 (0.9)</td>
<td>1,17</td>
<td>4.04</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>395.0 (8.8)</td>
<td>379.4 (8.7)</td>
<td>1,17</td>
<td>1.06</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>1.5 (0.4)</td>
<td>1.3 (0.2)</td>
<td>1,17</td>
<td>0.37</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>29.1 (2.0)</td>
<td>27.3 (2.0)</td>
<td>1,17</td>
<td>1.83</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>26.7 (1.7)</td>
<td>27.4 (3.0)</td>
<td>1,17</td>
<td>0.72</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>31.4 (2.7)</td>
<td>27.3 (2.1)</td>
<td>1,17</td>
<td>2.11</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>4376.6 (567.9)</td>
<td>3520.8 (338.3)</td>
<td>1,17</td>
<td>0.72</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>T x Task</td>
<td>4079.4 (539.3)</td>
<td>3486.3 (486.8)</td>
<td>1,15</td>
<td>4.82</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>T x Task</td>
<td>4673.8 (677.6)</td>
<td>3555.2 (373.6)</td>
<td>1,15</td>
<td>0.71</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>-0.11 (0.05)</td>
<td>-0.06 (0.05)</td>
<td>1,16</td>
<td>1.43</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>T x Task</td>
<td>0.00 (0.07)</td>
<td>0.05 (0.08)</td>
<td>1,16</td>
<td>0.77</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>T x Occl</td>
<td>-0.22 (0.06)</td>
<td>-0.17 (0.05)</td>
<td>1,16</td>
<td>0.00</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>T x Occl</td>
<td>-0.11 (0.04)</td>
<td>-0.06 (0.02)</td>
<td>1,16</td>
<td>0.00</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>-0.12 (0.06)</td>
<td>-0.09 (0.05)</td>
<td>1,16</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>T x Occl</td>
<td>-0.10 (0.07)</td>
<td>-0.04 (0.07)</td>
<td>1,16</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>T x Occl</td>
<td>0.01 (0.09)</td>
<td>0.05 (0.08)</td>
<td>1,16</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>T x Speed</td>
<td>-0.21 (0.05)</td>
<td>-0.14 (0.04)</td>
<td>1,16</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>T x Speed</td>
<td>-0.12 (0.04)</td>
<td>-0.10 (0.03)</td>
<td>1,16</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>72.8 (3.3)</td>
<td>71.9 (3.3)</td>
<td>1,17</td>
<td>2.47</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>T x Ses</td>
<td>3614.4 (239.1)</td>
<td>4132.3 (204.4)</td>
<td>1,17</td>
<td>5.82</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>3759.9 (226.9)</td>
<td>3568.8 (194.0)</td>
<td>1,17</td>
<td>1.24</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>2044.4 (177.2)</td>
<td>2432.3 (152.3)</td>
<td>1,17</td>
<td>0.69</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>5184.4 (391.1)</td>
<td>5832.3 (328.2)</td>
<td>1,17</td>
<td>0.69</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>T x Task x Ses</td>
<td>2432.3 (152.3)</td>
<td>2568.9 (168.1)</td>
<td>1,17</td>
<td>0.69</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>T x Task x Ses</td>
<td>5832.3 (328.2)</td>
<td>4950.9 (371.0)</td>
<td>1,17</td>
<td>0.69</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>T x Task x Ses</td>
<td>5184.4 (391.1)</td>
<td>5137.9 (311.3)</td>
<td>1,17</td>
<td>0.69</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Note that 1/ F tests are reported for both main effects and interactions, where main effects refer to drug effects on overall task performance and interactions refer to the interaction of drug effects with specific aspects of the task. 2/ Where there is a significant interaction between drug and session order, the means and standard errors are presented separately for subjects who consumed d,l-methamphetamine in their first session and subjects who consumed d,l-methamphetamine in their second session (however, where the interaction was not significant, the means for both sessions combined (first and second) are displayed in the ‘1st Session’ column). 3/ Tests in brackets represent the subsets of the preceding test. 4/ ‘d,l-meth’ = d,l-methamphetamine, ‘DV’ = Digit Vigilance, ‘T’ = Treatment Main Effect, ‘Ses’ = Session Order, ‘Occl’ = Occlusion.

8.3.5.2 Exploratory Analyses
No significant correlations were found between the level of d,l-methamphetamine in the blood and cognitive performance, with the strongest a positive association with reaction time in the Digit Vigilance task \[r (19) = 0.54, p = .02\].

8.3.6 Effect of d,l-methamphetamine on the Standardised Field Sobriety Test (SFSTs) Performance
8.3.6.1 Horizontal Gaze Nystagmus (HGN) Test
The percentage of individuals exhibiting each of the signs recorded during the HGN test for both the placebo and d,l-methamphetamine conditions are illustrated in Figure 8.2. In addition, the percentage of individuals classified as impaired using the HGN test with and without the inclusion of HMJ in the scoring procedure, is depicted in Figure 8.2.

![Figure 8.2 Percentage of Individuals Exhibiting Each Sign of the HGN Test across Drug Conditions](image-url)
As illustrated in Figure 8.2, the majority of the HGN signs were not observed in the $d,l$-methamphetamine condition. HMJ was observed more frequently than any other HGN sign in both the $d,l$-methamphetamine and placebo conditions, however, the difference between drug conditions was not statistically significant ($d,l$-methamphetamine 6/20 impaired; placebo 3/20 impaired), $p > 0.05$, 95% CI = -0.37 to 0.09. No individuals were found to be impaired on the HGN test, therefore $d,l$-methamphetamine was not found to impair performance on the HGN test ($d,l$-methamphetamine 0/20 impaired; placebo 0/20 impaired), $p > 0.05$, 95% CI = -0.17 to 0.17. Including HMJ in the HGN test scoring procedure, did increase the percentage of individuals classified as impaired using the HGN test. However, this increase was seen in both the $d,l$-methamphetamine and placebo condition, therefore, this was not statistically significant ($d,l$-methamphetamine 1/20 impaired; placebo 1/20 impaired), $p > 0.05$, 95% CI = -0.17 to 0.17.

8.3.6.2 Walk and Turn (WAT) Test

The percentage of individuals exhibiting each of the signs recorded during the WAT test for both the placebo and $d,l$-methamphetamine conditions are illustrated in Figure 8.3. In addition, the percentage of individuals classified as impaired using the WAT test is shown in Figure 8.3.

![Figure 8.3 Percentage of Individuals Exhibiting Each Sign of the WAT Test across Drug Conditions](image)

As can be seen in Figure 8.3, Incorrect Turn (IT) and Arms Used to Maintain Balance (AB) was observed more frequently in the $d,l$-methamphetamine condition than any other sign of the WAT test. Although more errors were observed in the $d,l$-methamphetamine
condition relative to the placebo condition, and a greater percentage of individuals were classified as impaired during the WAT test, \textit{d,l}-methamphetamine was not found to significantly affect overall WAT performance (\textit{d,l}-methamphetamine 4/20 impaired; placebo 1/20 impaired), $p > 0.05$, 95\% CI = -0.36 to 0.05.

8.3.6.3 One Leg Stand (OLS) Test
The percentage of individuals exhibiting each of the signs recorded during the OLS test for both the placebo and \textit{d,l}-methamphetamine conditions are shown in Figure 8.4. In addition, the percentage of individuals classified as impaired using the OLS test is shown in Figure 8.4.

![Figure 8.4 Percentage of Individuals Exhibiting Each Sign of the OLS Test across Drug Conditions](image)

As depicted in Figure 8.4, a higher percentage of individuals manifested errors on the OLS test during the placebo condition relative to the \textit{d,l}-methamphetamine condition. However, overall, the percentage of individuals classified as impaired using the OLS test were similar across the placebo and \textit{d,l}-methamphetamine conditions. \textit{d,l}-methamphetamine, therefore, was not found to significantly impair overall OLS performance (\textit{d,l}-methamphetamine 1/20 impaired; placebo 1/20 impaired), $p > 0.05$, 95\% CI = -0.19 to 0.19.

8.3.6.4 Overall SFSTs Performance
The percentage of individuals classified as impaired using the SFSTs is illustrated in Figure 8.5. Figure 8.5 also depicts whether including HMJ in the HGN test scoring procedure increased the percentage of individuals classified as impaired on overall SFSTs.
Figure 8.5 Percentage of Individuals Classified as Impaired on the SFSTs across Drug Conditions

Figure 8.5 illustrates that \textit{d,\textit{l}-methamphetamine} does not impair overall SFSTs performance (\textit{d,\textit{l}-methamphetamine} 0/20 impaired; placebo 0/20 impaired), \( p > 0.05 \), 95% CI = -0.19 to 0.16. Including HMJ in the HGN test scoring procedure did not change the percentage of individuals classified as impaired using the SFSTs. Table 8.5 summarises the accuracy of the SFSTs in identifying the presence of \textit{d,\textit{l}-methamphetamine}.

\begin{table}[h]
\centering
\begin{tabular}{lcc}
\hline
 & Impaired & Not Impaired \\
\hline
HGN & 0 & 20 \\
WAT & 4 & 16 \\
OLS & 1 & 19 \\
Overall SFSTs & 0 & 20 \\
HMJ & 6 & 14 \\
\hline
\end{tabular}
\caption{Number of Participants Classified as Impaired or Not Impaired Using the SFSTs Following the Administration of \textit{d,\textit{l}-methamphetamine}}
\end{table}

8.4 Discussion

8.4.1 Effect of \textit{d,\textit{l}-methamphetamine} on Simulated Driving Performance

The present experiment did not find that 0.42mg/kg \textit{d,\textit{l}-methamphetamine} produced a significant reduction in driving performance, irrespective of the driving task scenario (day/night). Furthermore, the results did not reveal that \textit{d,\textit{l}-methamphetamine} significantly impaired performance on any of the individual driving behaviours.
Although no significant changes in driving ability were noted following *d*,*l*-methamphetamine, it is useful to note that the findings did reveal a trend for *d*,*l*-methamphetamine to reduce overall driving performance. Furthermore, there was a trend for drivers in the *d*,*l*-methamphetamine condition to drive too fast for the driving conditions compared to the placebo condition, and a trend for *d*,*l*-methamphetamine to affect appropriate braking when stopping. Finally, there was a trend for drivers in the *d*,*l*-methamphetamine to travel slower on the freeway at the time that an emergency situation occurred.

As the driving simulator task was completed within the 2-3 hour post-drug administration period, and as methamphetamine blood concentrations are relatively constant during this period, it is reasonable to conclude that mean blood and saliva *d*,*l*-methamphetamine concentrations of approximately 90 ng/ml and 400 ng/ml, respectively, do not significantly impair driving performance. However, it should be noted that the present cognitive findings (refer to Section 8.4.2) did not indicate significant associations between *d*-amphetamine blood concentrations and cognitive performance. Although significant driving impairments were noted when *d*-amphetamine (Experiment 1; Chapter 7) blood concentrations were of similar levels to those found in the present study (90 ng/ml), this difference in significant findings for driving performance may be attributed to *d*-amphetamine being more potent than *d*,*l*-methamphetamine (which contains the *l*-isomer; refer to Section 2.1.2.1), and therefore produces more notable psychodynamic effects. Although previous reports have observed decrements in driving performance with methamphetamine blood concentrations as low as 50 ng/ml (Logan *et al*., 1998), these low concentrations were likely to be attributable to the withdrawal phase associated with methamphetamine use rather than acute concentrations as reported in the present study (Logan *et al*., 1998).

It is also worth pointing out that the considerable variations in saliva concentrations in comparison to blood concentrations, are most likely attributed to the fact that ion tapping in the more acidic saliva matrix resulted in higher saliva concentrations. It is also useful to note that blood and saliva concentrations similarly increased across time, where both continued to increase at 240 min after *d*,*l*-methamphetamine was consumed.
There are limited studies that have examined the acute effects of methamphetamine on driving performance using a driving simulator. Unlike the present findings, that found no significant driving impairments effects, but only a weak indication that driving may be impaired following \( d,l \)-methamphetamine, or those reported for Experiment 1 (Chapter 7), in which driving performance was shown to significantly decrease following \( d \)-amphetamine consumption, Mitler et al. (1993) found that driving ability improved following methamphetamine consumption. This difference in driving performance appears to be attributable to differences in drug dose. For both the present experiment and Experiment 1 (Chapter 7), 30mg doses of amphetamines were administered, whereas in the study by Mitler et al. (1993), a 10mg dose of methamphetamine was administered. This latter dose is considerably lower than those administered in the present thesis, and thus may be the reason for the differences in performance. Moreover, it has previously been argued that doses ranging between 5-10 mg of amphetamine are unlikely to produce decrements in performance (Logan, 2002). Therefore, although Mitler et al. (1993) reported improvements in driving performance following methamphetamine administration, the results did not indicate that the improvement in driving ability would be maintained at higher doses. Although the present study did not find \( d,l \)-methamphetamine to significantly reduce driving performance, there was no suggestion that it improved performance either. If anything, the present results, to some extent, are consistent with the findings reported in Experiment 1 (Chapter 7), which suggest that at higher doses, amphetamines may produce decreases in driving performance.

Although \( d,l \)-methamphetamine was not found to produce any significant impairments to specific driving behaviours, there is some value in discussing the trend-level findings, as they were similar to those found with \( d \)-amphetamine (Experiment 1). In both studies there was an indication that following amphetamine consumption drivers manifested difficulties with maintaining appropriate vehicle speed control. Specifically, during the \( d,l \)-methamphetamine and the \( d \)-amphetamine condition (Experiment 1; Chapter 7), participants generally drove too fast for the driving conditions. Furthermore, drivers in the amphetamine conditions tended to travel at a slower speed on the freeway at the time that an emergency situation occurred. As was discussed earlier (Section 7.4.1), this latter driving behaviour is not consistent with the epidemiological literature, which indicates that drivers under the influence of methamphetamine tend to speed more (Logan, 1996). Although it appears that the present thesis results indicate more cautious driving, the
reduction in speed observed in the laboratory setting may also be interpreted as a compensatory mechanism to permit drivers to attend to other aspects of driving, particularly as participants were aware that their performance was being assessed.

The present findings are not consistent with the epidemiological driving literature that indicates a significant association between amphetamine consumption and driving impairments (Logan, 1996; Logan et al., 1998). In a study examining the records of drivers arrested or killed in traffic accidents while intoxicated with methamphetamine, Logan (1996) found that 57% of the drivers involved in an accident were responsible for the crash. The most typical driving behaviours associated with the road accidents were drifting out of the lane of travel, such as onto the shoulder, into stationary objects, or into oncoming traffic. Similar driving behaviours were also reported in a later study (Logan et al., 1998). However, Logan (1996, 1998) attributed these adverse driving behaviours to withdrawal-related fatigue following extended methamphetamine use, rather than the effects of the amphetamines itself. It may be that this disparity in driving deficits is attributable to considerable differences between the methamphetamine blood concentrations found in apprehended and fatally injured drivers, and those levels reported in the present study.

Although no significant \(d, l\)-methamphetamine-related driving effects were found, the trends point to decrements rather than improvements in performance. This, therefore, can be seen as inconsistent with the cognitive literature, which generally indicates improvements in cognitive functioning following acute amphetamine administration (Rapoport et al., 1980; Hurst, 1987; Kelly et al., 1991; Halliday et al., 1994; Fleming et al., 1995; Comer et al., 1996; Kumari et al., 1997; Servan-Shreiber et al., 1998; Wachtel and de Wit 1999; Cami, et al., 2000; de Wit et al., 2000; Johnson et al., 2000; Mattay et al., 2000; de Wit et al., 2002; Asghar et al., 2003; Barch and Carter, 2005). However, there is some evidence to suggest that the ability to perceive and predict motion appropriately is affected with stimulants, possibly attributable to stimulant-related increases in risk taking behaviour (Lamers et al., 2003; Experiment 1). Although not significant, the trend in the present results and those reported in Experiment 1 (Chapter 7), provide some support for this hypothesis as there was some indication that amphetamines may affect a driver’s ability to estimate movement, as indicated by modulations in vehicle speed control. However, further research is required to corroborate this hypothesis.
In conclusion, the present findings indicated that a single acute therapeutic dose of $d,l$-methamphetamine did not significantly impair driving performance in recreational stimulant users. Furthermore, $d,l$-methamphetamine was not shown to significantly impair performance on any of the individual driving behaviours. These results are inconsistent with previous epidemiological reports that indicate that methamphetamine impairs driving ability. However, this inconsistency may be attributable to substantial differences in methamphetamine blood concentrations. Furthermore, the present results are not consistent with those reported for Experiment 1 (Chapter 7), which indicated a significant driving impairment when $d$-amphetamine blood concentrations were similarly approximately 90ng/mL.

8.4.2 Effect of $d,l$-methamphetamine on Driving-Related Cognitive Processes

The present experiment examined the acute effects of 0.42mg/kg $d,l$-methamphetamine on cognitive measures that are important for driving, including attention, psychomotor function, and perceptual speed. The results revealed improvements in aspects of attention and psychomotor functioning. Specifically, reaction time was reduced in the Digit Vigilance task, performance improved on the DSST (when $d,l$-methamphetamine was consumed in the second session), and less time was spent in error during the Tracking tasks. It is difficult to relate the present $d,l$-methamphetamine results with previous research, as the literature is scarce. The findings are, however, consistent with Johnson et al. (2000) who reported improvements in attention following 0.42mg/kg $d$-methamphetamine. Furthermore, these findings are consistent with previous $d$-amphetamine research that have similarly shown improvements in attention and psychomotor performance following $d$-amphetamine doses ranging from 5mg to 30mg (de Wit et al., 2002; Wachtel & de Wit, 1999; Cami et al., 2000; Kelly et al., 1991; Ward et al., 1997; Comer et al., 1996).

In terms of the Digit Vigilance task, response speed was faster in the $d,l$-methamphetamine condition compared to the placebo condition. This finding is consistent with the trend-level results from Experiment 1 (Chapter 7) and previous amphetamine research (Kelly et al., 1991; Koelega 1993; Comer et al., 1996). Furthermore, improved reaction time following amphetamine consumption has been consistently shown to occur using a range of tasks and amphetamine doses (Rapoport et al., 1980; Callaway et al., 1994; Halliday et al., 1994; Fleming et al., 1995; Kumari et al., 1997; Ward et al., 1997; Servan-Shreiber et al., 1998;
McKetin et al., 1999; Johnson et al., 2000; Asghar et al., 2003; Fillmore et al., 2005). Also consistent with the present findings, improvements in attention and psychomotor performance using the DSST and tracking tasks have been previously reported following amphetamine consumption (Kelly et al., 1991; Comer et al., 1996; Ward et al., 1997; Wachtel & de Wit, 1999; de Wit et al., 2002; Cami et al., 2000). In addition, the improvements observed in psychomotor function following $d,l$-methamphetamine consumption are consistent with the results from Experiment 1 (Chapter 7), which found a trend for $d$-amphetamine to decrease the time spent in error during the tracking tasks.

The present cognitive findings support the notion that $d,l$-methamphetamine levels in the blood and $d,l$-methamphetamine behavioural effects are generally dissociable in healthy subjects following a single therapeutic dose of $d,l$-methamphetamine (Angrist et al., 1987; Brauer et al., 1996; Asghar et al., 2003), as no associations were found between blood $d,l$-methamphetamine levels and cognitive performance. This is also consistent with the results from Experiment 1 (Chapter 7), which similarly found no associations between $d$-amphetamine level in blood and cognitive performance. These results are supported by previous epidemiological research, which have shown that methamphetamine concentrations required to evoke adverse driving behaviours vary considerably across individuals, as a result of differences in patterns of drug use, drug tolerance, fatigue, and alcohol or other drug use (Logan, 1996). This suggests that specific amphetamine levels in blood do not necessarily indicate impairment, as there are many factors that can influence performance differently across individuals, thus making a direct association inherently difficult.

Although no significant driving impairment was found with $d,l$-methamphetamine, it is important to note, that a trend level decrease (rather than improvement) in driving performance was observed with $d,l$-methamphetamine, which is inconsistent with the $d,l$-methamphetamine-related improvements to cognitive functioning. This difference in the direction of performance may be because the dose was too low to elicit deficits to specific cognitive processes using cognitive tasks. As was argued in the previous chapter (refer to Section 7.4.1), it is difficult to draw strong parallels between driving performance and cognitive functioning as there are notable differences in task attributes and difficulty levels that can produce differing results. This notion is supported, to some extent, with the present results and those reported for Experiment 1 (Chapter 7), which provide some
indication of decrements to driving performance and improvements in cognitive performance, following amphetamine consumption.

In summary, consistent with the results from Experiment 1 (Chapter 7) and previous cognitive research, the present findings indicate that a single acute therapeutic dose of \( d,l \)-methamphetamine improves aspects of attention and psychomotor functioning, specifically relating to sustained attention, response speed, and visuomotor coordination. The present results substantiate the findings from Experiment 1 (Chapter 7) that indicate low \( d,l \)-methamphetamine levels in the blood and \( d,l \)-methamphetamine-related behavioural effects are generally dissociable in healthy subjects. As no significant driving impairment was found following \( d,l \)-methamphetamine, it is not surprising that no considerable decrements to cognitive functioning were observed following a similar dose. It appears that the dose administered in the present experiment was too low to elicit any significant decrements to performance.

### 8.4.3 Efficiency of the Standardised Field Sobriety Tests (SFSTs) in Detecting \( d,l \)-methamphetamine Impairment

The present experiment found that 0.42mg/kg \( d,l \)-methamphetamine did not impair performance on the SFSTs. Using these sobriety tests, impairment associated with a single acute therapeutic dose of \( d,l \)-methamphetamine was not reported in any cases when blood and saliva \( d,l \)-methamphetamine concentration levels were approximately 90 ng/ml and 400 ng/ml respectively.

The present results are consistent with those reported for Experiment 1 (Chapter 7), that found that \( d \)-amphetamine did not impair performance on the SFSTs. Furthermore, using the SFSTs, impairment associated with \( d \)-amphetamine was identified in only 5% of cases, which is comparable to that of the present findings which observed a 0% success rate. These results are not surprising given that the SFSTs were primarily designed to detect impairment associated with significantly higher amphetamine concentrations than those observed in the present thesis. Furthermore, the results from the present study indicate that the degree of impairment following the present dosing conditions were so small that it is likely that any observed impairments were below the threshold of the sensitivity of the SFSTs.
To the author’s knowledge, there are no other studies that have investigated the efficiency of the SFSTs alone in detecting the presence of amphetamines, as previous studies have administered the SFSTs in conjunction with other behavioural and physiological tests (i.e. the DEC Program; Bigelow et al., 1984; Compton, 1986). However, the extremely low percentage of participants identified as being intoxicated with \(d,l\)-methamphetamine or \(d\)-amphetamine (Chapter 7), is consistent with other reports that have highlighted the difficulty of detecting this stimulant drug class. Specifically, Heishman et al. (1998) found that the majority of subjects dosed with \(d\)-amphetamine were classified as ‘not impaired’ by the Drug Recognition Examiners (DRE), and that in only 2% of cases where \(d\)-amphetamine was administered, the classification was correct. Furthermore, the DRE’s classified subjects as dosed with other drugs more frequently, than with the amphetamines dose administered. Similarly, Shinar et al. (2000) also found stimulants, to be the most difficult to identify, with only 7.8% of cases correctly classified.

\(d,l\)-methamphetamine was not found to impair performance on the HGN test. In fact, with the exception of Lack of Smooth Pursuit, which was observed in only 2 cases, none of the traditionally scored signs were observed with \(d,l\)-methamphetamine, suggesting that the low \(d,l\)-methamphetamine dosing condition produced little or no HGN impairment. These findings are consistent with those reported in Experiment 1 (Chapter 7), which similarly found that following the consumption of \(d\)-amphetamine, no traditionally reported HGN signs were observed. Although these findings suggest that any impairments produced by these low doses are too small to be detected with the HGN test, these results are consistent with the DRE instructor’s manual (1993) and other reports, which indicate that stimulants do not affect performance on the Horizontal Gaze Nystagmus, Lack of Smooth Pursuit, Vertical Gaze Nystagmus, and Lack of Convergence tests (Kosnoski, et al., 1998; Adler and Burns, 1994).

Including HMJ in the HGN test scoring procedure did not significantly increase the percentage of \(d,l\)-methamphetamine-related impairment classifications. However, consistent with Experiment 1 (Chapter 7) and previous cannabis research (Papafotiou et al., 2005b), HMJ was observed more frequently in the \(d,l\)-methamphetamine condition than any other sign. However, also similar to the results reported in Experiment 1, HMJ was present in 15% of subjects during the placebo condition, thus increasing the risk for false positives in a drug evaluation. Therefore, although there may be some value in
considering HMJ in the scoring procedure, further research is warranted with amphetamine concentrations that are more likely to produce impairments in SFSTs performance.

d, l-methamphetamine was not found to significantly impair performance on the WAT test, however, more errors were observed during the d, l-methamphetamine condition relative to the placebo, and a higher percentage of individuals were correctly classified as impaired on the WAT test. Improper Turn (IT) and Arms Used to Maintain Balance (AB) were observed more frequently in the d, l-methamphetamine condition than any other sign of the WAT test. However, it should be noted that Arms Used to Maintain Balance (AB) was observed in more cases during the placebo session than the active drug session. The present results are inconsistent with Experiment 1 (Chapter 7), which observed few errors on the WAT test compared to placebo. Furthermore, in Experiment 1 (Chapter 7), Improper Turn (IT) was observed more frequently than any other WAT sign, across both the placebo and d-amphetamine conditions, whereas in the present experiment (Experiment 2), IT was observed frequently during only the d, l-methamphetamine condition. However, as no significant differences in WAT performance were reported between the placebo and d, l-methamphetamine conditions, consistent with the findings reported in Experiment 1 (Chapter 7), the doses administered in the present experiments appear to be too low to elicit significant impairments on the WAT test.

Finally, a single acute therapeutic dose of d, l-methamphetamine did not impair performance on the OLS test. Although not significant, it is of interest to note that similar to the results in Experiment 1, more errors were observed in the placebo condition than during the d, l-methamphetamine condition. These findings are, to some extent, consistent with other reports that have indicated a decrease in errors on the OLS test to be the third best predictor for the presence of low levels of d-amphetamine (Heishman et al., 1998). Furthermore, previous cognitive reports have demonstrated amphetamine-related improvements to attention and psychomotor performance, which are processes that the SFSTs were designed to assess (Kennedy et al., 1990; Kelly et al., 1991; Koelega 1993; Comer et al., 1996; Johnson et al., 1996, 2000; Ward et al., 1997; McKetin et al., 1999; Wachtel & de Wit, 1999; Cami et al., 2000; de Wit et al., 2002). However, this aside, the findings from Experiment 1 and the present study, indicate that the various amphetamine doses administered were too low to produce any significant impairment on the OLS test.
As no significant driving impairment was found following a low dose of \(d,l\)-methamphetamine, this provides some validation of the use of the SFSTs for the detection of drug-induced driving impairment, as performance on the SFSTs was also found not to be impaired. As previously mentioned, the SFSTs were designed to detect gross impairment associated with considerably higher amphetamine concentrations, thus it appears that the dose administered in the present study was too low to elicit any significant impairments.

In conclusion, the results from the present experiment suggest that following the administration of 0.42mg/kg \(d,l\)-methamphetamine, performance on the SFSTs is not impaired. Using the SFSTs, impairment associated with low dose \(d,l\)-methamphetamine was identified in 0% of cases. These findings indicate that the \(d,l\)-methamphetamine dose administered in the present study was too low to elicit any type of impairment that the SFSTs were designed to detect. Furthermore, as the dose of \(d,l\)-methamphetamine was insufficient to produce a significant driving impairment, this provides validation of the SFSTs in that they did not produce any false positive results.

8.4.4 Summary of the Acute Effects of \(d,l\)-methamphetamine on Simulated Driving Performance, Driving-Related Cognitive Processes, and SFSTs Performance

In summary, the results of the present experiment indicate that 0.42mg/kg \(d,l\)-methamphetamine does not significantly impair driving performance in recreational stimulant users, 2-3 hours post-drug administration. Furthermore, \(d,l\)-methamphetamine was not shown to significantly impair performance on any of the individual driving behaviours. These results are inconsistent with previous epidemiological reports that indicate methamphetamine impairs driving ability. However, this inconsistency may be attributable to the substantial differences in methamphetamine blood concentrations in the two scenarios. Furthermore, the present results are not consistent with those reported for Experiment 1 (Chapter 7), which indicated a significant driving impairment when \(d\)-amphetamine blood concentrations were similarly approximately 90ng/mL.

The present cognitive results indicate that a low dose of \(d,l\)-methamphetamine improves aspects of attention and psychomotor functioning, specifically relating to sustained attention, response speed, and visuomotor coordination. The present results further support the findings from Experiment 1 (Chapter 7) that suggest low amphetamine levels in the
blood and amphetamine-related behavioural effects are generally dissociable in healthy subjects, thus highlighting the complex nature of the amphetamines. In terms of driving, the present results provide limited data as to how acute d,l-methamphetamine use may reduce driving performance. It appears that the dose administered in the present study was too low to elicit any significant decrements to performance.

Finally, the present study indicated that following the administration of 0.42mg/kg d,l-methamphetamine, performance on the SFSTs is not impaired. Using the SFSTs, impairment associated with low dose d,l-methamphetamine was identified in 0% of cases. These findings indicate that the d,l-methamphetamine dose administered in the present study was too low to elicit any type of impairment that the SFSTs were designed to detect. Furthermore, as the d,l-methamphetamine dose was insufficient to produce a significant driving impairment, the SFSTs results are reliable in not producing a false positive result.
Chapter 9.

Experiment 3: The Effect of d-methamphetamine on Simulated Driving Performance, Driving-Related Cognitive Functions, and the SFSTs

9.1 Introduction

As was argued in Chapter 1 (Introduction) and Chapter 3 (Amphetamine and Driving), it is important to examine the acute effects of various forms of amphetamines on driving performance to determine how amphetamine use may be associated with amphetamine-related decrements to driving ability. The results from Experiment 1 (Chapter 7) indicated that a single acute therapeutic dose of d-amphetamine produced some impairment in driving performance (Chapter 7). Although a significant decrement in driving performance was not observed in Experiment 2 (Chapter 8), there was a trend towards a decrease in driving performance in the d,l-methamphetamine condition. Possible differences in drug potency between the two studies may elucidate the reason why a significant effect was not observed with d,l-methamphetamine. As Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8) are the only studies (with the exception of one other study that examined the acute effects of 10mg methamphetamine on driving performance (Milter et al., 1993)) that have examined the effects of an acute dose of amphetamine on simulated driving performance, further research is necessary to confirm these findings, particularly with a more potent form of methamphetamine. As methamphetamine is considered to be one of the most popular abused stimulants amongst drivers, and Experiment 2 (Chapter 8) did not find significant driving decrements following the less potent form of methamphetamine, d,l-methamphetamine, on simulated driving performance, the present experiment will assess the acute effects of the more potent form of methamphetamine, d-methamphetamine, on driving performance. The results of this experiment will further help understand how a single acute therapeutic dose of various amphetamines may affect driving performance.

Although research using simulator driving tasks can provide useful information on the effect of amphetamine consumption on driving performance, these tests are not able to establish whether there are specific cognitive functions that become impaired due to amphetamines. The results from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8)
provide limited data as to how acute amphetamine use may contribute to driving fatalities, with the only possible link being the results from the movement estimation task in Experiment 1 (Chapter 7). The results from this task indicated that the ability to perceive and predict motion and ‘time to contact’ was affected following $d$-amphetamine consumption. In terms of traffic safety, this reduction in safe driving could lead to serious road accidents. Thus, for these reasons additional research is necessary to further explore this issue.

Therefore, Experiment 3 employed the same cognitive tasks as were administered for Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), to further explore the acute effects of amphetamine consumption on cognitive functioning. Specifically, the present experiment administered: the Digit Span Test as a measure of working memory and efficiency of attention; Digit Vigilance to assess sustained attention; a Movement Estimation Task to assess estimation of movement speed and ‘time to contact’; Digit Symbol Substitution Test and a Tracking Task as measures of psychomotor performance; the Trail-Making Test to assess visual scanning ability; and Inspection Time to assess perceptual speed. These tests were selected as they specifically measure cognitive functions that have been reported to be important in safe driving (Hurst, 1987; Lamers et al., 2003; Anstey et al., 2005).

In response to the increasing number of ‘drug other than alcohol’ related road accidents, a second aim of the present experiment was to investigate the efficiency of the SFSTs to identify impairment associated with $d$-methamphetamine use in drivers. Although the results from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8) indicate that the degree of impairment elicited with the low level amphetamine doses administered in Experiments 1 and 2 appear to be below the threshold of the sensitivity of the SFSTs, these are the only investigations to examine the efficiency of these sobriety tests (not in conjunction with other behavioural and physiological tests) to identify possible impairment in healthy, stimulant-using, non-fatigued adults, in a controlled laboratory setting. Therefore, further research is warranted to confirm these previous findings. The present experiment therefore examined the acute effects of $d$-methamphetamine on SFSTs performance. The results of this experiment will provide useful information as to the sensitivity of the SFSTs to detect possible impairment associated with single acute therapeutic dose of $d$-methamphetamine.
The present experiment assessed the acute effects of \( d \)-methamphetamine on simulated driving performance, driving-related cognitive processes, and performance on the SFSTs, using a repeated-measures, counter-balanced, double blind, placebo-controlled design. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \( d \)-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The present chapter will describe the materials and methodologies employed, the results, and provide a discussion of the results.

9.2 Materials and Methods

9.2.1 Participants

9.2.1.1 Selection Criteria

The selection criteria for the present experiment was the same as for Experiment 1 (Chapter 7). Refer to Section 7.2.1.1 for full description.

9.2.1.2 Psychological and Physical Health

Psychological and Physical Health was assessed with the same procedure as described for Experiment 1 (Chapter 7). Refer to Section 7.2.1.2 for full description.

9.2.1.3 Sample Characteristics

Twenty healthy illicit stimulant users (10 males; 10 females), aged between 21 and 32 years (mean = 25.4 years, SD = 3.3 years), with an average male weight of 75.6kg (SD = 11.5), and an average female weight of 62.9kg (SD = 4.5) were recruited. All participants had a minimum of 12 years education, and a valid, full driver’s license. All participants were consumers of caffeine, with an average daily intake of 1.6 cups of coffee (range 0-3). Of the 20 participants, 8 were self-assessed smokers, averaging 3.7 cigarettes a day (range 0-20). Note that the participants in the present experiment were different to the participants in Experiment 1 and Experiment 2.

Participants were provided with an information sheet outlining details of the research project (see Appendix C for information sheet), and all participants gave written informed consent (see Appendix D for consent form). Participants were informed that they were free to withdraw from the study at any time. The Swinburne University Human Research Ethics Committee approved the research.
9.2.2 Drug

*d*-methamphetamine (Lipomed, Arlesheim, Switzerland) was prepared by mixing *d*-methamphetamine with lactose, which was encapsulated in soft gelatine capsules to render them visually indistinguishable from the placebo capsules, which contained only lactose. Capsules contained 20 mg, 10mg, 5mg or 2mg *d*-methamphetamine. Each participant was administered an oral dose of 0.42mg/kg *d*-methamphetamine. As was argued in Section 1.3 (*Project Aims; Introduction*), in order to simulate as close to real-life amphetamine-induced effects as is ethically viable, oral doses of 0.42mg/kg *d*-methamphetamine was administered, as it is one of the highest approved (by Research Ethics Committees) doses administered to humans for controlled experimental research purposes. It must be highlighted that although the results of the present study will not be directly representative of behaviours typically observed with recreational amphetamine abusers (as amphetamine concentrations are generally significantly higher in the real-world population of amphetamine-impaired drivers than those administered in the present study), the results will provide some useful indications as to how a single therapeutic dose of *d*-methamphetamine affects performance, which subsequently, if impairments are observed, can provide important information of possible impairments associated with considerably higher doses.

9.2.3 Experimental Design

A repeated-measures, counter-balanced, double blind, placebo-controlled design was employed. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg *d*-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The wash-out period was two weeks based on the results from Experiment 1 (Chapter 7), which indicated the possibility of *d*-amphetamine-related residual psychological effects and/or practice effects following only a 1 week wash-out period (refer to Section 7.3.4 for full details). Although there is no evidence, other than that described in Chapter 7, that residual psychological effects can occur 7 days after amphetamine administration, there is also no evidence to negate this possibility. Therefore, to control for this possibility a two-week washout period was introduced. All participants consented to refrain from consuming alcohol for at least 24 hours prior to each testing session and illicit drugs for at least 7 days prior to each testing session.
9.2.4 Materials

9.2.4.1 Questionnaires

Demographic details (see Appendix E for complete questionnaire) and drug use history (see Appendix F for complete questionnaire) was obtained using the same questionnaires as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.1.1 and 7.2.4.1.2 respectively, for a full description. In addition, consistent with the methodology employed in Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the Profile of Mood Scale (POMS) was administered at the beginning of the two experimental sessions (prior to drug consumption) to establish whether there were any baseline differences in mood between the placebo and d-methamphetamine sessions (see Appendix G for POMS). Refer to Section 7.2.4.1.3 for a full description of the POMS.

9.2.4.2 Snellen Eye Chart

Similar to the rational employed for Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the Snellen Eye Chart was administered in the present experiment to clarify whether any methamphetamine related changes in driving performance were associated with gross changes in visual acuity. Consistent with Experiment 1 (Chapter 7), the Snellen Eye Chart was administered following standard operating procedures. Refer to Section 7.2.4.2 for full description.

9.2.4.3 Driving Simulator

The driving simulator task was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.3 for full description of the task.

9.2.4.4 Neuropsychological Measures

The same battery of neuropsychological tests were administered in the present experiment as those described for Experiment 1 (Chapter 7). These tests were selected to examine the effect of methamphetamine on cognitive functions related to driving. Specifically, aspects of attention (Digit Span, Digit Vigilance, Digit Symbol Substitution Test, Movement Estimation), psychomotor function (Digit Symbol Substitution Test, Tracking Task, Trail Making) and perceptual speed (Inspection Time) were assessed. Refer to the following sections for a full description of each task: Digit Span 7.2.4.4.1, Digit Vigilance 7.2.4.4.2, Movement Estimation 7.2.4.4.3, Digit Symbol Substitution Test 7.2.4.4.4, Tracking Task 7.2.4.4.5, Trail-Making Test 7.2.4.4.6, and Inspection Time 7.2.4.4.7.
9.2.4.5 The Standardised Field Sobriety Tests (SFSTs)
The SFSTs were the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.5 for full description. For details relating to specific tests of the SFSTs refer to Section 7.2.4.5.1 for description of the Horizontal Gaze Nystagmus (HGN) test, Section 7.2.4.5.2 for the Walk and Turn (WAT) test, Section 7.2.4.5.3 for One Leg Stand (OLS) test, and Section 7.2.4.5.4 for Overall SFSTs performance.

9.2.4.6 Blood and Saliva Samples
Three blood and three saliva samples were taken from each participant by a registered nurse during each experimental session. Consistent with Experiment 1, the first blood and saliva sample was obtained 120 minutes after administration of the drug, the second sample 170 minutes after administration of the drug, and the third sample 240 minutes after the administration of the drug. Blood and saliva samples were obtained and analysed similarly as described for Experiment 1 (Chapter 7; refer to Section 7.2.4.6 for full details).

9.2.5 Procedure
The procedure was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.5 for full description of the procedure followed in the present experiment. Table 9.1 summarises the testing protocol adhered to during the two experimental sessions. Note that the protocol was the same during both experimental sessions.

<table>
<thead>
<tr>
<th>Elapsed Time (min)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>POMS</td>
</tr>
<tr>
<td>5</td>
<td>Practice City Traffic Driving Task</td>
</tr>
<tr>
<td>10</td>
<td>Treatment Administered Orally</td>
</tr>
<tr>
<td>130</td>
<td>1st Blood and Saliva Sample</td>
</tr>
<tr>
<td>145</td>
<td>Snellen Eye Test</td>
</tr>
<tr>
<td>150</td>
<td>Driving Simulator Task</td>
</tr>
<tr>
<td>175</td>
<td>Standardised Field Sobriety Tests</td>
</tr>
<tr>
<td>185</td>
<td>2nd Blood and Saliva Sample</td>
</tr>
<tr>
<td>200</td>
<td>Neuropsychological Tests</td>
</tr>
<tr>
<td>240</td>
<td>3rd Blood and Saliva Sample</td>
</tr>
<tr>
<td>255</td>
<td>End of Session (Taxi)</td>
</tr>
</tbody>
</table>

9.2.6 Statistical Analyses
All statistical analyses employed in the present experiment were the same as described for Experiment 1 (Chapter 7). Refer to the following sections for a full description of each of
the analyses conducted: Simulated Driving Performance refer to Section 7.2.6.1, POMS refer to Section 7.2.6.2, Neuropsychological Measures refer to Section 7.2.6.3, and the Standardised Field Sobriety Tests refer to Section 7.2.6.4.

9.3 Results

9.3.1 Demographic Characteristics of Participants

Demographic characteristics of the participants are summarised in Table 9.2.

Table 9.2 Demographics and Recreational Drug Use for Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.4</td>
<td>3.3</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.4</td>
<td>2.1</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Current amphetamine use (per year)</td>
<td>3.3</td>
<td>4.8</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Amphetamine use when consumed most (per year)</td>
<td>9.1</td>
<td>12</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using amphetamine (years)</td>
<td></td>
<td>0.5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Current ecstasy use (per year)</td>
<td>4.2</td>
<td>3.8</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Ecstasy use when consume most (per year)</td>
<td>20.3</td>
<td>16</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using ecstasy (years)</td>
<td></td>
<td>0.5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Current marijuana use (per year)</td>
<td>24.4</td>
<td>65.7</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Marijuana use when consume most (per year)</td>
<td>132</td>
<td>141.3</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Period of time using marijuana (years)</td>
<td></td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Current cocaine use (per year)</td>
<td>0.7</td>
<td>0.7</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Period of time using cocaine (years)</td>
<td></td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Alcohol per week (units)</td>
<td>13.6</td>
<td>10</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>

Note that N=20 and that 'drug use' refers to number of occasions the specific drug was consumed in a year.

Table 9.2 indicates that 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 24 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 1-2 times a 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 2-3 times a week in that year (132 times).

9.3.2 Level of d-methamphetamine in Blood and Saliva

Figure 9.1 summarises the mean level of d-methamphetamine detected in blood and saliva at three time points following drug administration: 120, 170 and 240 minutes after drug administration.
As depicted in Figure 9.1, the mean level of \(d\)-methamphetamine detected in blood and saliva at 120 minutes after drug administration was 72ng/ml (SD=12.2) and 285ng/ml (SD=161.9) respectively, at 170 minutes after drug administration was 67ng/ml (SD=10.0) and 223ng/ml (SD=96.5) respectively, and at 240 minutes after drug administration was 59ng/ml (SD=10.4) and 190ng/ml (SD=104.8) respectively. For the raw data of blood and saliva concentrations for each subject across the three time points, refer to Appendix K.

### 9.3.3 Simulated Driving Performance

#### 9.3.3.1 Main Analyses

\(d\)-methamphetamine (mean = 102.4, Std Error = 6.9) was not found to significantly affect simulated driving performance compared to placebo (mean = 95.3, Std Error = 3.8), \(F(1, 18) = 2.17, p = .19\). The difference in simulated driving performance between the placebo and \(d\)-methamphetamine conditions was not different for the day time and night time driving scenarios, \(F(1, 18) = 0.09, p = .76\). Moreover, there was no significant difference in simulated driving performance for the day and night time driving task scenarios, \(F(1, 18) = 1.00, p = .33\).

#### 9.3.3.2 Exploratory Analyses

**Effect of \(d\)-methamphetamine on Individual Driving Variable Performance**

Table 9.3 summarises the means and standard deviations for the individual driving simulator variables for the placebo and \(d\)-methamphetamine drug conditions. Note that performance for the day and night time driving scenarios were combined for each
individual driving variable, as no significant differences were found between day and night time driving performance (refer to Section 9.3.3.1 for results).

### Table 9.3 Driving Simulator Variable Results for Placebo and $d$-methamphetamine Conditions

<table>
<thead>
<tr>
<th>Driving Simulator Variables</th>
<th>Placebo Mean (SD)</th>
<th>$d$-methamphetamine Mean (SD)</th>
<th>$T$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision</td>
<td>4.0 (6.0)</td>
<td>4.5 (6.1)</td>
<td>30.5</td>
<td>.81</td>
</tr>
<tr>
<td>Dangerous action skid</td>
<td>0.1 (0.5)</td>
<td>0.1 (0.2)</td>
<td>1</td>
<td>.66</td>
</tr>
<tr>
<td>No signal cancel when entering freeway</td>
<td>2.2 (3.0)</td>
<td>2.6 (3.3)</td>
<td>13.5</td>
<td>.48</td>
</tr>
<tr>
<td>No signal when entering freeway</td>
<td>3.8 (4.6)</td>
<td>4.3 (4.9)</td>
<td>8</td>
<td>.59</td>
</tr>
<tr>
<td>Incorrect signalling at intersection</td>
<td>7.0 (5.7)</td>
<td>6.8 (8.0)</td>
<td>37</td>
<td>.87</td>
</tr>
<tr>
<td>No signal cancel at intersection</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Wheels not straight on approaching intersection</td>
<td>0.2 (0.7)</td>
<td>0.3 (0.9)</td>
<td>2</td>
<td>.56</td>
</tr>
<tr>
<td>No signal when changing lane</td>
<td>30.5 (15.6)</td>
<td>28.3 (16.4)</td>
<td>57</td>
<td>.35</td>
</tr>
<tr>
<td>No signal cancel when changing lane</td>
<td>19.6 (7.4)</td>
<td>21.2 (10.1)</td>
<td>55.5</td>
<td>.52</td>
</tr>
<tr>
<td>No signal when moving off</td>
<td>31.0 (16.7)</td>
<td>34.5 (17.0)</td>
<td>43.5</td>
<td>.34</td>
</tr>
<tr>
<td>No signal cancel when moving off</td>
<td>9.4 (7.0)</td>
<td>9.6 (7.3)</td>
<td>44</td>
<td>.91</td>
</tr>
<tr>
<td>Waited too long before moving off</td>
<td>1.0 (0.8)</td>
<td>0.6 (0.8)</td>
<td>29</td>
<td>.24</td>
</tr>
<tr>
<td>No signal cancel when overtaking (left)</td>
<td>3.6 (3.9)</td>
<td>3.4 (3.5)</td>
<td>22</td>
<td>.95</td>
</tr>
<tr>
<td>No signal cancel when overtaking (right)</td>
<td>4.6 (5.7)</td>
<td>7.4 (6.8)</td>
<td>35.5</td>
<td>.16</td>
</tr>
<tr>
<td>No signal when overtaking (left)</td>
<td>1.8 (3.4)</td>
<td>0.5 (1.5)</td>
<td>6</td>
<td>.16</td>
</tr>
<tr>
<td>No signal when overtaking (right)</td>
<td>3.0 (5.7)</td>
<td>3.5 (6.9)</td>
<td>15.5</td>
<td>.72</td>
</tr>
<tr>
<td>Speed Control Brake Inappropriate</td>
<td>5.1 (4.0)</td>
<td>5.3 (4.8)</td>
<td>45</td>
<td>.63</td>
</tr>
<tr>
<td>Driving too fast</td>
<td>0.8 (2.5)</td>
<td>1.5 (3.3)</td>
<td>4</td>
<td>.33</td>
</tr>
<tr>
<td>No safe following distance</td>
<td>44.5 (22.7)</td>
<td>48.3 (27.0)</td>
<td>62.5</td>
<td>.51</td>
</tr>
<tr>
<td>Driving too slow</td>
<td>3.2 (0.7)</td>
<td>3.3 (0.6)</td>
<td>27.5</td>
<td>.59</td>
</tr>
<tr>
<td>Straddled barrier line</td>
<td>0.8 (1.5)</td>
<td>0.8 (1.5)</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Steering Wandering</td>
<td>5.0 (4.3)</td>
<td>3.5 (2.7)</td>
<td>57</td>
<td>.12</td>
</tr>
<tr>
<td>Steering Wide/cut</td>
<td>2.4 (4.2)</td>
<td>1.6 (2.4)</td>
<td>16</td>
<td>.42</td>
</tr>
<tr>
<td>Released brake inappropriately when stopping</td>
<td>0.0 (0.0)</td>
<td>0.1 (0.5)</td>
<td>0</td>
<td>.32</td>
</tr>
<tr>
<td>Not sufficient clear space when stopping</td>
<td>0.4 (0.8)</td>
<td>0.3 (0.7)</td>
<td>2</td>
<td>.56</td>
</tr>
<tr>
<td>Unnecessary/needless stopping</td>
<td>1.0 (0.8)</td>
<td>0.5 (0.7)</td>
<td>15</td>
<td>.05</td>
</tr>
<tr>
<td>Did not stop at red traffic light</td>
<td>1.0 (3.1)</td>
<td>4.1 (7.6)</td>
<td>7</td>
<td>.11</td>
</tr>
<tr>
<td>Straddled the solid line</td>
<td>1.3 (1.8)</td>
<td>1.0 (2.6)</td>
<td>13.5</td>
<td>.52</td>
</tr>
<tr>
<td>Exceeded speed limit</td>
<td>7.2 (7.4)</td>
<td>6.0 (7.3)</td>
<td>63</td>
<td>.19</td>
</tr>
<tr>
<td>Advanced situation collision</td>
<td>1.0 (3.1)</td>
<td>2.0 (4.1)</td>
<td>7</td>
<td>.41</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (freeway)</td>
<td>106.1 (9.3)</td>
<td>103.0 (10.3)</td>
<td>44</td>
<td>.02</td>
</tr>
<tr>
<td>Speed of vehicle when emergency situation occurred (city)</td>
<td>37.0 (8.9)</td>
<td>35.5 (10.0)</td>
<td>100</td>
<td>.85</td>
</tr>
<tr>
<td>Reaction time (emergency stop)</td>
<td>16.9 (2.2)</td>
<td>16.1 (5.4)</td>
<td>93</td>
<td>.65</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (freeway)</td>
<td>97.3 (25.4)</td>
<td>99.7 (31.9)</td>
<td>103</td>
<td>.94</td>
</tr>
<tr>
<td>Stopping distance from vehicle/object at emergency stop (city)</td>
<td>22.8 (6.9)</td>
<td>23.6 (10.6)</td>
<td>63</td>
<td>.52</td>
</tr>
</tbody>
</table>

*Note that alpha is .05*
As can be seen in Table 9.3, drivers dosed with $d$-methamphetamine travelled significantly slower on the freeway at the time that an emergency situation occurred relative to the placebo condition ($T = 44, p < .05$). In addition, during the placebo condition there was a trend-level increase in the number of unnecessary/needless stops relative to the $d$-methamphetamine condition ($T = 15, p > .05$).

9.3.3.2.2  **Effect of $d$-methamphetamine on Visual Acuity and its Relation to Driving Ability**

There was no significant difference in visual acuity between the placebo and $d$-methamphetamine conditions for the left eye, $t (18) = 0.09, p = .93$ or the right eye, $t (18) = 0.64, p = .53$. Therefore, no further analyses were conducted.

9.3.4  **POMS**

Prior to drug administration, there was a trend for participants in the $d$-methamphetamine condition to report more negative moods relative to the placebo condition ($T = 50, p = .07$). Although only a trend level finding, in order to reduce error variance (resulting from Type II error) the session that $d$-methamphetamine was administered was included as a between subject factor for all cognitive analyses. This was done based on the possibility of practice and/or carry-over effects that were found in Experiment 1 (Chapter 7; refer to Section 7.3.5.1 for full details of $d$-amphetamine cognitive results) and Experiment 2 (Chapter 8; refer to Section 8.3.5.1 for full details of $d,l$-methamphetamine cognitive results).

9.3.5  **Neuropsychological Measures**

9.3.5.1  **Main Analyses**

Details of the results for all main effects and interactions for the cognitive tasks, including means and standard errors, are summarised in Table 9.4. Results for all post hoc tests are given in the text below, and all $p$-values reported are corrected $p$-values. The number of outliers excluded from analyses can be determined by the degrees of freedom reported in Table 9.4.
<table>
<thead>
<tr>
<th>Test</th>
<th>1st session</th>
<th>2nd session</th>
<th>d.f.</th>
<th>F</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 9.4 Overview of Main Effects of D-methamphetamine on Cognitive and Psychomotor Performance</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor</strong></td>
<td>1st session</td>
<td>2nd session</td>
<td>d.f.</td>
<td>F</td>
<td>p value</td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Forward) &amp; (Backward)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>6.5 (0.2)</td>
<td>6.5 (0.2)</td>
<td>1.16</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>(Forward)</td>
<td>7.3 (0.2)</td>
<td>7.3 (0.2)</td>
<td>1.16</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>(Backward)</td>
<td>5.7 (0.2)</td>
<td>5.6 (0.3)</td>
<td>1.16</td>
<td>0.20</td>
<td>0.66</td>
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<td>DSST</td>
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<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td>73.9 (3.1)</td>
<td>66.6 (2.6)</td>
<td>1.18</td>
<td>33.95</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T</td>
<td>65.5 (2.8)</td>
<td>72.4 (2.4)</td>
<td>1.18</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>DV / Accuracy</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td>98.3 (0.6)</td>
<td>100.0 (0.0)</td>
<td>1.14</td>
<td>0.67</td>
<td>0.43</td>
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<td>T</td>
<td>1.00</td>
<td>1.00</td>
<td>1.14</td>
<td>8.22</td>
<td>0.01</td>
</tr>
<tr>
<td>DV / Reaction Time</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>T x Ses</td>
<td>396.7 (6.0)</td>
<td>387.6 (6.6)</td>
<td>1.16</td>
<td>1.38</td>
<td>0.26</td>
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<tr>
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<td>3.3</td>
<td>3.3</td>
<td>1.16</td>
<td>3.03</td>
<td>0.10</td>
</tr>
<tr>
<td>DV / False Alarms</td>
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</tr>
<tr>
<td>T x Ses</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.1)</td>
<td>1.17</td>
<td>4.16</td>
<td>0.06</td>
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<tr>
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<td>0.1</td>
<td>0.11</td>
<td>1.17</td>
<td>0.03</td>
<td>0.86</td>
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<td>Track/No. of errors</td>
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<td></td>
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</tr>
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<td>T x Ses</td>
<td>25.4 (3.1)</td>
<td>30.1 (2.6)</td>
<td>1.16</td>
<td>5.27</td>
<td>0.04</td>
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<tr>
<td>T</td>
<td>27.3 (2.8)</td>
<td>22.1 (2.4)</td>
<td>1.16</td>
<td>0.002</td>
<td>0.96</td>
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<tr>
<td>(Tracking Only)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Task x Ses</td>
<td>25.6 (3.6)</td>
<td>34.4 (4.4)</td>
<td>1.16</td>
<td>2.46</td>
<td>0.14</td>
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<tr>
<td>(Dual Tracking)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T x Task</td>
<td>25.3 (3.9)</td>
<td>25.7 (2.9)</td>
<td>1.16</td>
<td>0.001</td>
<td>0.96</td>
</tr>
<tr>
<td>(Tracking Only)</td>
<td>25.6 (3.6)</td>
<td>34.4 (4.4)</td>
<td>1.16</td>
<td>2.46</td>
<td>0.14</td>
</tr>
<tr>
<td>(Dual Tracking)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Track/Time in error</td>
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</tr>
<tr>
<td>T x Ses</td>
<td>3164.2 (472.2)</td>
<td>4020.7 (574.4)</td>
<td>1.16</td>
<td>4.72</td>
<td>0.05</td>
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<tr>
<td>T</td>
<td>3289.1 (427.1)</td>
<td>2956.7 (519.6)</td>
<td>1.16</td>
<td>0.09</td>
<td>0.77</td>
</tr>
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<td>(Tracking Only)</td>
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</tr>
<tr>
<td>T x Task x Ses</td>
<td>3176.6 (460.3)</td>
<td>5266.8 (989.8)</td>
<td>1.16</td>
<td>1.46</td>
<td>0.25</td>
</tr>
<tr>
<td>(Dual Tracking)</td>
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</tr>
<tr>
<td>T x Task</td>
<td>3151.9 (689.6)</td>
<td>2774.7 (428.7)</td>
<td>1.16</td>
<td>1.46</td>
<td>0.25</td>
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<td>Movement Est.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td>-0.22 (0.04)</td>
<td>-0.10 (0.04)</td>
<td>1.17</td>
<td>0.98</td>
<td>0.34</td>
</tr>
<tr>
<td>T</td>
<td>-0.16 (0.06)</td>
<td>-0.05 (0.06)</td>
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<tr>
<td>(Easy Task)</td>
<td></td>
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<tr>
<td>T x Task</td>
<td>-0.28 (0.04)</td>
<td>-0.16 (0.04)</td>
<td>1.17</td>
<td>0.36</td>
<td>0.56</td>
</tr>
<tr>
<td>(Difficult Task)</td>
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</tr>
<tr>
<td>T x Occl</td>
<td>-0.09 (0.02)</td>
<td>-0.06 (0.02)</td>
<td>1.17</td>
<td>6.98</td>
<td>0.02</td>
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<tr>
<td>(Small Occlusion)</td>
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<td></td>
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</tr>
<tr>
<td>T x Occl</td>
<td>-0.24 (0.05)</td>
<td>-0.13 (0.04)</td>
<td>1.17</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>(Medium Occlusion)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T x Occl</td>
<td>-0.33 (0.07)</td>
<td>-0.15 (0.07)</td>
<td>1.17</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>(Large Occlusion)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Speed</td>
<td>-0.23 (0.06)</td>
<td>-0.06 (0.08)</td>
<td>1.17</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>(Slow Speed)</td>
<td></td>
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<tr>
<td>T x Speed</td>
<td>-0.33 (0.07)</td>
<td>-0.15 (0.07)</td>
<td>1.17</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td>(Fast Speed)</td>
<td></td>
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<td></td>
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<tr>
<td>Inspection Time</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td>65.0 (3.2)</td>
<td>63.9 (3.4)</td>
<td>1.18</td>
<td>3.17</td>
<td>0.09</td>
</tr>
<tr>
<td>T</td>
<td>1.00</td>
<td>1.00</td>
<td>1.18</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Trail-Making A &amp; B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T x Ses</td>
<td>3433.6 (123.9)</td>
<td>3529.2 (194.9)</td>
<td>1.16</td>
<td>2.71</td>
<td>0.12</td>
</tr>
<tr>
<td>T</td>
<td>3529.2 (194.9)</td>
<td>3433.6 (123.9)</td>
<td>1.16</td>
<td>0.48</td>
<td>0.48</td>
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<tr>
<td>(Trail A)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>T x Task</td>
<td>2125.4 (112.3)</td>
<td>2181.0 (129.8)</td>
<td>1.16</td>
<td>0.05</td>
<td>0.83</td>
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<tr>
<td>(Trail B)</td>
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<td></td>
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</tr>
<tr>
<td>T x Task</td>
<td>4741.8 (202.2)</td>
<td>4877.3 (314.6)</td>
<td>1.16</td>
<td>0.05</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Note that 1/ F tests are reported for both main effects and interactions, where main effects refer to drug effects on overall task performance and interactions refer to the interaction of drug effects with specific aspects of the task. 2/ Where there is a significant interaction between drug and session order, the means and standard errors are presented separately for subjects who consumed d-methamphetamine in their first session and subjects who consumed d-methamphetamine in their second session (however, where the interaction was not significant, the means for both sessions combined (first and second) are displayed in the ‘1st Session’ column). 3/ Tests in brackets represent the subsets of the preceding test. 4/ ‘d-meth’ = d-methamphetamine, ‘DV’ = Digit Vigilance, ‘T’ = Treatment Main Effect, ‘Ses’ = Session Order, ‘Occl’ = Occlusion.

As depicted in Table 9.4, in the Digit Vigilance task there was an improvement in accuracy ($p=.01$) and a trend-level reduction of reaction time ($p=.10$) in the d-methamphetamine condition. In the Movement Estimation Task there was a significant improvement in estimation of ‘time to contact’ in the d-methamphetamine condition ($p=.02$). Furthermore, in the d-methamphetamine condition participants underestimated ‘time to contact’ less for all occlusions relative to the placebo condition ($p=.02$). This difference increased as a function of occlusion size.

A significant interaction of session order with drug was found in the DSST ($p<.01$). A series of paired samples t-tests revealed that when d-methamphetamine was consumed in the first session, participants performed significantly worse in the d-methamphetamine condition compared to placebo [$t(8) = 5.22, p < .01$], however, when d-methamphetamine was consumed in the second session, participants performed significantly better in the d-methamphetamine condition compared to placebo [$t(10) = 3.65, p < .01$]. In order to normalise the data, square root transformations were conducted on the Tracking Task data. Although no main effect for drug was found in terms of the number of errors made or the total time spent in error on the Tracking tasks, a significant interaction of session order was observed for both, number of errors made ($p=.04$), and total time spent in error ($p=.05$). However, a series of post hoc tests revealed no significant differences between drug conditions in the number of errors made or the total time spent in error, irrespective of whether d-methamphetamine was consumed in the first session [$t(7) = 1.41, p = .40$; $t(7) = 1.34, p = .44$, respectively] or the second session [$t(9) = 2.00, p = .15$; $t(9) = 1.73, p = .24$, respectively].
9.3.5.2 Exploratory Analyses

No significant correlations were found between the level of \( d \)-methamphetamine in blood and cognitive performance.

9.3.6 Effect of \( d \)-methamphetamine on the Standardised Field Sobriety Test (SFSTs) Performance

9.3.6.1 Horizontal Gaze Nystagmus (HGN) Test

The percentage of individuals exhibiting each of the signs recorded during the HGN test for both the placebo and \( d \)-methamphetamine conditions are illustrated in Figure 9.2. In addition, the percentage of individuals classified as impaired using the HGN test with and without the inclusion of HMJ in the scoring procedure is depicted in Figure 9.2.

![Figure 9.2 Percentage of Individuals Exhibiting Each Sign of the HGN Test across Drug Conditions](image)

As can be seen in Figure 9.2, \( d \)-methamphetamine did not produce many errors during the HGN test. HMJ was observed more frequently in the \( d \)-methamphetamine and placebo conditions than any other sign of the HGN test. However, the difference between the drug conditions was not found to be significant (\( d \)-methamphetamine 4/20 impaired; placebo 3/20 impaired), \( p > 0.05 \), 95% CI = -0.29 to 0.19. In terms of overall HGN performance, \( d \)-methamphetamine did not significantly impair performance (\( d \)-methamphetamine 1/20 impaired; placebo 0/20 impaired), \( p > 0.05 \), 95% CI = -0.24 to 0.12. Including HMJ in the
HGN test scoring procedure did not change the percentage of individuals classified as impaired using the HGN test.

9.3.6.2 Walk and Turn (WAT) Test
The percentage of individuals exhibiting each of the signs recorded during the WAT test for both the placebo and d-methamphetamine conditions are illustrated in Figure 9.3. In addition, the percentage of individuals classified as impaired using the WAT test is shown in Figure 9.3.

Figure 9.3 Percentage of Individuals Exhibiting Each Sign of the WAT Test across Drug Conditions

Figure 9.3 demonstrates that Incorrect Turn (IT) was observed more frequently than any other sign of the WAT test for both the d-methamphetamine and placebo condition. Overall, during the d-methamphetamine condition, a higher percentage of individuals were classified as impaired on the WAT test relative to the placebo condition. However, this difference did not reach statistical significance (d-methamphetamine 5/20 impaired; placebo 2/20 impaired), $p > 0.05$, 95% CI = -0.35 to 0.45.

9.3.6.3 One Leg Stand (OLS) Test
The percentage of individuals exhibiting each of the signs recorded during the OLS test for both the placebo and d-methamphetamine conditions are shown in Figure 9.4. In addition, the percentage of individuals classified as impaired using the OLS test is highlighted in Figure 9.4.
As can be seen in Figure 9.4, more errors were observed during the placebo condition relative to the \(d\)-methamphetamine on the OLS test. Furthermore, a higher percentage of individuals were classified as impaired on overall OLS performance in the placebo condition compared to the \(d\)-methamphetamine condition. However, this difference was not statistically significant (\(d\)-methamphetamine 3/20 impaired; placebo 5/20 impaired), \(p > 0.05\), 95% CI = -0.12 to 0.32.

9.3.6.4 Overall SFSTs Performance
The percentage of individuals classified as impaired using the SFSTs is illustrated in Figure 9.5. Figure 9.5 also depicts whether including HMJ in the HGN test scoring procedure increased the percentage of individuals classified as impaired on overall SFSTs performance.

Figure 9.4 Percentage of Individuals Exhibiting Each Sign of the OLS Test across Drug Conditions

Figure 9.5 Percentage of Individuals Classified as Impaired on the SFSTs across Drug Conditions
As can be seen in Figure 9.5, one participant was classified as impaired using the SFSTs in both the $d$-methamphetamine and placebo conditions, therefore, $d$-methamphetamine was not found to significantly impair overall SFSTs performance ($d$-methamphetamine 1/20 impaired; placebo 1/20 impaired), $p > 0.05$, 95% CI = -0.17 to 0.17. Including HMJ in the HGN test scoring procedure did not change the percentage of individuals classified as impaired using the SFSTs. Table 9.5 summarises the accuracy of the SFSTs in identifying the presence of $d$-methamphetamine.

**Table 9.5** Number of Participants Classified as Impaired or Not Impaired Using the SFSTs Following the Administration of $d$-methamphetamine

<table>
<thead>
<tr>
<th></th>
<th>Impaired</th>
<th>Not Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGN</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>WAT</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>OLS</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Overall SFSTs</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>HMJ</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

### 9.4 Discussion

#### 9.4.1 Effect of $d$-methamphetamine on Simulated Driving Performance

The present experiment found that 0.42mg/kg $d$-methamphetamine did not significantly impair driving performance 2-3 hours post-drug administration, when blood and saliva $d$-methamphetamine concentrations were approximately 70ng/ml and 250ng/ml respectively. Consistent with the $d$-amphetamine (Chapter 7) and $d,l$-methamphetamine (Chapter 8) results, further analyses revealed that drivers dosed with $d$-methamphetamine travelled slower on the freeway at the time that an emergency situation occurred relative to the placebo condition. In addition, during the placebo condition there was a trend increase in the number of unnecessary or needless stops relative to the $d$-methamphetamine condition.

Although the present study did not find that a single acute therapeutic dose of $d$-methamphetamine significantly impaired driving performance, it is worth noting that the mean driving scores were in the same direction as those reported in Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), indicating possible decreases in driving ability following $d$-methamphetamine administration relative to placebo.
Overall, the results of the present thesis suggest that a single acute therapeutic dose of various preparations of amphetamines does not significantly impair driving performance. However, it is important to note that there is some indication that amphetamines may produce some minimal decreases to driving performance. Although the amphetamine concentrations observed in the present thesis are not directly comparable to those seen in real-life amphetamine-related road accidents and fatalities, the present results provide some, albeit very weak, indication that low levels of amphetamines may produce some driving decrements.

It is also important to note that although the present thesis provides only minimal suggestion of possible reductions to driving performance, this was observed following a single acute therapeutic dose of amphetamine (30mg), where mean blood amphetamine concentrations were below 100ng/ml. This is substantially lower than the amphetamine concentrations found in the blood of fatally injured drivers which have been reported, in some cases, to be as high as 2600 ng/ml (Logan, 1996; Logan et al., 1998). Thus, if any indications of decreases to driving ability were noted following the consumption of an acute therapeutic dose of amphetamines, it is possible that doses considerably higher will produce more pronounced driving decrements.

The considerable variations in saliva concentrations in comparison to blood concentrations, are most likely attributed to the fact that ion tapping in the more acidic saliva matrix resulted in higher saliva concentrations. However, it is also useful to address the finding that blood and saliva concentrations similarly decreased across time, with both showing concentration peaks at 120 min after \(d\)-methamphetamine was consumed. Furthermore, it is of interest to note that at the time that the driving simulator task was administered, \(d\)-methamphetamine concentrations in blood (120 min 72ng/mL; 170 min 67ng/mL) were considerably lower to that of \(d\)-amphetamine (120 min 83ng/mL; 170 min 98ng/mL) and \(d,l\)-methamphetamine (120 min 90ng/mL; 170 min 95ng/mL) concentrations, even though the same doses were given. Although these differences in concentration levels are a little surprising (in that \(d\)-methamphetamine is considered to be the most potent of the three amphetamine derivatives (Logan, 2002), therefore it would be expected that it would produce the highest concentrations in the blood), this may explain why \(d\)-methamphetamine produced the weakest overall driving effects of the three drugs administered in the present thesis. However, it should also be noted that no significant
associations between amphetamine blood concentrations and cognitive performance were found across the three experiments.

Consistent with the results from Experiment 1 (Chapter 7) and, to some extent, Experiment 2 (Chapter 8), the present experiment found that during the \( d \)-methamphetamine condition, drivers travelled at a slower speed on the freeway at the time that an emergency situation occurred, relative to the placebo condition. This is an interesting finding in that it is the only driving behaviour that was observed across all three amphetamine conditions. Interestingly, the effect is in the direction that would not be expected following amphetamine consumption, particularly as previous epidemiological reports consistently report that drivers under the influence of amphetamines tend to speed more (Logan, 1996). It is thus difficult to interpret the present finding. It can be argued that these results indicate more cautious driving, however, it may also be the case that this reduction in speed acted as a compensatory mechanism to permit drivers to attend to other aspects of driving, particularly as drivers were aware that their performance was being assessed. These findings suggest that amphetamines appear to have some effects on speed control. However, the small difference in the mean driving scores observed between the amphetamines and placebo conditions, makes further interpretation difficult. Thus, further research addressing this driving behaviour is warranted. In addition, the present experiment found that during the placebo condition, there was a trend increase in the number of unnecessary or needless stops, relative to the \( d \)-methamphetamine condition. It is difficult to interpret what these results may suggest, particularly as the difference in means was minimal. Again, further research is necessary to confirm these findings.

In conclusion, the present experiment found that 0.42mg/kg \( d \)-methamphetamine did not significantly impair driving performance, 2-3 hours post-drug administration. Overall, the results of the present thesis suggest that a single acute therapeutic dose of various preparations of amphetamine does not produce considerable driving impairment. Consistent with the \( d \)-amphetamine (Chapter 7) and, to some extent, the \( d,l \)-methamphetamine (Chapter 8) results, further analyses revealed that drivers dosed with \( d \)-methamphetamine travelled at a slower speed on the freeway at the time that an emergency situation occurred, relative to the placebo condition.
9.4.2 Effect of d-methamphetamine on Driving-Related Cognitive Processes

The present experiment examined the acute effects of 0.42mg/kg d-methamphetamine on cognitive measures that are important for driving, including attention, psychomotor function, and perceptual speed. The results revealed improvements in aspects of attention. Specifically, d-methamphetamine improved accuracy and reaction time (trend-level) on the Digit Vigilance task. Interestingly, when d-methamphetamine was administered in the second session, d-methamphetamine improved DSST performance, however, when d-methamphetamine was administered in the first session, d-methamphetamine decreased DSST performance. Finally, d-methamphetamine was shown to improve ‘time to contact’ error during the Movement Estimation Task. This latter improvement is interpreted as an impairment, as the smaller difference found between estimated and actual ‘time to contact’ may reflect less safe driving.

It is difficult to relate the present methamphetamine results to previous methamphetamine research as the literature is scarce. The findings are, however, consistent with Johnson et al. (2000) who reported improvements in attention following 0.42mg/kg d-methamphetamine. Furthermore, these findings are consistent with previous d-amphetamine research that has similarly shown improvements in attention following d-amphetamine doses ranging from 5mg to 30mg (Kelly et al., 1991; Koelega 1993; Comer et al., 1996; Ward et al., 1997; Wachtel & de Wit, 1999; Cami et al., 2000; de Wit et al., 2002).

In terms of the Digit Vigilance task, the present d-methamphetamine results are consistent with previous research, as d-amphetamine has been shown to have no effect on false alarm rates, but has been shown to improve accuracy (Kelly et al., 1991; Koelega 1993). Furthermore, although only a trend level finding, reaction time was faster in the vigilance task during the d-methamphetamine condition compared to the placebo condition. This is consistent with the results from Experiment 1 (trend-level; Chapter 7) and Experiment 2 (Chapter 8), and also previous amphetamine research (Kelly et al., 1991; Koelega 1993; Comer et al., 1996). Moreover, improved reaction time following amphetamine consumption has been consistently shown to occur for a range of tasks and amphetamine doses (Rapoport et al., 1980; Callaway et al., 1994; Halliday et al., 1994; Fleming et al., 1995; Kumari et al., 1997; Ward et al., 1997; Servan-Shreiber et al., 1998; McKetin et al., 1999; Johnson et al., 2000; Asghar et al., 2003; Fillmore et al., 2005).
Consistent with the literature, the results of the present experiment provide some evidence to suggest that \textit{d}-methamphetamine enhanced DSST performance (de Wit \textit{et al.}, 2002; Wachtel \\& de Wit, 1999; Cami \textit{et al.}, 2000; Kelly \textit{et al.}, 1991; Ward \textit{et al.}, 1997; Comer \textit{et al.}, 1996). However, this was observed only for participants who received \textit{d}-

methamphetamine during the second session. Consistent with this, in Experiment 2 (Chapter 8) \textit{d,l}-methamphetamine was shown to improve DSST performance only when \textit{d,l}-methamphetamine was consumed in the second session. Interestingly, in the present experiment, when \textit{d}-methamphetamine was consumed in the first session, participants performed significantly worse on the DSST relative to placebo. This difference in DSST performance following \textit{d}-methamphetamine consumption, suggests that the results may be influenced by practice effects or differential learning effects associated with treatment, thus illustrating that future research should incorporate adequate practice sessions to avoid Type II errors.

The present experiment revealed that for the movement estimation task, the difference between estimated ‘time to contact’ and actual ‘time to contact’ was significantly smaller in the \textit{d}-methamphetamine condition compared to the placebo condition. However, for both the placebo and \textit{d}-methamphetamine conditions, participants consistently underestimated ‘time of contact’. These results can be interpreted in several ways. However, currently there is insufficient evidence to support one interpretation over any of the others. The first explanation is that \textit{d}-methamphetamine merely improved movement estimation. The second is that \textit{d}-methamphetamine increased risk-taking behaviour. For instance, it is possible that following the administration of \textit{d}-methamphetamine, participants became more impatient and hasty in their decisions, thus, responded earlier than under normal conditions (placebo). This is consistent with previous research, where increases in risk taking behaviour have been noted following \textit{d}-amphetamine administration (Hurst, 1962; Hurst \textit{et al.}, 1967). The driving literature also argues that many amphetamine-related road fatalities are associated with risk taking behaviours (Logan, 1996; Logan \textit{et al.}, 1998). Thus, following this notion, the larger difference between estimated ‘time to contact’ and actual ‘time to contact’ observed in the placebo condition, can be interpreted as safer and more cautious driving, as there is more time to respond appropriately if a sudden change occurs in the traffic environment. The third interpretation is that \textit{d}-methamphetamine may have decreased impulsive responding relative to the placebo condition, where inhibition and delay of response have been argued.
to be important aspects of movement estimation (Lamers et al., 2003). This is consistent with previous research that has shown that an acute therapeutic dose of \( d \)-amphetamine can improve the ability to inhibit responses (de Wit et al., 2000; 2002).

Unlike the present results, the findings from Experiment 1 (Chapter 7) revealed that \( d \)-amphetamine produced overestimations in ‘time to contact’ (only for participants who consumed \( d \)-amphetamine in the first session), rather than underestimations of ‘time to contact’. However, it is important to note that the difference between estimated ‘time to contact’ and actual ‘time to contact’ was consistently smaller for both the \( d \)-amphetamine and \( d \)-methamphetamine conditions, relative to the placebo conditions. Furthermore, previous reports have shown stimulants to produce decrements in movement estimation in terms of both overestimation and underestimation of ‘time to contact’ (Lamers et al., 2003). In addition, it has been argued that any drug-induced impairment in the ability to judge motion is unacceptable, due to its negative implications to traffic safety (Lamers et al., 2003).

Consistent with the present interpretation of results and those reported in Experiment 1 (Chapter 7), Lamers et al. (2003) found that an acute dose of MDMA (75 mg) impaired the ability to perceive and predict motion, resulting from both the overestimation and underestimation of actual ‘time to contact’. The authors argued that this observation of overestimation and underestimation was in accordance with previous reports that have shown MDMA to produce shorter gap acceptance in car-following behaviour (Ward et al., 2000). Consistent with this notion, both \( d \)-amphetamine and \( d \)-methamphetamine were found to produce smaller gaps between estimated and actual ‘time to contact’ relative to placebo, thus suggesting possible reductions in safe driving, as there is less time to respond appropriately if a sudden change occurs in the traffic environment. Therefore, the results from the present experiment, Experiment 1 (Chapter 7), and Lamers et al. (2003), provide some suggestion that stimulants may affect movement estimation, which, applied to real-life traffic safety, may result in dangerous driving.

Consistent with the results from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the present experiment did not find \( d \)-methamphetamine levels in blood to be associated with cognitive performance following a single therapeutic dose of \( d \)-methamphetamine. These results support previous reports that low amphetamine levels in the blood and
amphetamine behavioural effects are generally dissociable in healthy subjects (Angrist et al., 1987; Brauer et al., 1996; Asghar et al., 2003). In addition, these results substantiate previous epidemiological reports, which have indicated that methamphetamine concentrations, required to evoke adverse driving behaviours, vary considerably across individuals as a result of differences in patterns of drug use, drug tolerance, fatigue, and alcohol or other drug use (Logan, 1996). Based on these results it can be argued that specific amphetamine levels in blood do not necessarily indicate impairment or improvement, as there are many additional factors that can influence performance differently across individuals, thus making a direct association inherently difficult.

Furthermore, it is of interest to note that at the time that the cognitive tasks were administered, there were considerable differences in the absorption kinetics of the three drugs administered. Specifically, at 170 and 240 minutes after drug administration $d$-amphetamine concentrations were 98ng/mL and 96ng/mL, respectively; $d,l$-methamphetamine was 95 ng/mL and 105ng/mL; and $d$-methamphetamine concentrations were 67ng/mL and 59ng/mL. These differences in absorption kinetics are surprising in that $d$-methamphetamine is considered to be the most potent drug of the three yet produced the lowest concentrations, while $d,l$-methamphetamine is considered the least potent of the three drugs yet produced the highest peak concentrations. These considerable differences in concentrations are likely to be attributed to differences in the population samples tested. However, these differences in absorption kinetics may elucidate some of the cognitive findings, in that $d$-methamphetamine was found to produce few cognitive changes (improvements or impairments), whereas $d$-amphetamine and $d,l$-methamphetamine had concentration levels that were comparable at these time points and similarly produced more notable cognitive effects. It is also worth mentioning that $d$-amphetamine concentrations peaked during the time window that the cognitive tasks were administered, $d,l$-methamphetamine concentrations were still increasing after all the cognitive tasks were completed, whereas $d$-methamphetamine peak concentrations were achieved by the first blood sample (120 minutes after drug administration 72ng/mL) and dropped markedly by the time the cognitive tasks were completed (59ng/mL). It is likely that these differences in peak concentrations resulted in the fewer cognitive effects with $d$-methamphetamine.

Furthermore, as no baseline cognitive measures were obtained, it cannot be determined whether these inconsistent findings in cognitive (and driving) performance across the three
amphetamine conditions, were not also attributable to differences in the populations baseline performances. Obtaining baseline performance would have ensured that the interpretation of differences in performance across sessions and the different amphetamines were due to differences in the drug itself, rather than differences in baseline performance (prior to drug administration).

Overall, the present results provide little indication as to how a single acute therapeutic d-methamphetamine dose may impair driving performance. However, as no significant driving impairment was found with d-methamphetamine, it is not surprising that no robust decrements to cognitive functioning were observed following a similar dose. This lack of any significant decrements to performance appears likely to be attributable to the low d-methamphetamine concentrations. However, research examining the effects of higher methamphetamine doses on cognitive performance is required to assess this. However, the present results do provide one possible link as to how driving ability may be negatively affected with amphetamines, which is consistent with Experiment 1 (Chapter 7). Specifically, during the movement estimation task, the smaller difference found between estimated and actual ‘time to contact’ following d-methamphetamine and d-amphetamine (Chapter 7) consumption, relative to placebo, can be understood as a reduction in safe driving, as there is less time to respond appropriately if a sudden change occurs in the traffic environment. This may be attributed to possible amphetamine-induced increases in risk taking behaviours.

The notion of stimulants affecting movement estimation is further supported with the simulated driving results reported in Experiment 1 (Chapter 7), and to a lesser extent, Experiment 2 (Chapter 8) and the present experiment. These results suggest that the amphetamines specifically affected driving behaviours associated with motion, such as driving too fast, driving too slow, and the notably smaller stopping distance between the vehicle and other objects during emergency situations (trend-level). However, since the experiments of the present thesis are, to the author’s knowledge, the only experiments that have assessed the effects of amphetamines on movement estimation, further research is warranted to support this interpretation.

In summary, consistent with the results from Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), the present findings indicate that a low dose of d-methamphetamine has
minimal effects on cognitive functioning, with only some minor indications of improvements to aspects of attention, specifically during a sustained attention task. However, the present findings also indicate that the ability to perceive and predict motion and ‘time to contact’, assessed with the movement estimation task, was affected following \(d\)-methamphetamine consumption. The present results substantiate the findings from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8) that indicate low amphetamine concentrations in the blood and amphetamine-related behavioural effects are generally dissociable in healthy subjects.

As the findings from the present experiment indicated that a single acute therapeutic dose of \(d\)-methamphetamine does not significantly impair driving performance, it is not surprising that the present cognitive results provide limited evidence as to how low \(d\)-methamphetamine concentrations may impair driving performance, with the only possible link being the results from the movement estimation task. Specifically, the smaller difference found between estimated and actual ‘time to contact’ following \(d\)-methamphetamine consumption (compared to placebo), is argued to reflect a reduction in safe driving. The notion of amphetamines affecting movement estimation was further supported with the simulated driving results reported in the present thesis. These results suggest that amphetamines specifically affected driving behaviours associated with movement estimation, such as driving too fast, driving too slow, and the notably smaller stopping distance between the vehicle and other objects during emergency situations.

9.4.3 Efficiency of the Standardised Field Sobriety Tests (SFSTs) in Detecting \(d\)-methamphetamine Impairment

The present experiment found that 0.42mg/kg \(d\)-methamphetamine did not impair performance on the SFSTs. Using these sobriety tests, impairment associated with a single acute therapeutic dose of \(d\)-methamphetamine was detected in only 5% of cases when blood and saliva amphetamine concentration levels were approximately 70ng/ml and 250ng/ml respectively.

Consistent with the present results, in Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), amphetamines did not impair performance on the SFSTs. Furthermore, using the SFSTs, impairment associated with \(d\)-amphetamine use was identified in only 5% of cases, and \(d,l\)-methamphetamine-related impairment was identified in 0% of cases, which is
comparable to that of the present findings which report a 5% success rate. To the author’s knowledge, there are no other studies that have investigated the efficiency of the SFSTs alone in detecting impairment associated with amphetamine use, as previous studies have administered the SFSTs in conjunction with other behavioural and physiological tests (i.e. the DEC Program; Bigelow et al., 1984; Compton, 1986). However, the extremely low percentage of participants identified as being intoxicated by \(d\)-methamphetamine, \(d\)-amphetamine (Chapter 7), and \(d,l\)-methamphetamine (Chapter 8), is consistent with previous reports that have highlighted the difficulty of detecting this stimulant drug class (Heishman et al., 1998; Shinar et al., 2000). However, it is important to note that the present results are not surprising given that the SFSTs were primarily designed to detect impairment associated with significantly higher amphetamine concentrations than those observed in the present thesis. Furthermore, the results from the present study indicate that the degree of impairment following the present dosing conditions were so small that it is likely that any observed impairments were below the threshold of the sensitivity of the SFSTs.

Consistent with the \(d\)-amphetamine (Chapter 7) and \(d,l\)-methamphetamine (Chapter 8) results, \(d\)-methamphetamine did not impair performance on the HGN test. Furthermore, consistent with the \(d\)-amphetamine (Chapter 7) and \(d,l\)-methamphetamine (Chapter 8) results, many of the traditionally scored signs were not observed following \(d\)-methamphetamine consumption. Although these findings suggest that any impairments produced by these low amphetamine doses are too small to be detected with the HGN test, the present results do substantiate previous claims that stimulants do not affect performance on Horizontal Gaze Nystagmus, Lack of Smooth Pursuit, Vertical Gaze Nystagmus, and Lack of Convergence tests (Kosnoski, et al., 1998; Adler and Burns, 1994).

Including HMJ in the HGN test scoring procedure did not significantly increase the percentage of \(d\)-methamphetamine-related impairment classifications. However, consistent with Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and previous cannabis research (Papafotiou et al., 2005b), HMJ was observed more frequently in the \(d\)-methamphetamine condition, than any other HGN sign. However, also similar to Experiment 1 and Experiment 2, HMJ was present in 10-15% of subjects during the placebo condition. Therefore, although there may be some value in considering HMJ in the scoring procedure,
further research is required that assesses HMJ at considerably higher amphetamine concentrations which are more likely to produce impairments in SFSTs performance. Consistent with Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), d-methamphetamine did not significantly impair performance on the WAT test. However, it is interesting to note that, similar to the effects reported for d,l-methamphetamine (Chapter 8), more errors were observed during the d-methamphetamine condition relative to the placebo, and a higher percentage of individuals were correctly classified as impaired on the WAT test. Improper Turn (IT) was observed more frequently, across both the placebo and d-methamphetamine condition, than any other sign of the WAT test. This is consistent with the results from Experiment 1 (Chapter 7) and previous cannabis research (Papafotiou et al., 2005b), in which IT was observed similarly across both placebo and drug conditions. These results highlight that IT is likely to be observed irrespective of drug consumption, thus, it may be inappropriate to include this sign in the scoring procedure. Future research should address this concern, as the IT sign appears to be an inaccurate indication of drug consumption, and exclusion from the scoring protocol may improve the accuracy of the sobriety test. Finally, as d-methamphetamine was not shown to significantly impair performance on the WAT test, the present findings substantiate the d-amphetamine (Chapter 7) and d,l-methamphetamine (Chapter 8) results, indicating that the amphetamine doses administered in the present thesis were too low to elicit significant impairments on the WAT test.

Finally, consistent with Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), d-methamphetamine did not impair performance on the OLS test. Furthermore, although not significant, it is useful to note that consistent with Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), more errors were observed in the placebo condition than during the d-methamphetamine condition. Moreover, a higher percentage of individuals were classified as impaired on the OLS test during the placebo condition. However, as significant effects were not found across any of the three studies, it cannot be concluded that low amphetamine concentrations improves performance on the OLS test. Although, previous reports have shown a decrease in errors on the OLS test to be the third best predictor for the presence of low-levels d-amphetamine (Heishman et al., 1998). Furthermore, it is unlikely that an improvement in OLS test performance would be observed with substantially higher amphetamine concentrations where gross impairment is more likely to occur.
As the present study did not find that a single acute therapeutic dose of \( d \)-methamphetamine significantly impaired driving performance, it is not surprising that a commensurate impairment in SFSTs performance was not observed. As previously mentioned, the SFSTs were designed to detect impairment and not presence of a drug. Therefore, since no significant driving impairment was observed with low \( d \)-methamphetamine concentrations, the present SFSTs results highlight that these tests are unlikely to produce a false positive during police drug evaluation procedures for amphetamine-related impairments.

In conclusion, consistent with Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the results from the present experiment suggest that following the administration of 0.42mg/kg \( d \)-methamphetamine SFSTs performance is not impaired. Using the SFSTs, impairment associated with low dose \( d \)-methamphetamine was identified in 5% of cases. These findings support Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), which indicate that the doses administered in the present thesis were too low to elicit any type of impairment that the SFSTs were designed to detect. Furthermore, as the dose of \( d \)-methamphetamine was insufficient to produce a significant driving impairment, the SFSTs findings provide support for their use as they did not produce any false positive results.

### 9.4.4 Summary of the Acute Effects of \( d \)-methamphetamine on Simulated Driving Performance, Driving-Related Cognitive Processes, and SFSTs Performance

In summary, the present experiment found that 0.42mg/kg \( d \)-methamphetamine did not significantly impair simulated driving performance, in recreational stimulant users, 2-3 hours post-drug administration. Overall, the results of the present thesis suggest that a single acute therapeutic dose of various preparations of amphetamines does not significantly impair driving performance. Consistent with the \( d \)-amphetamine (Chapter 7) and \( d,l \)-methamphetamine (trend-level; Chapter 8) results, further analyses revealed that drivers dosed with \( d \)-methamphetamine travelled at a slower speed on the freeway at the time that an emergency situation occurred, relative to the placebo condition.

Consistent with the results from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the present cognitive results indicate that a low dose of \( d \)-methamphetamine has minimal effects on cognitive functioning, with only some suggestions of improvements to aspects of attention, specifically during a sustained attention task. However, the present findings
also indicate that the ability to perceive and predict motion and ‘time to contact’, assessed
with the movement estimation task, was affected following \textit{d}-methamphetamine
consumption. Specifically, the smaller difference found between estimated and actual ‘time
to contact’ following \textit{d}-methamphetamine consumption (compared to placebo), was
interpreted as a reduction in safe driving as there is less time to respond appropriately if a
sudden change occurs in the traffic environment. These findings are consistent with
Experiment 1 (Chapter 7) and previous research. In addition, the present experiment
supports the findings from Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8) that
indicate low amphetamine levels in the blood and amphetamine-related behavioural effects
are generally dissociable in healthy subjects, thus highlighting the complex nature of the
amphetamines.

As a single acute therapeutic dose of \textit{d}-methamphetamine was not found to significantly
impair driving performance it is not surprising that the present cognitive results provided
limited evidence as to how low \textit{d}-methamphetamine concentrations may impair driving
performance. However, the results from the movement estimation task do provide some
suggestion of how amphetamines, in general, may affect driving. This is substantiated in
that decrements to specific simulated driving behaviours associated with movement
estimation were reported in the present thesis. These driving behaviours included driving
too fast, driving too slow, and the notably smaller stopping distance between the vehicle
and other objects during emergency situations (trend-level).

Finally, consistent with Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), the
results from the present experiment suggest that following the administration of 0.42mg/kg
\textit{d}-methamphetamine SFSTs performance is not impaired. These findings support
Experiment 1 (Chapter 7) and Experiment 2 (Chapter 8), which indicate that the doses
administered in the present thesis were too low to elicit any type of impairment that the
SFSTs were designed to detect. Furthermore, as the \textit{d}-methamphetamine dose was
insufficient to produce a significant driving impairment, the present SFSTs results
highlight that these tests are unlikely to produce a false positive during police drug
evaluation procedures for amphetamine-related impairments.
Chapter 10.

Experiment 4: Effect of d-amphetamine on Event-Related Potential Measures of Visual and Auditory Processing

10.1 Introduction

As was discussed in Chapter 1 (Introduction), the epidemiological driving literature highlights an association between amphetamine use and road crashes (refer to Chapter 3, Amphetamine and Driving for detail). However, it remains unclear how amphetamines should be related to adverse driving due to the findings from experimental cognitive research that generally indicates that amphetamines have cognitive enhancing properties (refer to Chapter 4, Amphetamine and Driving-Related Cognitive Performance for detail). Although this inconsistency appears to be attributable to differences in amphetamine concentrations (as the amphetamine concentrations observed in real-world driving situations are considerably higher than those reported in laboratory settings where ethical restrictions prevail), the findings from Experiment 1 (Chapter 7), of the present thesis, appear to further highlight the ambiguity in the role of amphetamine use in amphetamine-related driving impairments. Specifically, the results from the present thesis demonstrate that although 0.42mg/kg d-amphetamine significantly decreased simulated driving performance, it improved performance on some cognitive tasks that assessed functions important to safe driving (refer to Chapters 7.3, 8.3 and 9.3). Furthermore, although a similar single acute therapeutic dose of d,l-methamphetamine and d-methamphetamine did not significantly impair driving performance, the pattern of results were in a similar direction to that of d-amphetamine, possibly indicating a general amphetamine-related decrease in driving performance and improvement to cognitive functioning.

The results from the present thesis thus, provide some suggestion that a single therapeutic dose of various forms of amphetamine may produce some minimal driving decrements, and yet the present thesis also suggests that a single therapeutic dose of amphetamine may produce slight improvements to cognitive functions related to driving. Although there are many factors that could explain the ambiguity between the effects of amphetamines on driving ability and driving-related cognitive processes (refer to Section 1.2, Research Question; Introduction), it is possible that the effect that low dose amphetamines have on
human functioning, are too subtle to be detected using standard cognitive measures. Therefore, employing more sensitive techniques, such as the electroencephalogram (EEG) and its derivations, may help to clarify the manner in which amphetamines affect driving performance, as such methods can assess the more subtle effects of amphetamines on cognitive processing that cannot be easily measured using standard cognitive tasks. Therefore, the present experiment assessed the effects of a single acute therapeutic dose of *d*-amphetamine on cognitive functioning using the EEG, in order to determine the effects that amphetamines have on visual and auditory processes that are important to safe driving.

As was discussed in Section 5.3 (*Amphetamine, Driving and Visual Processing*), driving is primarily a visual task, therefore, it is important to investigate the acute effects of amphetamines on visual processing. The present thesis thus focused on two fundamental aspects of visual processing: divergent visual system pathways, the magnocellular and the parvocellular pathways; and aspects of the visual field, specifically relating to the central relative to the peripheral visual field.

The magnocellular and parvocellular visual systems process visual information and transfer it to the cortex. Both the magnocellular and parvocellular pathways begin in the retina, and project via the lateral geniculate nucleus (LGN) to the primary visual cortex (striate cortex, V1) (Livingstone *et al*., 1991). From the primary visual cortex, magnocellular information is conveyed predominantly to the parietal-occipital cortex (the ‘where’ pathway), and parvocellular information is conveyed predominantly to the temporal-occipital cortex (the ‘what’ pathway) (Pitzalis *et al*., 2005). The magnocellular system transfers low contrast visual information rapidly to the cortex and is sensitive in detecting motion and coarse detail (Samar *et al*., 2002; Livingstone *et al*., 1991; Schechter *et al*., 2005). The parvocellular system transfers high contrast visual information to the cortex and is sensitive in detecting pattern and fine-grained stimulus information, as well as colour and object features (Brannan *et al*., 1998; Butler *et al*., 2005; Farrag *et al*., 2002; refer to Section 5.3.1, *Amphetamine, Driving and the Magnocellular and Parvocellular Visual Pathways* for more detail). In terms of driving, dysfunctions within either the magnocellular or parvocellular pathways could have negative consequences. For instance, decrements to the magnocellular system may result in deficits in the ability to process coarse details and the overall organisation of the traffic environment, such as, the movement of cars and pedestrians. Decrements to the parvocellular system could result in
deficits in the ability to distinguish colour and specific details of the traffic environment, such as that involved in the processing of traffic lights or road signs. Therefore, to further explore how a single therapeutic dose of amphetamine may affect driving ability, the present experiment assessed the acute effects of \( d \)-amphetamine on the functioning of these two visual systems. This involved the administration of a pattern reversal task, which consisted of the presentation of two checkerboard patterns that were designed to preferentially activate the magnocellular or parvocellular systems, by manipulating the physical features of the visual stimuli (Odom et al., 2004).

Further to this, previous research has demonstrated the important role that visual field functioning, particularly that of the peripheral visual field, has on driving performance. The visual field refers to the total visual area around the point of fixation in which information can be perceived and processed (Mackworth, 1965). The central visual field refers to the area that is in the fovea or the fixation point, and peripheral visual field refers to the area outside the fovea where information can still be perceived (refer to Section 5.3.2, Amphetamine, Driving and the Visual Field for more detail). Deterioration to aspects of the visual field can have significant consequences to driving. For instance, decrements to the peripheral visual field can result in a decrease in the ability to estimate vehicle speed, to detect road signs, and to avoid obstacles (Osaka, 1988; Troutbeck & Wood, 1994; Wood & Troubeck, 1993). Furthermore, previous reports have indicated that acute amphetamine use may produce impairments to the peripheral visual field (Mills et al., 2001). Therefore, to further explore how amphetamine may affect driving performance, the present experiment examined the acute effects of \( d \)-amphetamine on aspects of visual field processing. A simple visual task was employed, in which the location of target and nontarget stimuli was manipulated to activate central and peripheral visual field processing.

In addition, as was discussed in Section 5.4 (Amphetamine, Driving and Auditory Processing), although not as important as vision, driving a car also requires efficient auditory processing. Therefore, the present experiment also examined the acute effects of \( d \)-amphetamine on aspects of auditory processing, which are argued to be important to driving, such as, mismatch negativity, startle reflex and pre-pulse inhibition of the startle response, the N200 component, and the P300 component. Specifically, three auditory tasks were administered, a mismatch negativity task, a startle reflex/pre-pulse inhibition task,
and an auditory oddball task. These tasks were selected as they have been employed in a wide variety of theoretical, empirical, and clinical applications, however, few studies have examined performance on these tasks following the administration of amphetamine.

Mismatch Negativity (MMN) is an early event-related potential (ERP) component that provides a sensitive index of the perceptual detection of change in auditory stimulation (Näätänen, 1992; Näätänen et al., 2004). The MMN is generated by a ‘mismatch’ process between the auditory input from a ‘deviant’ stimulus and the auditory memory of a ‘standard’ stimulus. Thus, it is argued that the MMN reflects a short-term sensory memory comparison process (Näätänen, 1992). The MMN is generated in the supratemporal plane of the auditory cortex and is maximal over frontal-central areas of the scalp (Scherg et al., 1989; Giard et al., 1995; refer to Section 5.2.1.4, Mismatch Negativity (MMN) for more detail). In terms of driving, dysfunctions to the MMN response would result in a reduced ability to automatically detect key auditory changes in the traffic environment. For instance, while driving a car, many sounds are continually perceived from the surrounding environment but not attended to, such as, children playing on the street, passing motor vehicles, and rain. However, a sudden change in auditory stimulation, such as a car horn, needs to be immediately and automatically detected, irrespective of where attention is located at that time. Therefore, to further explore how a single therapeutic dose of amphetamine may affect driving performance, the present experiment examined the acute effects of $d$-amphetamine on the MMN response. This involved the administration of a standard auditory oddball paradigm, whereby, deviant auditory stimuli were presented infrequently amongst a sequence of rapidly presented repetitive, homogeneous, standard auditory stimuli (Muller-Gass & Campbell, 2002).

The startle reflex is an early primitive defence response that serves a protective function, avoiding injury and acting as a behavioural disruption that clears other processors in order to cope with a possible threat (Graham, 1979). The startle reflex can be inhibited when the startling stimulus is preceded by a weaker sensory stimulus (prepulse) (Graham, 1975). This is referred to as prepulse inhibition of the startle reflex (PPI). This inhibitory mechanism represents an operational measure of 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 prepulse (Graham, 1975). It is thought that sensorimotor gating reflects an individual’s ability to automatically
‘screen out’ irrelevant or intrusive sensory stimuli, thus preventing an overload of information (Blumenthal et al., 1996; Swerdlow, 1996; Swerdlow & Geyer, 1998). The PPI of the startle reflex helps regulate environmental inputs and selectively allocate attentional resources to relevant stimuli (refer to Section 5.2.1.2, Pre-pulse Inhibition of the Acoustic Startle Reflex for more detail). A disruption to the PPI response may be dangerous when driving, as a decrease in the drivers’ ability to filter out irrelevant or intrusive information appropriately, may result in an overload of information. This overload of information would subsequently increase the drivers’ risk of failing to attend to relevant information and potential traffic hazards. Therefore, to further explore how a single acute therapeutic dose of amphetamine may affect driving performance, the present experiment employed a task that assessed the startle reflex and pre-pulse inhibition response. This task involved the presentation of infrequent loud startling auditory stimuli, which were sometimes preceded by a weaker sensory stimulus (prepulse) (Graham, 1975).

In addition, it has previously been reported that following a low dose of d-amphetamine (5 mg), PPI is significantly reduced in smokers (Kumari et al., 1998; refer to Section 5.4.2 for details). Therefore, the present experiment endeavoured to confirm this result using a larger sample size, and administering a considerably higher dose of d-amphetamine.

The N200 is an attention-dependant ERP component that reflects stimulus discrimination and classification processes (Näätänen, 1992; refer to Section 5.2.1.3, N200 Component for more detail). It provides a measure of selective attention (Hillyard & Hansen, 1986). Assessing the N200 can provide useful information, such as, how efficiently a driver selectively attends to relevant information in the traffic environment. In terms of driving, disruptions in the ability to discriminate and selectively attend to information in the traffic environment, may result in an overload of information, and subsequent increase in the driver’s risk of failing to attend to important information and potential traffic hazards. Therefore, to further explore how a single therapeutic dose of amphetamine may affect driving ability, the present experiment examined the acute effects of d-amphetamine on selective attention. This involved the administration of a standard auditory oddball paradigm that involved the random occurrence of an infrequent (oddball) target stimulus presented among frequently (standard) occurring stimuli. The N200 is evoked when the subject attentively discriminates the rare stimulus from the frequent one (Näätänen, 1992).
Finally, the P300 is arguably the most prominent and extensively researched ERP component. The P300 provides an index of general cognitive efficiency (Donchin & Coles, 1988). In particular, it is considered to be an index of working memory (Donchin et al., 1986; Donchin & Coles, 1988), as it reflects the allocation of attentional resources and speed of processing (Johnson, 1986; Donchin & Coles, 1988; refer to Section 5.2.1.5, P300 Component for more detail). In relation to driving, assessing the P300 can provide useful information regarding how efficiently a driver processes information from the environment. Operating a motor vehicle requires the constant ‘updating of working memory’ as new information is integrated within the current schema of the traffic environment. This reflects aspects of the basic information processing mechanisms of attention allocation and immediate memory. Research has shown that speed of information processing and efficient allocation of attention are associated with safe driving, whereby deficits in either process can increase crash risk (for review see Anstey et al., 2005). The speed at which information is processed is an important aspect to responding appropriately to road situations. Information processing speed also influences decision-making as often there are only brief time periods during which drivers must make appropriate decisions and responses. Assessing the P300 response in the context of driving performance, can provide important information as to how and when information processing is affected following the consumption of amphetamine. Therefore, to further explore how a single therapeutic dose of amphetamine may affect driving performance, the present experiment assessed the acute effects of \textit{d}-amphetamine on the P300 component. The P300 was elicited using the same task as was administered to elicit the N200 component (i.e. an auditory oddball paradigm). The participant was required to attentively discriminate the rare stimulus from the frequent one, by noting the occurrence of only the target stimulus (Picton, 1992).

The present experiment examined the acute effects of \textit{d}-amphetamine on visual and auditory cognitive processes that are deemed important to safe driving, using a repeated-measures, counter-balanced, double blind, placebo-controlled design. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \textit{d}-amphetamine, separated by a one week wash-out period, to reduce residual effects of the drug from the first session. The present chapter will describe the materials and methodologies employed, the results, and provide a discussion of the results.
10.2 **Materials and Methods**

10.2.1 **Participants**

10.2.1.1 **Selection Criteria**

The selection criteria for the present experiment were the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.1.1 for full description.

10.2.1.2 **Psychological and Physical Health**

Psychological and Physical Health was assessed with the same procedure as described for Experiment 1 (Chapter 7). Refer to Section 7.2.1.2 for full description.

10.2.1.3 **Sample Characteristics**

Twenty healthy illicit stimulant users (10 males; 10 females) aged between 21 and 32 years (mean = 25.2 years, SD = 3.0 years), with an average male weight of 83.3 kg (SD = 8.8) and an average female weight of 61.9 kg (SD = 7.6) were recruited through advertisements. All participants had a minimum of 11 years education. All participants were consumers of caffeine with an average daily intake of 1.4 cups of coffee (range 0-4). Of the 20 participants, 14 were self-assessed smokers, averaging 6.1 cigarettes a day (range 0-20). It may be noted that the individuals in the present experiment were predominantly the same as those from Experiment 1 (Chapter 7), with the exception of four participants.

Participants were provided with an information sheet outlining details of the research project (see Appendix C for information sheet), and all participants gave written informed consent (see Appendix D for consent form). Participants were informed that they were free to withdraw from the study at any time. The Swinburne University of Technology Human Research Ethics Committee approved the research.

10.2.2 **Drug**

The drug administered was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.2 for full description.
10.2.3 Experimental Design

The experimental design was the same as described for Experiment 1 (Chapter 7). Refer to Section 7.2.3 for full description.

10.2.4 Materials

10.2.4.1 Questionnaires

Demographic details (see Appendix E for complete questionnaire) and drug use history (see Appendix F for complete questionnaire) was obtained using the same questionnaires as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.1.1 and 7.2.4.1.2, respectively, for full description.

10.2.4.2 Experimental Tasks

All visual and auditory stimuli were generated using the NeuroScan Stim System (NeuroScan, Inc.). Visual stimuli were presented on a 17 inch LCD monitor.

10.2.4.2.1 Pattern Reversal Task

The pattern reversal task consisted of the presentation of two different checkerboard patterns. The magnocellular pathway was assessed with a standard black and white checkerboard that changed phases (i.e. black to white and white to black) repeatedly, at a rate of 2 reversals per second. The total number of reversals was 203. There were an equal number of light and dark elements in the checkerboard, with 28 squares (1cm x 1cm) presented as a 34 cm (horizontally) by 27cm (vertically) grid. The stimulus pattern had a mean luminance of 80cd/m², 75% contrast level. The parvocellular pathway was measured with a green and red checkerboard that changed phases repeatedly, at a rate of 2 reversals per second. The total number of reversals was 203. There were an equal number of red and green squares in the checkerboard, with 6 squares (5.5cm x 4.5cm) presented as a 34 cm (horizontally) by 27cm (vertically) grid. The stimulus pattern had a mean luminance of 80cd/m², 75% contrast level (Odom et al., 2004).

In this task there was also a target stimulus, which was employed to keep attention constant. This was a small blue dot (4mm in diameter) located in the centre of the screen. The colour of the dot changed briefly, from blue to yellow, at a random rate (once every 1
to 4 seconds). Participants were instructed to maintain focus on the small dot in the centre of the screen, and press a response button whenever the blue dot changed to yellow. Participants were instructed to ignore the flashing checkerboard in the background and focus only on the fixation dot. The duration of the task was 4 minutes.

### 10.2.4.2.2 Visual Field Task

The visual field task assessed central and peripheral visual field processing. The visual stimuli were white letters, ‘X’ and ‘Y’ (2cm in height and 2cm in width), presented on a black background. A series of targets, defined by ‘X’, and nontargets, defined by ‘Y’, were flashed in random order, either centrally (left or right) or peripherally, (left or right), relative to a fixation cross (4mm in diameter) located in the centre of the computer screen (i.e. stimuli were presented along an x-axis located in the centre of the monitor). Central stimuli were presented 1cm from the fixation cross, and peripheral stimuli were presented 16.5cm from the fixation cross. These positions were selected so that when the participant was seated 60cm from the monitor, stimuli were presented in the participants central and peripheral visual fields. The stimulus onset asynchrony (SOA) varied randomly between 820 and 1180 ms (mean 1000ms). A total of 240 stimuli were delivered, where 48 were targets and 192 were nontargets

Participants were instructed to maintain focus on the fixation cross throughout the task, and respond as quickly as possible by pressing a button whenever a target stimulus was flashed in any of the four positions (central left and right; peripheral left and right). A practice task was administered which consisted of 25 stimuli, where 11 were targets and 14 were nontargets. If participants completed the practice trial incorrectly, the instructions were repeated, and the practice trial was readministered. The duration of the experimental task was approximately 5 minutes. Mean reaction time was recorded for the target stimuli only.

### 10.2.4.2.3 Mismatch Negativity Task (MMN)

The mismatch negativity task consisted of a series of ‘deviant’ and ‘standard’ tones presented via ear inserts. The stimulus intensity was set to 80dB. The deviant tones differed from the standard tones in duration only. Standard tones had a frequency of 1000Hz and 50ms duration (including 5ms rise and 5ms fall times). Deviant tones had a frequency of 1000 Hz and a 100ms duration (including 5ms rise and 5ms fall times). Tones
were binaurally presented to the participant in random order (91% standards, 9% deviants). The task consisted of 511 standard tones and 50 deviant tones, with variable SOA (0.45 to 0.55 seconds). During the task participants read self selected text and were instructed not to attend to the tones. The duration of the task was approximately 7 minutes.

10.2.4.2.4 Startle Reflex/Pre-Pulse Inhibition Task

The Startle Reflex/Pre-Pulse Inhibition Task consisted of a white-noise background against which a train of ‘startle’ stimuli were presented binaurally to participants through ear inserts. The task began with a 1 min acclimatisation period consisting of 70dB SPL continuous low level white noise, followed by 8 pulse alone (habituation) trials. Subsequently, the main task began, whereby 8 prepulse and 8 pulse alone stimuli were delivered, in a pseudorandom order. The SOA varied between 16 and 24 seconds, with a mean of 20 seconds. Pulse alone stimuli were 40ms (including <1ms rise and <1ms fall times) bursts of white noise presented at 108dB SPL, and prepulse stimuli were 20ms (including <1ms rise and <1ms fall times) bursts of white noise presented at 80dB SPL. ‘Pulse alone’ trials are those trials containing only a startle stimulus, and ‘prepulse’ trials are those containing both a startle stimulus and a prepulse stimulus that preceded the startle stimulus by 60ms.

Participants were instructed to keep their eyes open and look straight ahead at a fixation cross located on the monitor in front of them. They were told that they were going to hear a sequence of loud startling sounds, but to ignore them and sit quietly. The task took approximately 9 minutes to complete.

10.2.4.2.5 Auditory Oddball Task

The auditory oddball task consisted of a series of target and nontarget stimuli that were presented in random order, binaurally, through ear inserts. The SOA varied between 750 and 1150 ms (mean 950 ms). A total of 60 target tones and 390 nontarget tones were presented, where the overall probability of a target tone was 13% and a nontarget tone was 87%. Stimulus tones were presented at 80dB SPL with a 50ms duration (including 10ms rise and fall times). The target tone frequency was 1000 Hz and the nontarget tone frequency was 1100 Hz.
Participants were instructed to press a response button as quickly and as accurately as possible when the target stimulus was detected, and to refrain from responding when the nontarget was presented. Accuracy and response time were recorded. A practice task was administered which consisted of 15 stimuli, where 4 were targets and 11 were nontargets. If participants completed the practice trial incorrectly, the instructions were repeated, and the practice trial was readministered. The experimental task took approximately 8 minutes to complete, and was recorded with participants eyes open.

10.2.4.3 Blood and Saliva Samples

Two blood and two saliva samples were taken from each participant by a registered nurse during each EEG session. Consistent with Experiment 1 (Chapter 7), the first blood and saliva sample was obtained 120 minutes after administration of the drug, and the second sample was obtained 200 minutes after administration of the drug. Blood samples were screened for the seven major drug classes (opiates, amphetamines, benzodiazepines, cannabinoid, barbiturates, cocaine and methadone) using ELISA/EMIT screens. Subsequently, blood and saliva samples were analysed for specific amphetamine levels using the GC/MS method (refer to Section 7.2.4.6 for full description of how blood and saliva samples were obtained). In addition, a baseline saliva sample, obtained using a saliva drug testing device (Securetec Drugwipe), was administered to all participants prior to drug administration to ensure no recent drug use. The saliva drug testing device produced a result (positive or negative) immediately after a saliva sample was obtained. This sample was obtained to verify that inclusion criteria had been met. Therefore, no further analyses were conducted on the data.

10.2.5 Data Acquisition

Electroencephalographic (EEG) data were recorded using Neuroscan Synamps amplifiers (version 4.0 software, Neurosoft Inc., 1998). EEG was recorded from 62 scalp sites using the international 10-20 system (American Encephalographic Society, 1994), with a forehead ground and impedance at 5 KΩ or less at the start of the recording session. All scalp sites were referenced to the left mastoid (M1). Eye movements were monitored using horizontal electro-oculogram (EOG) with a bipolar recording from electrodes placed at the left and right outer canthi of the eyes. Eye blinks and vertical eye movements were recorded using an electrode placed below the left eye. An electrode was also placed at the
EEG activity was amplified with a gain of 50K by Neuroscan Synamps amplifiers (version 4.0 software, Neurosoft Inc., 1998). All signals were filtered (band-pass 0.05-500 Hz, 12dB/octave) online, with an analogue-to-digital sampling rate of 2000 Hz. Data were continuously written to hard disk.

10.2.6 Data Analysis

EEG activity was analysed using Neuroscan data acquisition software (version 4.0 software, Neurosoft Inc., 1998).

10.2.6.1 Pattern Reversal Task

The EEG was first filtered (band-pass 0.01-30 Hz, 12dB/octave), epoched -100 ms to +460 ms post stimulus, and baseline corrected. Epochs in which the EEG or EOG exceeded ±200 μV were rejected, and data were then EOG corrected to account for ocular artefact (Croft & Barry, 2000). Epochs were then averaged separately for each of the parvocellular and magnocellular stimuli, for each drug condition. Peak amplitudes and latencies for the early negative N100 and early positive P100 components were calculated for each subject in the following time window: N100 (30-150 ms) and P100 (80-170 ms) (Mangun & Hillyard, 1991; Di Russo & Spinelli, 1999; Schechter et al., 2005). Subsequently, peak P100 amplitude was calculated as the P100-N100 peak-to-peak amplitude as it is less susceptible to noise.

10.2.6.2 Visual Field Task

The EEG was first filtered (band-pass 0.01-30 Hz, 12dB/octave), epoched -200 ms to +1000 ms post stimulus, and baseline corrected. Epochs in which the EEG or EOG exceeded ±200 μV were rejected, and data were then EOG corrected to account for ocular artefact (Croft & Barry, 2000). Epochs were then averaged separately for each of the central, peripheral, target and nontarget stimuli, for each drug condition. Only target trials that received a correct response were included in the averages. The components of interest were the P100, N200 and P300. As the P100 is an early component, that occurs prior to discrimination of target stimuli from nontarget stimuli, target and nontarget stimuli were
combined for the central and peripheral averages, for each drug condition. However, for the N200 and P300 components only the target stimuli were included in the analyses, as only stimuli that require a response evoke these waveforms.

In order to improve signal-to-noise ratio, Principle Component Analyses (PCA) were conducted to clarify the ERP components resulting from this task (Arruda et al., 1996). PCA is useful in this context as it is sensitive to, and can enhance small but important sources of waveform variance that overlap with other sources of ‘nuisance’ variance (Chapman & McCreary, 1994). Separate PCAs were performed for each of the three components.

A grand average was calculated which included all placebo and d-amphetamine averages for target and nontarget, central and peripheral stimuli. To calculate the P100 component the period between 70 and 170 ms post-stimulus (Di Russo & Spinelli, 1999) was subjected to PCA. A PCA was performed using a covariance decomposition, with varimax rotation, where only factors with eigenvalues \( \geq 1 \) were retained. This resulted in 4 orthogonal factors. The P100 factor was selected as the only factor that satisfied all of the following conditions. It must have had a positive polarity peak with a parietal-occipital maxima occurring within the time range of 70 and 170 ms post-stimulus. The P100 waveform was then recomposed using the factor loadings from the selected factor, and the peak was obtained as the maximum within the time range of 70 and 170 ms post-stimulus. The factor loadings were applied to individual subjects for each condition separately.

To calculate the N200 component the period between 120 and 250 ms post-stimulus (Cooper et al., 2005) was subjected to PCA. Similar to the above P100 waveform, a PCA was performed using a covariance decomposition, with varimax rotation, where only factors with eigenvalues \( \geq 1 \) were retained. This resulted in 4 orthogonal factors. The N200 factor was selected as the only factor that satisfied all of the following conditions. It must have had a negative polarity peak with a frontal-central maxima occurring within the time range of 120 and 250 ms post-stimulus. The N200 waveform was then recomposed using the factor loadings from the selected factor, and the peak was obtained as the maximum within the time range of 120 and 250 ms post-stimulus (Cooper et al., 2005). The factor loadings were applied to individual subjects for each condition separately.
Finally, to calculate the P300 component the period between 250 and 600 ms post-stimulus (Cooper et al., 2005) was subjected to PCA. Similar to the above P100 and N200 waveforms, a PCA was performed using a covariance decomposition, with varimax rotation, where only factors with eigenvalues $\geq 1$ were retained. This resulted in 4 orthogonal factors. The P300 factor was selected as the only factor that satisfied all of the following conditions. It must have had a positive polarity peak with a parietal maxima occurring within the time range of 250 and 600 ms post-stimulus. The P300 waveform was then recomposed using the factor loadings from the selected factor, and the peak was obtained as the maximum within the time range of 250 and 600 ms post-stimulus (Cooper et al., 2005). The factor loadings were applied to individual subjects for each condition separately. It is important to note that due to the scaling involved with the PCA, the scale for all PCA derived peak amplitudes is arbitrary.

10.2.6.3 Mismatch Negativity Task (MMN)

The EEG was first filtered (band-pass 1-30Hz, 12dB/octave), epoched -100 ms to +600 ms post stimulus, and baseline corrected. Epochs in which the EEG or EOG exceeded $\pm 200 \mu V$ were rejected, and data were then EOG corrected to account for ocular artefact (Croft & Barry, 2000). Epochs were then averaged separately for each of the standard and the deviant stimuli, for each drug condition. To delineate the MMN response the standard stimulus ERPs were subtracted from the corresponding deviant stimulus ERPs, thus resulting in a difference waveform. MMN is known to revert in polarity between FZ and the left and right mastoids (Winsberg et al., 1997). Therefore, prior to peak detection, this waveform was rereferenced to the nose. The MMN amplitude and latency were measured from the responses referenced to the nose. The MMN peak latencies and amplitudes were identified as the most negative peak within a range of 100-250 ms from stimulus onset (Näätänen, 1995; Näätänen & Alho, 1995).

10.2.6.4 Startle Reflex/Pre-Pulse Inhibition Task

Note that as extra channels were not available to record electromyographic (EMG) in addition to EOG (which was recorded to account for eye movement activity), startle response was measured using EOG only. Although this may not be an ideal measure of startle response (Koch, 1999), it has been argued that EOG will produce an equivalent metric to that of EMG (Schmidt & Fox, 1998).
The EOG was first filtered (band-pass 0.01-8 Hz, 12dB/octave), rectified, epoched -100 ms to +798 ms post stimulus, and baseline corrected. Epochs were then averaged separately for each of the EOG prepulse and pulse alone stimuli, for each drug condition. Note that the habitation trials were not analysed. The prepulse and pulse alone was operationally defined as the peak EOG signal within 250 ms of the startle stimulus (Kumari et al., 1998; Swerdlow et al., 2000). Participants with negligible responses (where no visually discernible peak occurred within 250 ms of the startle stimulus) were discarded from the analysis as non-responders.

Prepulse inhibition (PPI) was defined as the difference in amplitude between the pulse alone and the prepulse stimuli. Therefore, the median value for the prepulse was subtracted from the median value for the pulse alone, and subsequently the total was divided by the pulse alone median; that is, PPI = (pulse alone – prepulse) / pulse alone. This procedure is typical of the PPI literature (Kumari et al., 1998; Hutchison & Swift, 1999; Hutchison et al., 1999). PPI was calculated separately for each participant across each drug condition.

10.2.6.5 Auditory Oddball Task

The EEG was first filtered (band-pass 0.01-30 Hz, 12dB/octave), epoched -100 ms to +798 ms post stimulus, and baseline corrected. Epochs in which the EEG or EOG exceeded ±200 μV were rejected, and data were then EOG corrected to account for ocular artefact (Croft & Barry, 2000). Epochs were then averaged separately for each drug condition. Only target trials that received a correct response were included in the averages.

The P300 component was defined as the largest positive peak occurring within the latency window of 250-600ms post-stimulus (Kröner et al., 1999). The N200 component was defined as the largest negative peak occurring within the latency window of 180-290ms post-stimulus (Winsberg et al., 1997). Peak amplitude was measured relative to the pre-stimulus baseline and peak latency was measured from the time of stimulus onset.

10.2.7 Procedure

In a preliminary session, on a separate day in which no drug was administered, participants read an information sheet (see Appendix C for information sheet), signed an informed consent form (see Appendix D for consent form), completed the demographics
questionnaire (see Appendix E for complete questionnaire) and the drug use history questionnaire (see Appendix F for complete questionnaire), and completed a medical examination (see Appendix A and B for complete medical questionnaires).

Participants were asked not to eat 4 hours prior to the two experimental sessions. Participants were also asked to refrain from consuming any products containing caffeine (e.g. coffee, tea, coca cola, chocolate) for at least 4 hours prior to each experimental session. In addition, participants were not permitted cigarettes throughout each experimental session. Testing times were kept constant for each participant across sessions, so that differences in time of day would not confound recordings. For all experimental sessions the experimenter and participant were blind to the treatment condition. A medical practitioner was on-call and a registered nurse was on-site throughout all experimental sessions.

At the beginning of each experimental session, toast with various spreads and orange juice were provided. After the participant completed eating, the research nurse administered the drug/placebo orally. While the drug reached its peak blood concentration (approximately 2 hours after drug administration), the experimenter prepared the participant for the EEG recording. A close-fitting cap containing 62 electrodes was placed on the participants scalp, and a small quantity of water-soluble conductive gel was used to ensure satisfactory impedance. As d-amphetamine has a peak blood concentration between two and four hours (Kupietz, et al., 1985; Angrist, et al., 1987; Brauer et al., 1996), and consistent with the methodology employed in the previous experiments (Chapter 7, Chapter 8, and Chapter 9), the first blood and saliva sample was obtained 120 minutes after drug consumption. Participants were then comfortably seated in a dimly lit, sound-attenuated, and electrically shielded room, 60cm from the computer screen. Participants were fitted with ear inserts and adequate hearing was ensured using a brief auditory task. Participants were instructed to relax as much as possible, and to try and minimise eye movement, muscle tension, and gross body movement, during each task. Stimuli were presented on a computer screen at a viewing distance of 60cm, where subject’s eyes were at centre monitor level. Instructions and practice trials were given immediately prior to task administration. The EEG recording took approximately one hour to complete, and upon completion a second blood and saliva sample was obtained. Participants were provided with a taxi voucher for transport home, and were escorted safely to a taxi by the experimenter. Table 10.1 illustrates the testing
protocol adhered to during the two EEG sessions. Note that the protocol was the same during both experimental sessions.

Table 10.1 | Testing Protocol
--- | ---
| Elapsed Time (min) | Event |
| 0 | Meal Provided |
| 10 | Treatment Administered Orally |
| 90 | Participant EEG Set-Up |
| 130 | 1st Blood and Saliva Sample |
| 145 | EEG Recording and Task Administration |
| 215 | Clean Up / 2nd Blood and Saliva Sample |
| 230 | End of Session (Taxi) |

10.2.8 Statistical Analyses

10.2.8.1 Visual Processing

10.2.8.1.1 Pattern Reversal Task

As the largest P100 responses are evoked over occipital region sites (Mangun & Hillyard, 1991), the amplitude and latency elicited at the OZ electrode were used as dependant variables in the statistical analyses. To determine the effect of d-amphetamine on the P100 response as a function of visual pathway, a 2 (Drug; placebo/d-amphetamine) x 2 (Pathway; magnocellular/parvocellular) repeated-measures planned contrast was performed for each of the two dependant variables (amplitude and latency). Specifically, for each of amplitude and latency, 1/ the main effect of Drug was tested to determine whether d-amphetamine had an effect on the P100 component for the visual pathways combined, and 2/ the interaction of Drug and Pathway was tested to determine whether the differential processing of the P100 component for the magnocellular and parvocellular pathways was modulated by d-amphetamine.

Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 2). All p-values reported are corrected p-values.
10.2.8.1.2 Visual Field Task

The amplitude and latency of the P100, N200 and P300 components (calculated using PCA), for the central and peripheral visual fields, were used as dependant variables in the statistical analyses. To determine the effect of d-amphetamine on the P100, N200 and P300 response as a function of visual field, a 2 (Drug; placebo/d-amphetamine) x 2 (Visual Field; central/peripheral) repeated-measures planned contrast was performed for each of the two dependant variables (amplitude and latency), for each of the three ERP components (P100, N200 and P300). Specifically, for each of amplitude and latency, for each of the P100, N200 and P300 components, 1/ the main effect of Drug was tested to determine whether d-amphetamine had an effect on the visual fields combined, and 2/ the interaction of Drug and Visual Field was tested to determine whether the differential processing of the central and peripheral visual fields was modulated by d-amphetamine. Therefore, a total of six repeated-measures planned contrasts were performed. Bonferroni adjustments were employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 2). All p-values reported are corrected p-values.

In addition, to determine the effect of d-amphetamine on reaction time as a function of visual field, a 2 (Drug; placebo/d-amphetamine) x 2 (Visual Field; central/peripheral) repeated measures ANOVA was performed for the dependant variable (reaction time). Specifically, the main effect of Drug was tested to determine whether d-amphetamine had an effect on the visual fields combined, and the interaction of Drug and Visual Field was tested to determine whether the differential processing of the central and peripheral visual fields was modulated by d-amphetamine. Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 2). All p-values reported are corrected p-values.

10.2.8.2 Auditory Processing

10.2.8.2.1 Mismatch Negativity Task (MMN)

As the largest MMN responses are evoked over frontal-central scalp regions (Näätänen, 1995), the amplitude and latency elicited at the FZ electrode were used as dependant variables in the statistical analyses. To determine the effect of d-amphetamine on the MMN response, a one-way (Drug; placebo/d-amphetamine) repeated measures ANOVA
was performed for each of the two dependant variables (amplitude and latency). Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 1). All $p$-values reported are corrected $p$-values.

10.2.8.2.2 Startle Reflex/Pre-Pulse Inhibition Task

To determine the effect of $d$-amphetamine on Pulse Alone and PPI, a one-way (Drug; placebo/$d$-amphetamine) repeated measures ANOVA was conducted for each of the two dependant variables (amplitude and latency), for each of the Pulse Alone and PPI conditions. Therefore, a total of four repeated-measures ANOVAs were performed. Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 1). All $p$-values reported are corrected $p$-values.

In addition, as it has previously been reported that a low dose of $d$-amphetamine (5 mg) reduces PPI in a small group of smokers ($n=6$) (Kumari et al., 1998; refer to Section 5.4.2 for details), the present study endeavoured to replicate this result using a larger sample size ($n=14$), and administering a considerably higher dose of $d$-amphetamine (0.42mg/kg, average 30 mg). In order to determine the effect of $d$-amphetamine on Pulse Alone and PPI in smokers, a one-way (Drug; placebo/$d$-amphetamine) repeated measures ANOVA was conducted for each of the two dependant variables (amplitude and latency), for each of the Pulse Alone and PPI conditions, using only a subgroup of smokers. Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 1). All $p$-values reported are corrected $p$-values.

10.2.8.2.3 Auditory Oddball Task

10.2.8.2.3.1 Main Analyses

As the N200 is maximal over frontal-central scalp regions (Winsberg et al., 1997), and the P300 is maximal over parietal scalp regions (Polich & Kok, 1995), the amplitude and latency elicited at the FZ and PZ electrodes, respectively, were used as dependant variables
in the statistical analyses. To determine the effect of \( d \)-amphetamine on the N200 and P300 components, a one-way (Drug; placebo/\( d \)-amphetamine) repeated measures ANOVA was conducted for each of the two dependent variables (amplitude and latency), for each of the two ERP components (N200 and P300). Therefore, a total of four repeated-measures ANOVAs were performed. Bonferroni adjustments were employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 1). All \( p \)-values reported are corrected \( p \)-values.

In addition, to determine the effect of \( d \)-amphetamine on reaction time, a one-way (Drug; placebo/\( d \)-amphetamine) ANOVA was performed, with the dependent variable of reaction time. Further, to determine the effect of \( d \)-amphetamine on accuracy, a Wilcoxon Signed-Rank Test was conducted, with the independent variable drug condition (placebo/\( d \)-amphetamine) and the dependent variable accuracy. This non-parametric test was employed as the data was not normally distributed and transformations could not normalise the distribution. Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean). A Bonferroni adjustment was employed to correct for Type 1 error by dividing alpha by the number of comparisons (i.e. 1). All \( p \)-values reported are corrected \( p \)-values.

10.2.8.3.2 Exploratory Analyses

In order to examine the relationship between changes in P300 latency and reaction time, and changes in P300 amplitude and accuracy, following the administration of amphetamine, two Spearman’s Rho measures of association were performed. Correlations were computed using difference scores (amphetamine-placebo), which were calculated for each variable. This analyses was performed in response to the ambiguity in the literature pertaining to how reaction time and P300 latency are modulated with amphetamine, and whether these two processes are affected similarly by amphetamine (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Halliday et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999; Cooper et al., 2005). Furthermore, there is some inconsistency in the literature pertaining to whether changes in P300 amplitude following amphetamine administration are related to changes in accuracy performance (Coons et al., 1981; Strauss et al., 1984; Brumaghim et al., 1987; McKetin et al., 1999;
Cooper et al., 2005; refer to Section 5.4.3 for details). No correction for multiple comparisons was made as these analyses were exploratory.

10.3 Results

10.3.1 Demographic Characteristics of Participants

Demographic characteristics of the participants are summarised in Table 10.2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.2</td>
<td>3</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.4</td>
<td>2.2</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Current amphetamine use (per year)</td>
<td>2.6</td>
<td>3.6</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Amphetamine use when consumed most (per year)</td>
<td>7.2</td>
<td>12.1</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using amphetamine (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Current ecstasy use (per year)</td>
<td>6.1</td>
<td>5.6</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Ecstasy use when consumed most (per year)</td>
<td>17</td>
<td>16.2</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using ecstasy (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Current marijuana use (per year)</td>
<td>16.2</td>
<td>17.8</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Marijuana use when consumed most (per year)</td>
<td>72.8</td>
<td>117.9</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Period of time using marijuana (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Current cocaine use (per year)</td>
<td>0.7</td>
<td>0.9</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Period of time using cocaine (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>5+</td>
</tr>
<tr>
<td>Alcohol per week (units)</td>
<td>11.73</td>
<td>10.8</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

Note that N=20 and that ‘drug use’ refers to number of occasions the specific drug was consumed in a year

As can be seen in Table 10.2, on average, participants consumed amphetamine, ecstasy, and cocaine, less than once a month in the preceding year, while marijuana was on average consumed approximately once a month over the preceding year (16 times). During the period when participants consumed drugs most frequently in their lifetime, amphetamine was on average consumed less than once a month (7 times), whereas ecstasy was consumed more than once a month (approximately 17 times). During the period when participants consumed marijuana most frequently, participants on average reported to have used marijuana around 1-2 times a week during that year (approximately 73 times).

10.3.2 Level of $d$-amphetamine in Blood and Saliva

The blood and saliva data were not available due to circumstances out of the experimenter’s control. They will thus not be reported.
10.3.3 Effect of \textit{d}-amphetamine on Event Related Potentials

Note that the reported means for the amplitude and latency of ERP components may not resemble the waveforms due to the effect of latency jitter, which is typical of ERP research.

10.3.3.1 Visual Processing

10.3.3.1.1 Effect of d-amphetamine on the Pattern Reversal task

Note that data from one participant was omitted from analyses due to technical difficulties. The grand averages for the P100 component, elicited at the OZ scalp site, for the magnocellular and parvocellular visual pathways, for placebo and \textit{d}-amphetamine conditions, are shown in Figure 10.1.

\textbf{Figure 10.1} Grand Averaged ERPs are shown for Magnocellular and Parvocellular Stimuli for \textit{d}-amphetamine and Placebo Drug Conditions Separately. \textit{Note that the P100 peaked approximately 100ms following stimulus onset for parvocellular stimuli and at approximately 120 ms for magnocellular stimuli. Also note that for parvocellular and magnocellular stimuli the P100 amplitude is larger for \textit{d}-amphetamine relative to placebo.}

As depicted in Figure 10.1, \textit{d}-amphetamine increased the amplitude of the P100 component for the visual pathways combined, relative to placebo, at a trend-level, $F(1, 17) = 5.46$, $p = .06$. As illustrated in Table 10.3, the differential processing of the P100
amplitude of the magnocellular and parvocellular pathways was not modulated by \(d\)-amphetamine, \(F(1, 17) = 0.60, p=.90\). As depicted in Figure 10.1, \(d\)-amphetamine had no effect on the latency of the P100 component for the visual pathways combined, relative to placebo, \(F(1, 13) = 1.24, p = .57\). In addition, the differential processing of the P100 latency of the magnocellular and parvocellular pathways was not modulated by \(d\)-amphetamine, \(F(1, 13) = 0.22, p = .65\).

Table 10.3 Means (Standard Deviations) for P100 Amplitude and Latency for the Magnocellular and Parvocellular Pathways across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>(d)-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magno Amplitude</td>
<td>7.10 (2.02)</td>
<td>8.00 (2.71)</td>
</tr>
<tr>
<td>Parvo Amplitude</td>
<td>13.20 (5.17)</td>
<td>14.77 (6.29)</td>
</tr>
<tr>
<td>Magno Latency</td>
<td>122.77 (16.66)</td>
<td>116.62 (17.42)</td>
</tr>
<tr>
<td>Parvo Latency</td>
<td>104.77 (11.71)</td>
<td>103.54 (14.07)</td>
</tr>
</tbody>
</table>

10.3.3.1.2 Effect \(d\)-amphetamine on the Visual Field Task

10.3.3.1.2.1 Behavioural

\(d\)-amphetamine (mean = 0.43, SD = 0.04) had no effect on reaction time for the visual fields combined, relative to placebo (mean = 0.45, SD = 0.04), \(F(1, 19) = 2.95, p = .20\). Furthermore, \(d\)-amphetamine had no effect on reaction time as a function of visual field, \(F(1, 19) = 0.89, p = .71\).

10.3.3.1.2.2 P100

The grand averages for the P100 component, for the central and peripheral visual fields, for placebo and \(d\)-amphetamine conditions, are shown in Figure 10.2. Note that as the P100 is an early component that occurs prior to discrimination of target from nontarget stimuli, target and nontarget stimuli were combined in each of the central and peripheral averages, for each drug condition.
Figure 10.2 Grand Averaged ERPs are shown for Central and Peripheral Visual Field Stimuli for \( d \)-amphetamine and Placebo Drug Conditions Separately. Note that the P100 peaked similarly for both central and peripheral stimuli, with little difference in P100 latency and amplitude between the two drug conditions.

\( d \)-amphetamine had no effect on the amplitude of the P100 component for the visual fields combined, relative to placebo, \( F(1, 19) = 0.56, p = .93 \). As depicted in Figure 10.2 and Table 10.4, the differential processing of the P100 amplitude of the central and peripheral visual fields was not modulated by \( d \)-amphetamine, \( F(1, 19) = 1.35, p = .52 \). \( d \)-amphetamine had no effect on the latency of the P100 component for the visual fields combined, relative to placebo, \( F(1, 19) = 0.65, p = .86 \). Furthermore, as can be seen in Table 10.4, the differential processing of the P100 latency of the central and peripheral visual fields was not modulated by \( d \)-amphetamine, \( F(1, 19) = 1.93, p = .36 \).

Table 10.4 Means (Standard Deviations) for P100 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>( d )-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>42.77 (20.70)</td>
<td>41.91 (24.08)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>31.64 (21.75)</td>
<td>35.45 (19.10)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>115.6 (17.26)</td>
<td>114.2 (21.15)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>116.00 (19.99)</td>
<td>120.9 (24.08)</td>
</tr>
</tbody>
</table>
The grand averages for the N200 component, for the central and peripheral visual fields, for placebo and d-amphetamine conditions, are shown in Figure 10.3. Note that only the target stimuli for the central and peripheral stimuli were included in the averages.

**Figure 10.3** Grand Averaged ERPs are shown for Central and Peripheral Visual Field Stimuli for d-amphetamine and Placebo Drug Conditions Separately. Note that for central and peripheral stimuli the N200 peaked at a similar time across drug conditions. Also note that the N200 amplitude for central stimuli is larger in the d-amphetamine condition relative to the placebo condition, however, for peripheral stimuli the N200 amplitude is larger in the placebo condition compared to the d-amphetamine condition. The P300 peaked earlier and had a larger amplitude for the central stimuli compared to the peripheral stimuli. Also note that for both central and peripheral stimuli there is little difference between the two drug conditions in the latency and amplitude of the P300.

d-amphetamine had no effect on the amplitude of the N200 component for the visual fields combined, relative to placebo, $F(1, 16) = 0.88, p = .72$. However, as can be seen in Figure 10.3, the differential processing of the N200 amplitude for the central and peripheral visual fields increased with d-amphetamine, relative to the placebo, at a trend level, $F(1, 16) = 5.80, p = .06$. This is highlighted in Table 10.5, where for centrally presented stimuli, d-amphetamine produced a larger amplitude relative to the placebo condition, whereas, for
peripherally presented stimuli, d-amphetamine produced a smaller amplitude relative to the placebo condition. In terms of N200 latency, d-amphetamine had no effect on the N200 component for the visual fields combined, relative to placebo, F(1, 16) = 3.64, p = .15. Furthermore, the differential processing of the N200 latency of the central and peripheral visual fields was not modulated by d-amphetamine, F(1, 16) = 0.02, p = .89.

Table 10.5 Means (Standard Deviations) for N200 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>-47.31 (72.95)</td>
<td>-88.22 (40.31)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>-71.39 (80.36)</td>
<td>-56.63 (65.99)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>166.82 (14.60)</td>
<td>156.94 (16.85)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>169.53 (22.93)</td>
<td>160.35 (25.42)</td>
</tr>
</tbody>
</table>

10.3.3.1.2.4 P300

The grand averages for the P300 component, for the central and peripheral visual fields, for placebo and d-amphetamine conditions, are shown in Figure 10.3. Note that only the target stimuli for the central and peripheral stimuli were included in the averages. d-amphetamine had no effect on the amplitude of the P300 component for the visual fields combined, compared to placebo, F(1, 18) = 1.07, p = .63. As can be seen in Figure 10.3, the differential processing of the P300 amplitude of the central and peripheral visual fields was not modulated by d-amphetamine, F(1, 18) = 0.20, p = .66. As the P300 latency data were not normally distributed, square root transformations were performed to normalise the data. d-amphetamine had no effect on the latency of the P300 component for the visual fields combined, relative to placebo, F(1, 16) = 0.72, p = .82. Furthermore, as depicted in Table 10.6, the differential processing of the P300 latency of the central and peripheral visual fields was not modulated by d-amphetamine, F(1, 16) = 0.51, p = 1.00.

Table 10.6 Means (Standard Deviations) for P300 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>487.90 (179.01)</td>
<td>527.13 (220.90)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>294.34 (106.95)</td>
<td>312.87 (96.71)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>408.94 (35.66)</td>
<td>411.18 (18.53)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>457.06 (74.01)</td>
<td>473.65 (66.87)</td>
</tr>
</tbody>
</table>
10.3.3.2 Auditory Processing

Data from one participant was omitted from all auditory analyses due to technical difficulties.

10.3.3.2.1 Effect of d-amphetamine on the Mismatch Negativity Task

Note that data from three participants were excluded from analyses as no clear MMN was observed in the placebo condition. Although not clearly illustrated in Figure 10.4, d-amphetamine (mean = -4.40, SD = 3.24) had no effect on the amplitude of the MMN response, relative to placebo (mean = -6.15, SD = 4.10), $F(1, 15) = 2.25$, $p = .15$. The MMN latency data were not normally distributed, therefore, square root transformations were performed to normalise the data. d-amphetamine (mean = 177.25, SD = 31.55) decreased the latency of the MMN response relative to placebo (mean = 192.25, SD = 21.16), at a trend-level, $F(1, 15) = 3.42$, $p = .08$.

![Figure 10.4](image-url) Grand Averaged ERPs are shown for MMN, at the FZ scalp site, for d-amphetamine and Placebo Drug Conditions Separately. *Note that MMN amplitude is larger for placebo compared to d-amphetamine, however, MMN peaked earlier in the d-amphetamine condition relative to placebo.*

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10.3.3.2.2 Effect of d-amphetamine on the Startle Reflex/Pre-Pulse Inhibition Task

The grand average for the startle response, for placebo and $d$-amphetamine conditions, is shown in Figure 10.5.

![Grand Averaged ERPs for Placebo and d-amphetamine conditions](image)

**Figure 10.5** Grand Averaged ERPs are shown for the Startle Response for $d$-amphetamine and Placebo Drug Conditions Separately. *Note that although the Startle Response appears to be larger in the $d$-amphetamine condition compared to placebo, the time of startle peak did not differ significantly for the drug conditions.*

As the startle response amplitude data were not normally distributed, square root transformations were performed to normalise the data. Although not clearly illustrated in Figure 10.5, $d$-amphetamine had no effect on the amplitude of the startle response relative to placebo, $F(1, 18) = 0.01, p = .94$. As can be seen in Table 10.7, $d$-amphetamine had no effect on the latency of the startle response relative to placebo, $F(1, 16) = 1.20, p = .29$. As the PPI amplitude data were not normally distributed, square root transformations were performed to normalise the data. As depicted in Table 10.7, $d$-amphetamine had no effect on the amplitude of the PPI relative to placebo, $F(1, 16) = 0.05, p = .83$. Similarly, $d$-amphetamine had no effect on the latency of the PPI relative to placebo, $F(1, 14) = 0.06, p = .80$. 
Table 10.7 Means (Standard Deviations) for Amplitude and Latency for the Startle Response and PPI across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startle Amplitude</td>
<td>163.11 (102.64)</td>
<td>170.47 (122.22)</td>
</tr>
<tr>
<td>Startle Latency</td>
<td>107.58 (8.71)</td>
<td>105.05 (6.27)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Amplitude</td>
<td>0.50 (0.24)</td>
<td>0.51 (0.30)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Latency</td>
<td>-0.48 (0.32)</td>
<td>-0.55 (0.28)</td>
</tr>
</tbody>
</table>

As it has previously been reported that a low dose of \( d \)-amphetamine (5mg) attenuates PPI in a subgroup of 6 smokers (Kumari et al., 1998; refer to Section 5.4.2 for details), the present study endeavoured to confirm this result. Therefore, the above analyses were repeated using only a subgroup of smokers, thus, the number of participants decreased from 19 to 14. As the startle response amplitude data were not normally distributed for the smoker subgroup, square root transformations were performed to normalise the data. \( d \)-amphetamine had no effect on the amplitude of the startle response in smokers, relative to placebo, \( F(1, 13) = 0.98, p = .34 \). As depicted in Table 10.8, \( d \)-amphetamine had no effect on the latency of the startle response in smokers, relative to placebo, \( F(1, 13) = 1.34, p = .27 \). As the PPI amplitude data were not normally distributed for the smoker subgroup, square root transformations were performed to normalise the data. \( d \)-amphetamine had no effect on the amplitude of the PPI in smokers, relative to placebo, \( F(1, 13) = 0.19, p = .67 \). Similarly, \( d \)-amphetamine had no effect on the latency of the PPI in smokers, relative to placebo, \( F(1, 12) < 0.01, p = .99 \).

Table 10.8 Means (Standard Deviations) for Amplitude and Latency for the Startle Response and PPI across Drug Conditions in Smokers

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startle Amplitude</td>
<td>186.15 (109.59)</td>
<td>162.59 (115.55)</td>
</tr>
<tr>
<td>Startle Latency</td>
<td>108.43 (9.55)</td>
<td>105.0 (6.06)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Amplitude</td>
<td>0.39 (0.40)</td>
<td>0.43 (0.38)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Latency</td>
<td>-0.57 (0.24)</td>
<td>-0.57 (0.25)</td>
</tr>
</tbody>
</table>

10.3.3.2.3 Effect of \( d \)-amphetamine on the Auditory Oddball Task

10.3.3.2.3.1 Behavioural

The reaction time data were not normally distributed, therefore, square root transformations were performed to normalise the data. \( d \)-amphetamine (mean = 0.36, SD =0.05) significantly decreased reaction time relative to placebo (mean = 0.38, SD = 0.04),
F(1, 19) = 8.90, \( p = .01 \). Furthermore, \( d \)-amphetamine (mean = 96.76, SD = 3.55) significantly increased accuracy relative to placebo (mean = 92.66, SD = 6.62), \( T = 28, p < .05 \).

10.3.3.2.3.2 **N200**

The grand average for the N200 component, elicited at the FZ scalp site, for placebo and \( d \)-amphetamine conditions, during the auditory oddball task, is shown in Figure 10.6. Note that only the target stimuli were included in the averages. Although not clearly illustrated in Figure 10.6, \( d \)-amphetamine (mean = -3.17, SD = 1.37) had no effect on the amplitude of the N200 component compared to placebo (mean = -2.77, SD = 2.56), F(1, 16) = 0.74, \( p = .40 \). Similarly, \( d \)-amphetamine (mean = 230.63, SD = 34.28) had no effect on the latency of the N200 component compared to placebo (mean = 230.32, SD = 26.35), F(1, 18) < 0.01, \( p = .98 \).

\[ \text{Figure 10.6 Grand Averaged ERPs are shown for the Auditory Oddball Task for } d\text{-amphetamine and Placebo Drug Conditions Separately. Note that peak amplitude of the N200 is larger in the } d\text{-amphetamine condition relative to the placebo condition. However, there is no difference between drug conditions in the time that the N200 peaks.} \]
10.3.3.2.3.3 P300

The grand average for the P300 component, elicited at the PZ scalp site, for placebo and d-amphetamine conditions, during the auditory oddball task, is shown in Figure 10.7. Note that only the target stimuli were included in the averages. Although not clearly illustrated in Figure 10.7, d-amphetamine (mean = 11.24, SD = 4.76) had no effect on the amplitude of the P300 component compared to placebo (mean = 10.33, SD = 4.28), F(1, 18) = 0.62, p = .44. As can be seen in Figure 10.7, d-amphetamine (mean = 358.25, SD = 10.40) significantly reduced the latency of the P300 component relative to placebo (mean = 378.50, SD = 26.47), F(1, 14) = 7.42, p = .02.

![Figure 10.7](image)

**Figure 10.7** Grand Averaged ERPs are shown for the Auditory Oddball Task for d-amphetamine and Placebo Drug Conditions Separately. *Note that peak amplitude of the P300 is larger and occurs earlier in the d-amphetamine compared to the placebo condition.*

10.3.3.2.3.4 Exploratory Analyses

Decreases in the latency of the P300 component following d-amphetamine consumption were found to be positively associated with decreases in reaction time following d-amphetamine consumption, r (19) = 0.51, p = .03, two-tailed. However, changes in P300 amplitude following d-amphetamine consumption were not found to be associated with increases in accuracy following d-amphetamine consumption, r (18) = 0.03, p = .91, two-tailed.
10.4 Discussion

The present experiment examined the acute effects of 0.42mg/kg \(d\)-amphetamine on visual and auditory processes relevant to driving. Specifically, these were: divergent visual system pathways (the magnocellular and the parvocellular visual pathways); aspects of visual field processing (central and peripheral visual fields); perceptual detection of auditory change; early sensory gating; selective attention; resource allocation; and speed of processing. As there is limited research that has examined the acute effects of amphetamine on specific ERPs, the present discussion will discuss trend level findings.

The present experiment found that the early processing of visual information, occurring within the magnocellular and parvocellular visual pathways, improved with \(d\)-amphetamine at a trend-level (denoted by an increase in the amplitude of the P100 component for the visual pathways combined). In addition, \(d\)-amphetamine differentially affected different regions of the visual field in terms of selective attention, at a trend-level (denoted by an increase in N200 amplitude for stimuli presented centrally, and a decrease in N200 amplitude for stimuli presented peripherally). In terms of auditory processing, there was a trend for \(d\)-amphetamine to improve the speed that a comparator process detects changes in auditory stimulation, noted by a decrease in MMN latency. Furthermore, \(d\)-amphetamine was found to improve the speed at which auditory information was processed (denoted by a decrease in P300 latency), which was substantiated with a corresponding improvement in reaction time and accuracy performance. Moreover, exploratory analyses revealed that this improvement in processing speed, following \(d\)-amphetamine consumption, was positively associated with improvements to reaction time.

10.4.1 Effect of \(d\)-amphetamine on Visual Processing

10.4.1.1 Effect of \(d\)-amphetamine on the Magnocellular and Parvocellular Visual Pathways

The present experiment found that \(d\)-amphetamine improved, at a trend level, early visual processing, denoted by an increase in P100 amplitude for the parvocellular and magnocellular visual pathways combined. It is difficult to directly relate the present results to previous research, as there have been no studies that have examined the acute effects of \(d\)-amphetamine, or any other dopamine agonists, on these divergent visual system pathways.
However, as the P100 component is modulated as a function of visual attention (Heinze et al., 1990; Hillyard & Anllo-Vento, 1998; Luck et al., 1994; Mangun, 1995; Mangun & Hillyard, 1990), the trend-level increase in P100 amplitude noted in the present experiment, following d-amphetamine consumption, can be argued to support previous cognitive research that has consistently shown amphetamines to improve attentional functions (Kelly et al., 1991; Koelega, 1993; Comer et al., 1996; Ward et al., 1997; McKetin et al., 1999; Wachtel & de Wit, 1999; de Wit et al., 2002; Cami et al., 2000; Johnson et al., 2000). Furthermore, the present results are consistent with the findings reported in Experiment 1 (Chapter 7), Experiment 2 (Chapter 8) and Experiment 3 (Chapter 9), which demonstrate that aspects of attention improved following the administration of amphetamines. However, by extension, the present results indicate that previously reported amphetamine-related improvements in attention may be associated with amphetamine-induced enhancements in the early processing of visual information within the visual pathways.

The relationship between early visual processing and attention is further highlighted by previous studies that have consistently shown that individuals characterised by poor attention function, such as in schizophrenia, demonstrate significant dysfunctions in early-stage visual processing (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006). Specifically, research has shown that the early P100 component is significantly impaired in schizophrenia (Romani et al., 1986; Matsuoka et al., 1996; Basinka, 1998; Butler et al., 2001, 2005; Foxe et al., 2001; Doniger et al., 2002; Keri et al., 2002, 2004, 2005; Spencer et al., 2003; Schechter et al., 2005; Kim et al., 2006). As amphetamines have consistently been shown to improve attention (Experiment 1 (Chapter 7), Experiment 2 (Chapter 8) and Experiment 3 (Chapter 9) of present thesis; Kelly et al., 1991; Koelega, 1993; Comer et al., 1996; Ward et al., 1997; McKetin et al., 1999; Wachtel & de Wit, 1999; de Wit et al., 2002; Cami et al., 2000; Johnson et al., 2000), and previous clinical research has shown that individuals characterised by poor attention manifest deficits to the P100 component, the present results are in accordance with these reports, as an increase in P100 amplitude was noted with d-amphetamine. These results are, therefore, consistent with the view that the P100 is modulated by attention (Heinze et al., 1990; Hillyard & Anllo-Vento, 1998; Luck et al., 1994; Mangun, 1995; Mangun & Hillyard, 1990).
In terms of driving, the present results indicate that the minimal driving impairment reported in Experiment 1, 2-3 hrs following \textit{d}-amphetamine consumption, does not appear to be associated with impairments to early visual processing in general, nor with the differential functioning of the parvocellular and magnocellular visual pathways. Specifically, the present findings indicate that a single low dose of \textit{d}-amphetamine enhances a driver’s efficiency in processing fine detailed information and colour (such as, traffic lights or road signs), in addition to enhancing a driver’s capacity to rapidly detect motion and the overall detail of the traffic environment (such as, the movement of cars and pedestrians).

In summary, the present results demonstrate that an acute dose of 0.42mg/kg \textit{d}-amphetamine improves, at a trend level, the processing of high contrast, pattern, colour and fine-detailed stimulus information, in addition to the rapid processing of coarse visual stimuli and motion (denoted by an increase in the amplitude of the P100 component for the visual pathways combined). In terms of driving, the present results indicate that impairments to the magnocellular and parvocellular visual processing systems do not appear to be associated with the minimal decreases to simulated driving performance observed following \textit{d}-amphetamine consumption (Experiment 1; Chapter 7), as \textit{d}-amphetamine was shown to improve early visual processing in general.

\subsection*{10.4.1.2 Effect of \textit{d}-amphetamine on the Central and Peripheral Visual Fields}

The present experiment revealed a trend for \textit{d}-amphetamine to enhance indices of selective attention for information presented in the central visual field (denoted by increases in N200 amplitude), whereas it produced decrements to indices of selective attention for information presented in the peripheral visual field (denoted by decreases in N200 amplitude). These results provide only limited evidence to support the notion that \textit{d}-amphetamine differentially affects different regions of the visual field.

It is difficult to directly relate the present results to previous research, as there have been no ERP studies that have examined the acute effects of \textit{d}-amphetamine, or any other dopamine agonists, on the central and peripheral visual fields. However, previous behavioural research that has examined the differential effects of \textit{d}-amphetamine on different regions of the visual field, have indicated that \textit{d}-amphetamine improves
performance for stimuli presented centrally, with little or no change observed for stimuli presented in the periphery (Mills et al., 2001). The present d-amphetamine findings are, to some extent, consistent with this, as d-amphetamine improved attention for information presented centrally and impaired attentional processes for information presented in the periphery. These results, thus, provide some support for the ‘tunnel vision’ hypothesis (discussed in Section 5.3.2).

Interestingly, d-amphetamine differentially affected different regions of the visual field in terms of selective attention (N200) only, and not for the earlier visual processes (P100) or later stimulus evaluation and response processes (P300). This is to some extent consistent with the results from the Pattern Reversal Task discussed in Section 10.4.1.1. These results revealed that d-amphetamine enhanced early peripheral and central processing (denoted by a trend-level increase in P100 amplitude), which represents improvements to magnocellular and parvocellular processing (whereby magnocells receive information from larger regions of the visual field and parvocellular neurons receive input from smaller regions of the visual field).

In terms of driving, the present results suggest that the minimal d-amphetamine-related driving impairment reported in the present thesis, may be associated with possible amphetamine-induced decrements in selectively attending to information presented in the periphery. Although only a trend level finding, it has previously been argued that efficient use of the peripheral visual field is particularly important to driving, and impairments to this function can have negative implications to traffic safety (Johnson & Keltner, 1983; Szlyk et al., 1991, 1992; Wood & Troutbeck, 1992, 1993, 1994; Owsley, Ball et al., 1998; Owsley, McGwin et al., 1998; Sims et al., 2000).

The d-amphetamine-induced reduction to the N200 component for information presented in the periphery, suggests that driver’s under the influence of d-amphetamine may not efficiently attend to and discriminate objects in the periphery, such as traffic lights. Furthermore, the noted improvement in indices of selective attention for information presented in the fovea (indexed by an increase in N200 amplitude), suggests that driver’s may be restricting attention to their focal point, which may be consequently impairing attentional mechanisms available for peripheral processing (i.e. ‘tunnel vision’ effects).
Thus, the results of the present experiment provide some support for an amphetamine-induced ‘tunnel vision’ hypothesis. However, as the present findings were only trend-level, additional research is warranted to explore this possibility further, particularly as previous reports have highlighted the important function that the peripheral visual field has in safe driving (Johnson & Keltner, 1983; Szlyk et al., 1991, 1992; Wood & Troutbeck, 1992, 1993, 1994; Owsley, Ball et al., 1998; Owsley, McGwin et al., 1998; Sims et al., 2000).

In summary, the present findings suggest that, at a trend level, an acute dose of 0.42mg/kg d-amphetamine enhances indices of selective attention when information is presented in the central visual field (as indexed by an increase in N200 amplitude), but impairs indices of selective attention when information is presented in the peripheral visual field (as indexed by a decrease in N200 amplitude). In terms of driving, the present results suggest that the decreases in driving performance observed following a single acute therapeutic dose of d-amphetamine (Chapter 7), may be attributed to decrements to peripheral visual field processing. Furthermore, the present results provide some suggestion that ‘tunnel vision’ effects may be associated with the amphetamine-related driving impairment.

10.4.2 Effect of d-amphetamine on Auditory Processing

10.4.2.1 Effect of d-amphetamine on Mismatch Negativity (MMN)

The present experiment found d-amphetamine improved, at a trend-level, the speed at which changes in auditory information were automatically detected. This was denoted by a decrease in the latency of the MMN response. It is difficult to directly relate these results to previous research, as there have been no studies that have examined the acute effects of d-amphetamine on this early pre-attentive comparative process. However, there has been limited research that has examined the effects of other dopamine agonists, namely methylphenidate and apomorphine, on the MMN response.

Previous research has generally shown that dopamine agonist drugs, such as methylphenidate and apomorphine, do not modulate MMN (Hansenne et al., 2003; Winsberg et al., 1997). Several factors could explain the possible inconsistency in results between previous dopamine research and the present results. For instance, although d-amphetamine and dopamine agonist drugs, such as methylphenidate and apomorphine, both have similar effects on dopamine activity, d-amphetamine also influences other
neurotransmitter activity, namely norepinephrine and serotonin. This difference in neurotransmitter activity may consequently produce different effects to this early pre-attentive component.

Furthermore, differences in population sample between previous research and the present experiment may be associated with the inconsistent results. Specifically, the present experiment assessed the effects of amphetamine on healthy adults, whereas, in the study by Winsberg et al. (1997), the sample assessed were ADHD children. Although the present results indicate that $d$-amphetamine improved the speed of the ‘mismatch’ process, this was only a trend-level finding. Furthermore, previous dopamine research has shown no effect on the MMN. Therefore, further research is necessary to confirm the present result.

In terms of driving, the present findings indicate that the $d$-amphetamine-related driving impairment reported in the present thesis (Experiment 1; Chapter 7), 2-3 hrs following $d$-amphetamine consumption, does not appear to be associated with disruptions to the MMN response. The present findings indicate that a low $d$-amphetamine dose has minimal, and possibly even enhancing, effects on a driver’s ability to automatically discriminate auditory changes within the traffic environment. This suggests that following a low dose of $d$-amphetamine, drivers can efficiently detect auditory changes, such as car horns, irrespective of where attention is currently located.

In summary, the present results indicate that, at a trend-level, an acute dose of 0.42mg/kg $d$-amphetamine speeds the process in which auditory information is automatically discriminated, as indexed by a decrease in MMN latency. Thus, in terms of driving, the present findings indicate that the $d$-amphetamine-related reduction in driving performance observed in the present thesis is unlikely to be related to deficits in the ability to unconsciously discriminate auditory changes in the traffic environment.

10.4.2.2 Effect of $d$-amphetamine on Pre-Pulse Inhibition of the Acoustic Startle Reflex

The present experiment found that an acute dose of $d$-amphetamine had no effect on PPI at 150-180 min following drug consumption, in healthy adults. Unlike much of the preclinical work, the present experiment did not find that an acute dose of $d$-amphetamine reduced PPI response following drug ingestion (Mansbach et al., 1988; Swerdlow et al., 1994,
The present results, however, support previous research using humans (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2002a; Alessi et al. 2003; Swerdlow et al., 2003), which have consistently failed to demonstrate that an acute dose of \(d\)-amphetamine (ranging from 5 mg to 20 mg \(d\)-amphetamine) attenuates PPI, 150-180 minutes after drug ingestion.

However, it is important to note that \(d\)-amphetamine has been shown to disrupt PPI in healthy adults, 90 min (Hutchison & Swift, 1999) and 25-40 min (Swerdlow et al., 2003) after the administration of 20 mg \(d\)-amphetamine. The decision to conduct the Startle Reflex/Pre-Pulse Inhibition Task, in the present experiment, at 150-180 min following \(d\)-amphetamine consumption, was based on the overriding priority to assess electrophysiological responses within a similar time frame as when driving performance was evaluated in Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and Experiment 3 (Chapter 9). This was to allow the effects of \(d\)-amphetamine on PPI to be discussed in relation to the effects of amphetamine on driving performance. This time frame was also selected based on the pharmacokinetic profile of orally administered \(d\)-amphetamine, which indicates that the duration of action, in terms of behavioural and physiological effects, ranges from 2-4 hrs after drug ingestion (Kupietz, et al., 1985; Angrist, et al., 1987; Brauer et al., 1996).

Although differences in the time that PPI was assessed may explain why a \(d\)-amphetamine disrupted PPI effect was not observed in the present study, as compared with the findings reported by Hutchison and Swift (1999) and Swerdlow et al. (2003), there are other factors that could also elucidate the discrepancy. These include, considerable differences in experimental design (for instance, Swerdlow et al. (2003) only noted a reduction in PPI when a within-subject design was employed, where pre- and post- drug performance was compared; whereas, in the present study the effect of \(d\)-amphetamine on PPI was assessed on a separate day to placebo), stimulus characteristics (i.e. prepulse intervals), response ranges, and other design features (refer to Table 10.9 for a comparison of the present study to the Hutchison and Swift (1999) study). These discrepancies in results highlight that future research need to employ consistent methodologies when investigating the effects of amphetamines on PPI, so that direct comparisons can be made between studies.
Table 10.9 Similarities and Differences between the Present Study and the Hutchison and Swift (1999) Study

<table>
<thead>
<tr>
<th>Present study</th>
<th>Hutchison &amp; Swift (1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Male and Female (n=38)</td>
</tr>
<tr>
<td>Dose amphetamine</td>
<td>0.42 mg/kg average 30 mg</td>
</tr>
<tr>
<td>Study Design</td>
<td>Within subject; no pretest baseline session</td>
</tr>
<tr>
<td>Measure of blink</td>
<td>EOG</td>
</tr>
<tr>
<td>Eyeblink side</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Background noise (dB (A))</td>
<td>70</td>
</tr>
<tr>
<td>Prepulse type</td>
<td>White noise</td>
</tr>
<tr>
<td>Prepulse duration</td>
<td>20ms (0ms rise/fall time)</td>
</tr>
<tr>
<td>Prepulse intensity (dB over background)</td>
<td>80</td>
</tr>
<tr>
<td>Prepulse interval (ms)</td>
<td>60</td>
</tr>
<tr>
<td>Pulse intensity (dB over background)</td>
<td>108</td>
</tr>
<tr>
<td>Pulse duration (ms)</td>
<td>40</td>
</tr>
<tr>
<td>Measurement times (min after drug ingestion)</td>
<td>150 - 180</td>
</tr>
</tbody>
</table>

The present findings do not support previous research that has shown d-amphetamine to disrupt PPI in smokers, 150 min following drug consumption (Kumari et al., 1998). This discrepancy in results may be understood in several ways, such as, differences in drug dose (the present study administered an average dose of 30 mg d-amphetamine, whereas Kumari et al. (1998) administered a 5 mg dose of d-amphetamine), drug condition comparisons (the present within-subject experiment compared placebo and d-amphetamine effects obtained on separate testing days, whereas, Kumari et al. (1998) compared d-amphetamine performance to performance prior to drug administration on the same day), and sample size (in the present study there were 14 smokers in each drug condition, whereas, in the Kumari et al. (1998) study there were only 6 smokers in the d-amphetamine condition). Although considerable differences in drug dose and experimental design are likely to be attributed to the discrepancy in results, further research is necessary to clarify this inconsistency.

In terms of driving, the present findings indicate that the reduction in simulated driving performance reported in Experiment 1 (Chapter 7), 120-180 min following d-amphetamine consumption, do not appear to be associated with disruptions to PPI. Consistent with previous research, the present results indicate that following a low dose of d-amphetamine, drivers are able to automatically ‘screen out’ irrelevant or intrusive sensory stimuli 150 min after drug consumption. This suggests that following the administration of d-amphetamine, drivers are able to regulate environmental inputs and selectively allocate attentional resources to relevant stimuli.
In summary, the results of the present experiment suggest that an acute dose of 0.42mg/kg \(d\)-amphetamine does not disrupt PPI, at 150-180 min following drug administration. In terms of driving, this suggests that the reduction in driving performance observed 120-180 min following \(d\)-amphetamine consumption, is unlikely to be related to disruptions to sensorimotor gating, as \(d\)-amphetamine was not found to affect this early inhibitory mechanism.

10.4.2.3 Effect of \(d\)-amphetamine on the Auditory Oddball Task

The present experiment found \(d\)-amphetamine improved the speed at which auditory information was processed, as indicated by decreases in P300 latency. This enhancement in information processing was consistent with improvements in reaction time and accuracy, following \(d\)-amphetamine consumption. Furthermore, the improvement in processing speed, following \(d\)-amphetamine consumption, was positively associated with improvements in reaction time, suggesting that the two were related.

Few studies have shown \(d\)-amphetamine to modulate the P300 component (Halliday et al., 1994; McKetin et al., 1999), which is argued to provide an index of general cognitive efficiency (Donchin & Coles, 1988). However, consistent with the present results, Halliday et al. (1994) found that 10 mg \(d\)-amphetamine speeded P300 latency and reaction time. Furthermore, similar to the present findings, Halliday et al. (1994) and McKetin et al., (1999) failed to report any \(d\)-amphetamine effects on P300 amplitude when assessed at the Pz scalp site. Interestingly, McKetin et al., (1999) found \(d\)-amphetamine increased P300 amplitude when this waveform was assessed at the vertex (Cz electrode). However, as it is well established that the P300 is maximal at parietal scalp sites (Picton, 1992; Polich & Kok, 1995), particularly at the Pz electrode, these latter findings need to be addressed with caution. To the author’s knowledge, there are no other studies that have examined the acute effects of \(d\)-amphetamine on the P300 component. However, consistent with the present findings, decreases in P300 latency have been observed following the administration of other stimulants, namely methylphenidate (Brunaghim et al., Study 2, 1987; Cooper et al., 2005).

In addition, the present experiment found that the speeding of the P300 component corresponded to improvements in reaction time and accuracy. Although this contradicts
much of the previous work that indicates that stimulants improve primarily post-evaluation processes (i.e. reaction time but not P300 latency; Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Halliday et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999), there have been some reports that are consistent with the present findings (Halliday et al., 1994; McKetin et al., 1999; Brumaghim et al., Study 2, 1987; Cooper et al., 2005), indicating that stimulants speed both evaluation and response time. This discrepancy in results may be attributed to differences in the drug administered. With exception to the study by Halliday et al. (1994) and McKetin et al. (1999), previous reports have explored the effects of methylphenidate on the P300 component. Although both methylphenidate and d-amphetamine facilitate dopaminergic activity and have similar pharmacodynamic effects, methylphenidate is less potent than d-amphetamine and, therefore, may modulate the P300 differently (National Institute on Drug Abuse (NIDA), 2006).

The present results are consistent with previous cognitive reports that have shown that a low dose of d-amphetamine improves perceptual speed, indicated by improvements in information processing (Kennedy et al., 1990; Fillmore et al., 2005) and reaction time (Fillmore et al., 2005; Asghar et al., 2003; McKetin et al., 1999; Servan-Shreiber et al., 1998; Kumari et al., 1997; Ward et al., 1997; Halliday et al., 1994; Fleming et al., 1995; Johnson et al., 2000; Rapoport et al., 1980). Furthermore, the results from Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and Experiment 3 (Chapter 9), indicated some minimal improvements in information processing following the administration of amphetamines.

Specifically, in Experiment 1 (Chapter 7), there was a trend for d-amphetamine to improve the speed at which information was processed measured with the Inspection Time task, and decrease reaction time during a sustained attention task. These findings were substantiated with those reported in Experiment 2 (Chapter 8) and Experiment 3 (Chapter 9), which similarly revealed methamphetamine improved reaction time during a sustained attention task. These results, therefore, support the present findings indicating that a low dose of amphetamine improves general cognitive efficiency. However, by extension, the present results indicate that amphetamine-related improvements in perceptual speed appear to be attributed to enhancements in the speed that information is evaluated and processed, in addition to response time.
In terms of driving, the present results suggest that following a low dose of \(d\)-amphetamine, drivers would show improvements in the speed at which information from the traffic environment is evaluated and processed. Furthermore, the present findings indicate that the accuracy at which traffic information is processed, and subsequently responded to, would also be enhanced following a low dose of \(d\)-amphetamine. Therefore, based on these results, it can be argued that the decrease in driving performance observed in Experiment 1, does not appear to be associated with decrements in the speed and accuracy that information is evaluated and processed, or in the time it takes the driver to respond to changes in traffic conditions.

In summary, the present findings suggest that an acute dose of 0.42mg/kg \(d\)-amphetamine improves information processing speed, by enhancing the speed (indexed by decreases in P300 latency) and quality at which information is evaluated (indexed by increases in accuracy) and responded to (indexed by decreases in reaction time). In terms of driving, the present findings indicate that the reduction in simulated driving performance, observed in Experiment 1, 2-3 hours following \(d\)-amphetamine consumption, is unlikely to be related to disruptions in the speed or accuracy at which information is evaluated and processed, or in the time it takes to respond to traffic conditions.

10.4.3 Summary of the Effect of \(d\)-amphetamine on Visual and Auditory Cognitive Processes and its Implications to Driving Performance

In summary, the present results provide some, albeit weak, suggestion that, \(d\)-amphetamine improved aspects of cognitive functioning, predominantly at a trend-level, assessed with indices of visual and auditory processes. Specifically, the present experiment found that the early processing of visual information, occurring within the magnocellular and parvocellular visual pathways, improved with \(d\)-amphetamine at a trend-level (denoted by an increase in the amplitude of the P100 component for the visual pathways combined). In addition, the present experiment found a trend for \(d\)-amphetamine to improve the speed that a comparator process automatically detects changes in auditory stimulation (noted by a decrease in MMN latency). Furthermore, \(d\)-amphetamine improved the speed at which auditory information was evaluated and processed (denoted by a decrease in P300 latency). This enhancement in information processing was consistent with improvements in reaction time and accuracy. Moreover, the improvement in processing speed, following the
administration of d-amphetamine, was positively associated with improvements in reaction time, suggesting that the two are related.

The present experiment also found d-amphetamine differentially affected different regions of the visual field in terms of selective attention, at a trend-level. This was indexed by an increase in N200 amplitude for stimuli presented centrally, and a decrease in N200 amplitude for stimuli presented peripherally. These results are consistent with the ‘tunnel vision’ hypothesis. However, as the present findings were only trend-level, additional research is warranted to explore this possibility further, particularly as previous reports have highlighted the important function that the peripheral visual field has in safe driving.

In terms of driving, the d-amphetamine-induced reduction to the N200 component for information presented in the periphery, suggests that driver’s under the influence of d-amphetamine, may not efficiently attend to and discriminate objects in the periphery, such as traffic lights. Furthermore, the noted enhancement to the N200 component for information presented in the fovea, suggests that driver’s may be restricting attention to their focal point, which may be consequently impairing attentional mechanisms available for peripheral processing. These results thus suggest that ‘tunnel vision’ effects may be associated with the d-amphetamine-related driving impairment.
Chapter 11.

Experiment 5: Effect of d-methamphetamine on Event-Related Potential Measures of Visual and Auditory Processing

11.1 Introduction

As was discussed in Chapter 1 (Introduction), the epidemiological driving literature highlights an association between amphetamine use and road crashes (refer to Chapter 3, Amphetamine and Driving for detail), however, it remains unclear how amphetamines should be related to adverse driving, due to the findings from experimental cognitive research that generally indicates that amphetamines have cognitive enhancing properties (refer to Chapter 4, Amphetamine and Driving-Related Cognitive Performance for detail). Although this inconsistency may be attributed to differences in amphetamine concentrations (as the amphetamine concentrations observed in real-world driving situations are considerably higher than those seen in laboratory settings), the findings from Experiment 1 (Chapter 7), of the present thesis, seem to highlight some ambiguity in the role that amphetamines have in amphetamine-related driving impairments. Specifically, the results from the present thesis demonstrate that although 0.42mg/kg d-amphetamine significantly decreased simulated driving performance, it produced some minimal improvements to cognitive functions that are important to safe driving (refer to Chapters 7.3, 8.3 and 9.3). Furthermore, although a similar single acute therapeutic dose of d,l-methamphetamine and d-methamphetamine did not significantly impair driving performance, the pattern of results were in a similar direction to that of d-amphetamine, indicating minimal decreases in driving performance, yet minimal improvements in cognitive functioning.

The results from the present thesis thus, provide some suggestion that a single therapeutic dose of amphetamines may produce some minimal driving decrements, and yet the present thesis and previous cognitive literature suggest that a single therapeutic dose of amphetamines enhances, albeit weak findings, cognitive functions related to driving. Although there are many factors that could explain the ambiguity between the effects of single therapeutic dose of amphetamines on driving ability and driving-related cognitive processes (refer to Section 1.2, Research Question; Introduction), it is possible that the effect that amphetamines have on human functioning, which subsequently result in driving
decrements, are too subtle to be detected using standard cognitive measures. Therefore, employing more sensitive techniques, such as the electroencephalogram (EEG) and its derivations, may help to clarify how acute amphetamine use affects driving performance, as such methods can assess the more subtle effects of amphetamine on cognitive processing, which cannot be easily measured using standard cognitive tasks.

In accordance with this, Experiment 4 (Chapter 10) examined the acute effects of *d*-amphetamine on cognitive functioning using EEG, in order to determine the effects that amphetamines have on visual and auditory processes which are important to safe driving. Although the results from Experiment 4 (Chapter 10) offered few indications as to how acute *d*-amphetamine may affect driving, the results provided some suggestion that *d*-amphetamine may produce decrements in the ability to attend to, and discriminate, information presented in the peripheral visual field. Furthermore, a improvement in attention was observed for stimuli presented in the fovea, suggesting that *d*-amphetamine may cause a restriction of attention to the focal point, which consequently may impair attentional mechanisms available for peripheral processing (‘tunnel vision’ effects). However, as the results from Experiment 4 (Chapter 10) were only trend-level findings, further research is necessary to clarify these findings.

Therefore, the present experiment employed the same experimental tasks as were administered in Experiment 4, to further explore the acute effects of amphetamines on driving-related visual and auditory cognitive processes using EEG (refer to Section 10.1 and 10.2.4.2 for details). However, as it is important to assess different amphetamines that are commonly used by drivers to allow for comparison to *in situ* driving, the present experiment examined the effects of *d*-methamphetamine on cognitive functions, using EEG. Methamphetamine is considered to be one of the most popular abused stimulants amongst drivers. Within the transport industry, particularly long-distance drivers, methamphetamine has long been used for its functional use of allowing longer and more sustained work performance. Although methamphetamine exists in two isomeric forms, dextro (*d*)- and levo (*l*)- (Logan, 2002), the present experiment administered *d*-methamphetamine, as it has greater central nervous system potency than the *l*-isomer or the racemic mixture (*d*,*l*) (Hardman & Limbird, 1996).
The present experiment assessed the acute effects of \textit{d}-methamphetamine on visual and auditory cognitive processes, using a repeated-measures, counter-balanced, double blind, placebo-controlled design. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \textit{d}-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The present chapter will describe the materials and methodologies employed, the results, and provide a discussion of the results.

11.2 **Materials and Methods**

11.2.1 **Participants**

11.2.1.1 **Selection Criteria**

The selection criteria were the same for the present experiment as described for Experiment 1 (Chapter 7). Refer to Section 7.2.1.1 for full description.

11.2.1.2 **Psychological and Physical Health**

Psychological and Physical Health was assessed with the same procedure as described for Experiment 1 (Chapter 7). Refer to Section 7.2.1.2 for full description.

11.2.1.3 **Sample Characteristics**

Twenty healthy illicit stimulant users (10 males; 10 females) aged between 21 and 32 years (mean = 25.6 years, SD = 3.8 years), with an average male weight of 76.5kg (SD = 11.0), and an average female weight of 62.7kg (SD = 5.5) were recruited. All participants had a minimum of 12 years education. All participants were consumers of caffeine with an average daily intake of 2.1 cups of coffee (range 0-3). Of the 20 participants, 9 were self-assessed smokers, averaging 3.8 cigarettes a day (range 0-20).

Participants were provided with an information sheet outlining details of the research project (see Appendix C for information sheet), and all participants gave written informed consent (see Appendix D for consent form). Participants were informed that they were free to withdraw from the study at any time. The Swinburne University of Technology Human Research Ethics Committee approved the research. Note that one participant did not complete the second EEG session and was, therefore, omitted from all analyses.

11.2.2 **Drug**
The drug administered was the same as described for Experiment 3 (Chapter 9). Refer to Section 9.2.2 for full description.

11.2.3 Experimental Design

A repeated-measures, counter-balanced, double blind, placebo-controlled design was employed. Participants completed two treatment conditions i) placebo and ii) 0.42mg/kg \( d \)-methamphetamine, separated by a two week wash-out period, to reduce residual effects of the drug from the first session. The wash-out period was two weeks based on the results from Experiment 1 (Chapter 7), which indicated the possibility of amphetamine-related residual psychological effects and/or practice effects following only a 1 week wash-out period (refer to Section 7.3.4 for full details). All participants consented to refrain from consuming alcohol for at least 24 hours prior to each testing session and illicit drugs for at least 7 days prior to each testing session.

11.2.4 Materials

11.2.4.1 Questionnaires

Demographic details (see Appendix E for complete questionnaire) and drug use history (see Appendix F for complete questionnaire) was obtained using the same questionnaires as described for Experiment 1 (Chapter 7). Refer to Section 7.2.4.1.1 and 7.2.4.1.2, respectively, for full description.

11.2.4.2 Experimental Tasks

The same battery of experimental tests were administered in the present experiment as those described for Experiment 4 (Chapter 10; refer to Section 10.2.4.2 for details). These tasks were selected to examine the acute effects of methamphetamine on visual and auditory cognitive processes that are important to safe driving. These included: divergent visual system pathways, specifically, the magnocellular and the parvocellular pathways; aspects of the visual field, specifically relating to the central and the peripheral visual field; mismatch negativity; startle reflex and prepulse inhibition response; the N200 component; and the P300 component. These visual and auditory indices were assessed with five tasks. Refer to the following chapters for a full description of each task: Section 10.2.4.2.1 for the Pattern Reversal Task (which assessed the visual pathways); Section 10.2.4.2.2 for the Visual Field Task; Section 10.2.4.2.3 for the Mismatch Negativity Task; Section 10.2.4.2.4
for the Startle Reflex/Pre-Pulse Inhibition Task; and Section 10.2.4.2.5 for the Auditory Oddball Task.

All tasks administered in the present experiment were administered in the same manner as described for Experiment 4 (Chapter 10; refer to Section 10.2.4.2 for details), with the exception of slight variations to task administration for the MMN task and the Startle Reflex/Pre-Pulse Inhibition Task. In Experiment 4 (Chapter 10), during the MMN task, participants were instructed to read self-selected text while a series of sounds were presented through ear inserts (refer to Section 10.2.4.2.3 for full details). Participants were instructed to ignore the sounds and focus on reading. This was implemented to direct attention away from the tones. In contrast, during the administration of the MMN task in the present experiment, attention was diverted away from the tones by implementing a simple secondary task. While the tones were presented, participants were instructed to press a response button as quickly as possible every time a face with a nose (as opposed to a face without a nose) flashed on the computer screen in front. Faces, with and without noses, were presented randomly at a rate of 1 every 7 seconds (range 1-13 seconds). However, as the secondary task was implemented only to direct attention away from the tones, the behavioural data was not used in any analyses.

Similarly, for the Startle Reflex/Pre-Pulse Inhibition Task, participants in Experiment 4 (Chapter 10) were instructed to fixate gaze straight ahead and ignore the loud startle tones presented throughout the task (refer to Section 10.2.4.2.4 for full details). In contrast, in the present experiment, participants were instructed to complete a simple secondary task while ignoring the startle tones. The secondary task was the same as that employed for the MMN paradigm, described in the previous paragraph. Similar to the MMN task, the behavioural data was not used in any analyses as the secondary task was implemented only to direct attention away from the tones.

11.2.4.3 Blood and Saliva Samples

Two blood and two saliva samples were taken from each participant by a registered nurse during each session. Consistent with Experiment 4 (Chapter 10), the first blood and saliva sample was obtained 120 minutes after administration of the drug, and the second sample was obtained 200 minutes after administration of the drug. Blood samples were screened for the seven major drug classes (opiates, amphetamines, benzodiazepines, cannabinoid,
barbiturates, cocaine and methadone) using ELISA/EMIT screens. Subsequently, blood and saliva samples were analysed for specific amphetamine levels using the GC/MS method (refer to Section 7.2.4.6 for full details). Consistent with Experiment 4 (Chapter 10), a baseline saliva sample, obtained using a saliva drug testing device (Securetec Drugwipe), was administered to all participants prior to drug administration to ensure no recent drug use. The saliva drug testing device produced a result (positive or negative) immediately after a saliva sample was obtained. This sample was obtained to verify that inclusion criteria had been met. Therefore, no further analyses were conducted on the data.

11.2.5 Data Acquisition

The data acquisition was the same as described for Experiment 4 (Chapter 10). Refer to Section 10.2.5 for full details.

11.2.6 Data Analysis

Data analysis was the same as described for Experiment 4 (Chapter 10). Refer to Section 10.2.6 for full details. For specific data analysis descriptions conducted for each task refer to the following sections: Section 10.2.6.1 for the Pattern Reversal Task; Section 10.2.6.2 for the Visual Field Task; Section 10.2.6.3 for the Mismatch Negativity Task; Section 10.2.6.4 for the Startle Reflex/Pre-Pulse Inhibition Task; and Section 10.2.6.5 for the Auditory Oddball Task.

11.2.7 Procedure

The procedure was the same as described for Experiment 4 (Chapter 10). Refer to Section 10.2.7 for full description of the procedure that was adhered to in the present experiment. Table 11.1 summarises the testing protocol for the two experimental sessions. Note that the protocol was the same during both experimental sessions.

**Table 11.1 Testing Protocol**

<table>
<thead>
<tr>
<th>Elapsed Time (min)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Meal Provided</td>
</tr>
<tr>
<td>10</td>
<td>Treatment Administered Orally</td>
</tr>
<tr>
<td>90</td>
<td>Participant EEG Set-Up</td>
</tr>
<tr>
<td>130</td>
<td>1st Blood and Saliva Sample</td>
</tr>
<tr>
<td>145</td>
<td>EEG Recording and Task Administration</td>
</tr>
<tr>
<td>215</td>
<td>Clean Up / 2nd Blood and Saliva Sample</td>
</tr>
<tr>
<td>230</td>
<td>End of Session (Taxi)</td>
</tr>
</tbody>
</table>
11.2.8 Statistical Analyses

All statistical analyses employed in the present experiment, were the same as described for Experiment 4 (Chapter 10; refer to Section 10.2.8 for full details). For specific tasks refer to the following sections for a full description of the analyses conducted: Pattern Reversal Task refer to Section 10.2.8.1.1; Visual Field Task refer to Section 10.2.8.1.2; Mismatch Negativity Task refer to Section 10.2.8.2.1; Startle Reflex/Pre-Pulse Inhibition Task refer to Section 10.2.8.2.2; and the Auditory Oddball task refer to Section 10.2.8.2.3.

11.3 Results

11.3.1 Demographic Characteristics of Participants

Demographic characteristics of the participants are summarised in Table 11.2.

Table 11.2 Demographics and Recreational Drug Use for Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.6</td>
<td>3.8</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Years of education</td>
<td>14</td>
<td>1.6</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Current amphetamine use (per year)</td>
<td>4.6</td>
<td>4.7</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Amphetamine use when consumed most (per year)</td>
<td>15.7</td>
<td>16.8</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using amphetamine (years)</td>
<td>0.5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current ecstasy use (per year)</td>
<td>5.9</td>
<td>4.9</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Ecstasy use when consume most (per year)</td>
<td>25.7</td>
<td>16.4</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Period of time using ecstasy (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Current marijuana use (per year)</td>
<td>12.1</td>
<td>24.7</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Marijuana use when consume most (per year)</td>
<td>140.7</td>
<td>140.1</td>
<td>1</td>
<td>300</td>
</tr>
<tr>
<td>Period of time using marijuana (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Current cocaine use (per year)</td>
<td>0.6</td>
<td>0.8</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Period of time using cocaine (years)</td>
<td></td>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol per week (units)</td>
<td>12.6</td>
<td>10.9</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

Note that N=20 and that ‘drug use’ refers to number of occasions the specific drug was consumed in a year

As depicted in Table 11.2, 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 month over the preceding year. During the period when participants consumed drugs most frequently in their lifetime, amphetamine was on average consumed more than once a month (approximately 16 times), whereas ecstasy was consumed approximately twice a month over the year (approximately 26 times). During the period
when participants consumed marijuana most frequently, participants on average reported to have used marijuana approximately 2-3 times a week in that year (approximately 140 times).

### 11.3.2 Level of $d$-methamphetamine in Blood and Saliva

The blood and saliva data were not available due to circumstances out of the experimenter’s control. They will thus not be reported.

### 11.3.3 Effect of $d$-methamphetamine on Event Related Potentials

Note that the reported means for the amplitude and latency of ERP components may not resemble the waveforms due to the effect of latency jitter, which is typical of ERP research.

#### 11.3.3.1 Visual Processing

11.3.3.1.1 Effect of $d$-methamphetamine on the Pattern Reversal task

The grand averages for the P100, elicited at the OZ scalp site, for the magnocellular and parvocellular visual pathways, for placebo and $d$-methamphetamine conditions, are shown in Figure 11.1.

![Figure 11.1](image.png)

**Figure 11.1** Grand Averaged ERPs are shown for Magnocellular and Parvocellular Stimuli for $d$-methamphetamine and Placebo Drug Conditions Separately. Note that the P100 peaked approximately 100ms following stimulus onset for parvocellular stimuli and at approximately 120
ms for magnocellular stimuli. Also note that for both parvocellular and magnocellular stimuli there were little difference in the amplitude of the P100 component for the two drug conditions. Although, not clearly manifested in the Figure, d-methamphetamine decreased the latency of the P100 component for the magnocellular visual pathway, however, did not modulate the latency for the parvocellular visual pathway.

\(d\)-methamphetamine had no effect on the amplitude of the P100 component for the visual pathways combined, relative to placebo, \(F(1, 16) = 1.73, p = .42\). As illustrated in Figure 11.1 and Table 11.3, the differential processing of the P100 amplitude of the magnocellular and parvocellular pathways was not modulated by \(d\)-methamphetamine, \(F(1, 16) = 0.10, p = .76\). As the P100 latency data were not normally distributed, square root transformations were performed to normalise the data. \(d\)-methamphetamine significantly decreased the latency of the P100 component for the visual pathways combined, relative to placebo, \(F(1, 14) = 6.59, p = .04\). Furthermore, the differential processing of the P100 latency of the magnocellular and parvocellular pathways decreased with \(d\)-methamphetamine, relative to placebo, at a trend-level, \(F(1, 14) = 4.62, p = .10\). This is highlighted in Table 11.3, where a decrease in latency was observed specifically for the magnocellular visual pathway with \(d\)-methamphetamine.

**Table 11.3** Means (Standard Deviations) for P100 Amplitude and Latency for the Magnocellular and Parvocellular Pathways across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>(d)-methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magno Amplitude</td>
<td>5.16 (1.48)</td>
<td>5.59 (1.21)</td>
</tr>
<tr>
<td>Parvo Amplitude</td>
<td>10.17 (4.33)</td>
<td>10.80 (4.61)</td>
</tr>
<tr>
<td>Magno Latency</td>
<td>120.53 (6.07)</td>
<td>117.20 (6.27)</td>
</tr>
<tr>
<td>Parvo Latency</td>
<td>104.67 (4.76)</td>
<td>104.27 (5.12)</td>
</tr>
</tbody>
</table>

11.3.3.1.2 Effect \(d\)-methamphetamine on the Visual Field Task

11.3.3.1.2.1 *Behavioural*

\(d\)-methamphetamine (mean = 0.36, SD = 0.02) significantly decreased reaction time for the visual fields combined, relative to placebo (mean = 0.38, SD = 0.03), \(F(1, 18) = 11.01, p < .01\). However, \(d\)-methamphetamine had no effect on reaction time as a function of visual field, \(F(1, 18) = 2.28, p = .30\).
11.3.3.1.2.2 P100

The grand averages for the P100 component, for the central and peripheral visual fields, for placebo and d-methamphetamine conditions, are shown in Figure 11.2. Note that as the P100 is an early component that occurs prior to discrimination of target from nontarget stimuli, target and nontarget stimuli were combined in each of the central and peripheral averages, for each drug condition.

![Figure 11.2](image)

Figure 11.2 Grand Averaged ERPs are shown for Central and Peripheral Visual Field Stimuli for d-methamphetamine and Placebo Drug Conditions Separately. Note that the P100 occurred earlier for the central stimuli compared to the peripheral stimuli. Also note that there is little difference between the placebo and d-methamphetamine conditions in the latency and amplitude of the P100 component, for both central and peripheral stimuli.

\[d\text{-methamphetamine had no effect on the amplitude of the P100 component for the visual fields combined, relative to placebo, } F(1, 17) = 0.07, \ p = .80.\]  
As depicted in Table 11.4, the differential processing of the P100 amplitude of the central and peripheral visual fields was not modulated by d-methamphetamine, \(F(1, 17) = 0.01, \ p = .92\). \(d\text{-methamphetamine had no effect on the latency of the P100 component for the visual fields combined, relative to placebo, } F(1, 18) = 0.62, \ p = .88.\]  
As can be seen in Figure 11.2, the differential processing of the P100 latency of the central and peripheral visual fields was not modulated by d-methamphetamine, \(F(1, 19) = 1.38, \ p = .51.\)
### Table 11.4 Means (Standard Deviations) for P100 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>17.81 (14.13)</td>
<td>17.20 (14.18)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>19.57 (12.28)</td>
<td>18.63 (12.38)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>100.42 (27.44)</td>
<td>91.89 (18.43)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>117.58 (26.62)</td>
<td>116.63 (29.16)</td>
</tr>
</tbody>
</table>

11.3.3.1.2.3 N200

The grand averages for the N200 component, for the central and peripheral visual fields, for placebo and d-methamphetamine conditions, are shown in Figure 11.3. Note that only the target stimuli for the central and peripheral stimuli were included in the averages.

![Grand Averaged ERPs](image)

**Figure 11.3** Grand Averaged ERPs are shown for Central and Peripheral Visual Field Stimuli for d-methamphetamine and Placebo Drug Conditions Separately. *Note that the N200 amplitude is larger for the central stimuli compared to the peripheral stimuli irrespective of drug condition. Also note that the amplitude of the N200 is larger for the placebo condition relative to the d-methamphetamine condition for both central and peripheral stimuli, however, there is no difference between drug conditions in the time the N200 peaks.*
d-methamphetamine had no effect on the amplitude of the N200 component for the visual fields combined, relative to placebo, F(1, 18) = 1.31, p = .53. As illustrated in Table 11.5, the differential processing of the N200 amplitude for the central and peripheral visual fields was not modulated by d-methamphetamine, F(1, 18) = 0.27, p = .61. d-methamphetamine had no effect on the latency of the N200 component for the visual fields combined, relative to placebo, F(1, 14) = 0.05, p = .83. As can be seen in Figure 11.3, the differential processing of the N200 latency for the central and peripheral visual fields was not modulated by d-methamphetamine, F(1, 14) = 0.76, p = .80.

Table 11.5 Means (Standard Deviations) for N200 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>-71.42 (39.62)</td>
<td>-62.36 (38.87)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>-48.58 (27.63)</td>
<td>-44.71 (29.05)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>157.47 (11.04)</td>
<td>152.93 (14.08)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>201.20 (42.23)</td>
<td>208.40 (41.57)</td>
</tr>
</tbody>
</table>

11.3.3.1.2.4 P300

The grand averages for the P300 component, for the central and peripheral visual fields, for placebo and d-methamphetamine conditions, are shown in Figure 11.4. Note that only the target stimuli for the central and peripheral stimuli were included in the averages.

Figure 11.4 Grand Averaged ERPs are shown for Central and Peripheral Visual Field Stimuli for d-methamphetamine and Placebo Drug Conditions Separately. Note that P300
amplitude is larger for the central stimuli compared to the peripheral stimuli irrespective of drug condition. Also note that the amplitude for centrally presented stimuli does not differ between the placebo and d-methamphetamine conditions; however, for peripheral stimuli the amplitude is larger for the placebo condition relative to the d-methamphetamine condition. Furthermore, the P300 peaks earlier in the d-methamphetamine condition compared to the placebo condition for both peripheral and central stimuli.

As the P300 amplitude data were not normally distributed, square root transformations were performed to normalise the data. d-methamphetamine had no effect on the amplitude of the P300 component for the visual fields combined, relative to placebo, F(1, 16) = 0.58, p = .90. As depicted in Figure 11.4, the differential processing of the P300 amplitude of the central and peripheral visual fields was not modulated by d-methamphetamine, F(1, 16) = 0.69, p = .84. The P300 latency data were not normally distributed, therefore, square root transformations were performed to normalise the data. As can be seen in Table 11.6, d-methamphetamine significantly decreased the latency of the P300 component for the visual fields combined, relative to placebo, F(1, 13) = 7.18, p = .04. However, the differential processing of the P300 latency of the central and peripheral visual fields was not modulated by d-methamphetamine, F(1, 13) = 2.91, p = .22.

### Table 11.6 Means (Standard Deviations) for P300 Amplitude and Latency for Central and Peripheral Visual Fields across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>d-methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Amplitude</td>
<td>145.81 (154.41)</td>
<td>133.08 (159.10)</td>
</tr>
<tr>
<td>Peripheral Amplitude</td>
<td>139.71 (133.60)</td>
<td>111.31 (152.90)</td>
</tr>
<tr>
<td>Central Latency</td>
<td>357.57 (25.87)</td>
<td>344.43 (24.91)</td>
</tr>
<tr>
<td>Peripheral Latency</td>
<td>392.43 (58.17)</td>
<td>348.71 (34.50)</td>
</tr>
</tbody>
</table>

11.3.3.2 Auditory Processing

11.3.3.2.1 Effect of d-methamphetamine on the Mismatch Negativity Task

Note that data from two participants were excluded from analyses as no clear MMN was observed in the placebo condition. As depicted in Figure 11.5, d-methamphetamine (mean = -6.21, SD = 2.42) had no effect on the amplitude of the MMN response, relative to placebo (mean = -6.87, SD = 2.92), F(1, 16) = 0.35, p = .56. Similarly, d-methamphetamine (mean = 196.42, SD = 21.44) had no effect on the latency of the MMN response, relative to placebo (mean = 199.88, SD = 17.20), F(1, 14) = 0.98, p = .34.
Figure 11.5 Grand Averaged ERPs are shown for MMN, at the FZ scalp site, for d-methamphetamine and Placebo Drug Conditions Separately. Note that the MMN did not differ for placebo and d-methamphetamine conditions in amplitude or time of MMN peak.

11.3.3.2.2 Effect of d-methamphetamine on the Startle Reflex/Pre-Pulse Inhibition Task

The grand average for the startle response, for placebo and d-methamphetamine conditions, is shown in Figure 11.6.

Figure 11.6. Grand Averaged ERPs are shown for the Startle Response for d-methamphetamine and Placebo Drug Conditions Separately. Note that the Startle Response is larger in the d-methamphetamine condition compared to placebo. However, time of startle peak did not differ for the drug conditions.
The startle response amplitude data were not normally distributed, therefore, square root transformations were performed to normalise the data. *d*-methamphetamine had no effect on the amplitude of the startle response relative to placebo, \(F(1, 18) = 0.89, p = .36\). As can be seen in Figure 11.6 and Table 11.7, *d*-methamphetamine had no effect on the latency of the startle response relative to placebo, \(F(1, 17) = 0.26, p = .62\). As the PPI amplitude data were not normally distributed, square root transformations were performed to normalise the data. As depicted in Table 11.7, *d*-methamphetamine significantly increased the amplitude of the PPI of the startle response relative to placebo, \(F(1, 17) = 4.35, p = .05\). However, *d*-methamphetamine had no effect on the latency of the PPI relative to placebo, \(F(1, 18) = 0.07, p = .80\).

**Table 11.7** Means (Standard Deviations) for Amplitude and Latency for the Startle Response and PPI across Drug Conditions

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th><em>d</em>-methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startle Amplitude</td>
<td>175.41 (135.53)</td>
<td>189.79 (126.00)</td>
</tr>
<tr>
<td>Startle Latency</td>
<td>114.17 (9.21)</td>
<td>113.22 (7.44)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Amplitude</td>
<td>0.58 (0.23)</td>
<td>0.67 (0.20)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Latency</td>
<td>-0.40 (0.28)</td>
<td>-0.42 (0.37)</td>
</tr>
</tbody>
</table>

It has previously been reported that PPI is attenuated following a low dose of *d*-amphetamine (5mg) in a subgroup of 6 smokers (Kumari *et al.*, 1998; refer to Section 5.4.2 for details). Experiment 4 did not find *d*-amphetamine reduced PPI in smokers (refer to Section 10.3.3.2.2). Thus, to confirm the findings reported in Experiment 4, the present experiment repeated the above analyses using only a subgroup of smokers. Therefore, the number of participants decreased from 19 to 9. As the startle response amplitude data were not normally distributed for the smoker subgroup, square root transformations were performed to normalise the data. As illustrated in Table 11.8, *d*-methamphetamine had no effect on the amplitude of the startle response in smokers, relative to placebo, \(F(1, 8) = 0.02, p = .90\). Similarly, *d*-methamphetamine had no effect on the latency of the startle response in smokers, relative to placebo, \(F(1, 7) < 0.01, p = .97\). As the PPI amplitude data were not normally distributed for the smoker subgroup, square root transformations were performed to normalise the data. *d*-methamphetamine had no effect on the amplitude of the PPI in smokers, relative to placebo, \(F(1, 8) = 2.29, p = .17\). Similarly, *d*-methamphetamine
had no effect on the latency of the PPI in smokers, relative to placebo, F(1, 8) = 0.54, \( p = .48 \).

**Table 11.8** Means (Standard Deviations) for Amplitude and Latency for the Startle Response and PPI across Drug Conditions in Smokers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo Amplitude (SD)</th>
<th>( d )-methamphetamine Amplitude (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startle Amplitude</td>
<td>197.76 (175.74)</td>
<td>197.07 (157.75)</td>
</tr>
<tr>
<td>Startle Latency</td>
<td>115.75 (10.35)</td>
<td>115.88 (7.64)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Amplitude</td>
<td>0.58 (0.21)</td>
<td>0.71 (0.18)</td>
</tr>
<tr>
<td>PPI=(pulse alone-prepulse)/pulse alone Latency</td>
<td>-0.34 (0.28)</td>
<td>-0.44 (0.38)</td>
</tr>
</tbody>
</table>

11.3.3.2.3 Effect of \( d \)-methamphetamine on the Auditory Oddball Task

11.3.3.2.3.1 Behavioural

\( d \)-methamphetamine (mean = 0.37, SD = 0.05) had no effect on reaction time relative to placebo (mean = 0.37, SD = 0.03), F(1, 17) = 0.87, \( p = .37 \). Furthermore, \( d \)-methamphetamine had no effect on accuracy (mean = 97.78, SD = 6.12) relative to placebo (mean = 95.50, SD = 13.28), T = 7, \( p = .11 \).

11.3.3.2.3.2 N200

The grand average for the N200 component, elicited at the FZ scalp site, for placebo and \( d \)-methamphetamine conditions, during the auditory oddball task, is shown in Figure 11.7. Note that only the target stimuli were included in the averages. As can be seen in Figure 11.7, \( d \)-methamphetamine (mean = -3.63, SD = 2.04) significantly decreased the amplitude of the N200 component relative to placebo (mean = -4.79, SD = 2.24), F(1, 16) = 5.44, \( p = .03 \). However, \( d \)-methamphetamine (mean = 253.20, SD = 34.31) had no effect on the latency of the N200 component relative to placebo (mean = 253.60, SD = 36.73), F(1, 14) < 0.01, \( p = .97 \).
11.3.3.2.3.3 **P300**

The grand average for the P300 component, elicited at the PZ scalp site, for placebo and d-methamphetamine conditions, during the auditory oddball task, is shown in Figure 11.8. Note that only the target stimuli were included in the averages. As the P300 amplitude data were not normally distributed, square root transformations were performed to normalise the data. Although it is not clear in Figure 11.8, d-methamphetamine (mean = 5.97, SD = 3.15) had no effect on the amplitude of the P300 component relative to placebo (mean = 6.72, SD = 3.68), F(1, 18) = 0.69, p = .42. Furthermore, d-methamphetamine (mean = 370.42, SD = 59.43) had no effect on the latency of the P300 component compared to placebo (mean = 394.63, SD = 65.23), F(1, 18) = 1.99, p = .18.

**Figure 11.7** Grand Averaged ERPs are shown for the Auditory Oddball Task for d-methamphetamine and Placebo Drug Conditions Separately. Note that although peak amplitude of the N200 is larger in the placebo condition relative to the d-methamphetamine condition, there is no significant difference between the drug conditions in the time that the N200 peaks.
Figure 11.8 Grand Averaged ERPs are shown for the Auditory Oddball Task for \(d\)-methamphetamine and Placebo Drug Conditions Separately. *Note that peak amplitude of the P300 is larger for placebo relative to \(d\)-methamphetamine. However, there is no difference between the drug conditions in the time that the P300 peaks.*

11.3.3.2.3.4 Exploratory Analyses

Changes in P300 latency following \(d\)-methamphetamine consumption were not found to be associated with changes in reaction time following \(d\)-methamphetamine consumption, \(r (19) = 0.17, p = .48,\) two-tailed. Similarly, changes in P300 amplitude following \(d\)-methamphetamine consumption were not found to be associated with changes in accuracy following \(d\)-methamphetamine consumption, \(r (18) = -0.40, p = .10,\) two-tailed.

11.4 Discussion

The present experiment examined the acute effects of 0.42mg/kg \(d\)-methamphetamine on visual and auditory cognitive processes relevant to driving. Specifically, these were: divergent visual system pathways (the magnocellular and the parvocellular pathways); aspects of visual field processing (central and peripheral visual fields); perceptual detection of auditory change; early sensory gating; selective attention; resource allocation; and speed of processing. As mentioned in Section 10.4, as there is limited research that has examined
the acute effects of amphetamines on specific ERPs, the present discussion will also
discuss trend level findings. The present experiment found that \( d \)-methamphetamine
improved the speed at which information was processed within the magnocellular and
parvocellular visual pathways (denoted by a decrease in the latency of the P100 component
for the visual pathways combined). Furthermore, there was a trend for \( d \)-methamphetamine
to differentially affect the speed at which information was processed by the visual
pathways, indexed by a more pronounced decrease in P100 latency for the magnocellular
visual pathway compared to the parvocellular visual pathway. In addition, \( d \)-
methamphetamine improved the speed at which information presented to the central and
peripheral visual fields was evaluated and processed (denoted by a decrease in P300
latency for the visual fields combined). This was substantiated with a corresponding
improvement in reaction time, irrespective of where in the visual field stimuli were
presented (denoted by a decrease in reaction time for the visual fields combined). In terms
of auditory processing, \( d \)-methamphetamine improved the ability to automatically ‘screen
out’ irrelevant and intrusive auditory information (indexed by an increase in PPI amplitude
of the startle response). Finally, \( d \)-methamphetamine reduced N200 amplitude during the
auditory oddball task, suggesting a decrease in selective attention.

11.4.1 Effect of \( d \)-methamphetamine on Visual Processing

11.4.1.1 Effect of \( d \)-methamphetamine on the Magnocellular and Parvocellular Visual
Pathways

The present experiment indicates that \( d \)-methamphetamine improves the speed at which
information is processed within the visual system, which manifested as a decrease in P100
latency for the visual pathways combined. Furthermore, \( d \)-methamphetamine differentially
affected the speed at which information was processed by the visual pathways at a trend-
level. This was indexed by a more pronounced decrease in P100 latency for the
magnocellular visual pathway compared to the parvocellular visual pathway. This suggests
that \( d \)-methamphetamine has a more marked effect on the processing speed of motion,
coarse details, and overall stimulus organisation (magnocellular), than the processing of
high contrast, pattern, colour, and fine-detailed stimulus information (parvocellular).

It is difficult to directly relate the present results to previous research, as there have been
no studies that have examined the acute effects of \( d \)-methamphetamine, or any other
dopamine agonists, on these divergent visual system pathways. However, the results of the present experiment are consistent with Experiment 4 (Chapter 10), which revealed a trend for \textit{d}-amphetamine to enhance early visual processing for information processed by both the magnocellular and parvocellular visual pathways (denoted by an increase in P100 amplitude for the visual pathways combined). However, in addition, the present results suggest that the improved speed at which visual information is processed is more pronounced for the magnocellular system following \textit{d}-methamphetamine consumption, which, although not significant, was similarly observed with \textit{d}-amphetamine in Experiment 4 (Chapter 10).

As the P100 component is modulated as a function of visual attention (Heinze \textit{et al.}, 1990; Hillyard & Anllo-Vento, 1998; Luck \textit{et al.}, 1994; Mangun, 1995; Mangun & Hillyard, 1990), and the magnocellular system is particularly involved in visual attention (Samar \textit{et al.}, 2002; Steinman \textit{et al.}, 1997; Butler \textit{et al.}, 2005; Schechter \textit{et al.}, 2005), it can be argued that the present results support previous cognitive research that has consistently shown amphetamines to improve attentional functions (Kelly \textit{et al.}, 1991; Koelega 1993; Comer \textit{et al.}, 1996; Ward \textit{et al.}, 1997; McKetin \textit{et al.}, 1999; Wachtel & de Wit, 1999; de Wit \textit{et al.}, 2002; Cami \textit{et al.}, 2000; Johnson \textit{et al.}, 2000). Furthermore, the present results support the findings reported in Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and Experiment 3 (Chapter 9), which demonstrate some improvements in attention following the administration of \textit{d}-amphetamine, \textit{d,l}-methamphetamine, and \textit{d}-methamphetamine. However, by extension, the present results, in addition to the findings reported in Experiment 4 (Chapter 10), indicate that previously reported amphetamine-related improvements in attention may be related to very early attentional enhancements following amphetamine consumption.

The present thesis results are thus consistent with the view that indicates a relationship between visual attention and early visual processing (indexed by the P100 component), particularly as the magnocellular system is involved in visual attention (Samar \textit{et al.}, 2002; Steinman \textit{et al.}, 1997; Butler \textit{et al.}, 2005; Schechter \textit{et al.}, 2005). This supports previous schizophrenia research which has shown that individuals characterised by poor attention demonstrate significant dysfunctions in early-stage visual processing, manifested by deficits to the P100 component, particularly within the magnocellular system (Romani \textit{et al.}, 1986; Matsuoka \textit{et al.}, 1996; Basinka, 1998; Butler \textit{et al.}, 2001, 2005; Foxe \textit{et al.},
In terms of driving, the present findings indicate that possible reductions in driving performance attributed to low amphetamine concentrations are not likely to be associated with impairments to early visual processing in general, nor with the differential functioning of the parvocellular and magnocellular visual pathways. Consistent with Experiment 4 (Chapter 10), the present findings indicate that a low dose of \( \text{d-methamphetamine} \) improves the speed at which driver’s process visual information, particularly in terms of detecting motion and crude details of the overall traffic environment (such as, the movement of cars and pedestrians). Furthermore, it has previously been argued that deficits to the magnocellular visual pathway are more likely to be associated with driving decrements (Herkes & Conlon, 2002; Steinman et al., 1994). Thus, the present trend-level improvement in the speed at which information is processed within the magnocellular system, further suggests that amphetamine-related impairments to early visual processing do not appear to be implicated in low level amphetamine-related driving deficits.

In summary, the present experiment indicates that an acute dose of 0.42mg/kg \( \text{d-methamphetamine} \), improves the speed at which visual information is processed (denoted by a decrease in the latency of the P100 component for the visual pathways combined). Furthermore, there was a trend for \( \text{d-methamphetamine} \) to differentially affect the speed at which information was processed by the visual pathways, which was indexed by a more pronounced decrease in P100 latency for the magnocellular visual pathway. Although consistent with the cognitive results reported in Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and Experiment 3 (Chapter 9), by extension, these ERP results indicate that amphetamine-related improvements in attention may be related to very early attentional enhancements. However, overall, the ERP and cognitive results reported in the present thesis provide evidence to suggest that low dose-amphetamine-related driving impairments are unlikely to be associated with deficits to visual attention.

However, it is important to note that there was a trend for \( \text{d-amphetamine} \) to produce decrements to indices of selective attention for information presented in the peripheral visual field (Experiment 4). These results, therefore, provide some suggestion that \( \text{d-amphetamine} \) may impair the processing of visual information at a discrimination level.
However, as this decrement was observed only for stimuli presented in the peripheral visual field it cannot be argued that \textit{d}-amphetamine impairs selective attention \textit{per se}. It can only be argued that selective attention is disrupted for information presented in the periphery. However, as measures of selective attention assessed in the visual modality, were not included in the present thesis, further research is required to explore this issue.

11.4.1.2 Effect of \textit{d}-methamphetamine on the Central and Peripheral Visual Fields

The present experiment found that \textit{d}-methamphetamine improved the speed at which visual information presented to the central and peripheral visual fields was processed, as indexed by decreases in P300 latency for the visual fields combined. This improvement in information processing speed was consistent with \textit{d}-methamphetamine-induced improvements in reaction time, irrespective of where in the visual field stimuli were presented. These results, therefore, provide no evidence to suggest that \textit{d}-methamphetamine differentially affected different regions of the visual field.

It is difficult to directly relate the present results to previous research, as there have been no ERP studies that have examined the differential effects of \textit{d}-methamphetamine, or any other dopamine agonists, on different regions of the visual field. Although previous behavioural research has indicated that \textit{d}-amphetamine improves performance for stimuli presented centrally, with little or no change observed for stimuli presented in the periphery (Mills \textit{et al.}, 2001), the present experiment did not find similar effects. However, Experiment 4 (Chapter 10) found a trend for \textit{d}-amphetamine to improve indices of selective attention (denoted by increases in N200 amplitude) for information presented centrally, and impair indices of selective attention (denoted by decreases in N200 amplitude) for information presented in the periphery. Therefore, unlike the present findings, these latter results provide some support for the ‘tunnel vision’ hypothesis (Mills \textit{et al.}, 2001; discussed in Section 5.3.2). The failure to find similar effects following the administration of \textit{d}-methamphetamine is difficult to interpret. The inconsistency in results may be attributed to differences in amphetamine type or amphetamine blood concentrations (unfortunately this latter point could not be assessed as the blood data was not available). However, as the literature is limited, further research is warranted to explore this discrepancy.
Although the present findings do not indicate that \textit{d}-methamphetamine differentially affected different regions of the visual field, the results indicate that a low dose of \textit{d}-methamphetamine improves the evaluation time and speed at which visual information is processed (indexed by a decrease in P300 latency for the visual fields combined). This improvement is to some extent consistent with the findings discussed in Section 11.4.1.1, which indicate that \textit{d}-methamphetamine improves the speed of early information processing within the visual pathways (indexed by a decrease in P100 latency for the visual pathways combined). These results, therefore suggest that the speed of early (P100) and late (P300) processing of visual information is enhanced with \textit{d}-methamphetamine.

In addition, the results from the Auditory Oddball Task in Experiment 4 (Chapter 10; Section 10.4.2.3), provide further support that the speed at which information is evaluated and processed (indexed by decreases in P300 latency) improves with \textit{d}-amphetamine. Furthermore, similar to the present results, the enhancement in auditory processing was consistent with improvements in reaction time and accuracy. These ERP results thus contribute important information to the amphetamine literature, in that these results demonstrate that amphetamines improve the speed and quality of early and late information processing.

The present results are consistent with previous cognitive reports that have shown that a low dose of amphetamines improves perceptual speed, indicated by improvements in information processing (Kennedy \textit{et al}., 1990; Fillmore \textit{et al}., 2005) and reaction time (Fillmore \textit{et al}., 2005; Asghar \textit{et al}., 2003; McKetin \textit{et al}., 1999; Servan-Shreiber \textit{et al}., 1998; Kumari \textit{et al}., 1997; Ward \textit{et al}., 1997; Halliday \textit{et al}., 1994; Fleming \textit{et al}., 1995; Johnson \textit{et al}., 2000; Rapoport \textit{et al}., 1980). Furthermore, the results from Experiment 1 (Chapter 7), Experiment 2 (Chapter 8), and Experiment 3 (Chapter 9), revealed some improvements in information processing with amphetamines. Specifically, enhancements in perceptual speed, reaction time and accuracy were observed with amphetamines, on tasks designed to assess attentional functioning and information processing, such as, the Digit Vigilance task, the Inspection Time task, and the Digit Symbol Substitution Task. However, by extension, the present ERP results indicate that amphetamines enhance both response processing and stimulus evaluation, indicated by improvements in reaction time and P300 latency.
In terms of driving, the present results do not suggest that any amphetamine-related driving impairment associated with therapeutic doses may be associated with decrements in the processing of information presented in the periphery. However, as the results from Experiment 4 (Chapter 10) indicate a trend for \( d \)-amphetamine to reduce selective attention for information presented in the peripheral visual field, and previous reports highlight the important function of the peripheral visual field in safe driving (Johnson & Keltner, 1983; Szlyk et al., 1991, 1992; Wood & Troutbeck, 1992, 1993, 1994; Owsley, Ball et al., 1998; Owsley, McGwin et al., 1998; Sims et al., 2000), further research is warranted.

In summary, the present findings suggest that an acute dose of 0.42mg/kg \( d \)-methamphetamine improves the evaluation and speed at which visual information is processed, irrespective of where in the visual field stimuli are presented (indexed by a decrease in P300 latency for the visual fields combined). This improvement in information processing speed was supported with corresponding improvements in reaction time. Overall, the results of the present thesis provide evidence to suggest that a therapeutic dose of amphetamines improves the processing speed of visual information, which in terms of driving, provides considerable evidence to suggest that at low amphetamine concentrations any observed impairments are unlikely to be associated with the early and late processing of visual information. Although inconsistent with the present ERP results, it is important to note that the results from Experiment 4 suggest that amphetamine-related decreases in driving ability may be attributed to decrements to peripheral visual field processing (in terms of selective attention), and possibly even ‘tunnel vision’ effects.

### 11.4.2 Effect of \( d \)-methamphetamine on Auditory Processing

#### 11.4.2.1 Effect of \( d \)-methamphetamine on Mismatch Negativity (MMN)

The present experiment did not find that an acute dose of \( d \)-methamphetamine modulated MMN, indicating that \( d \)-methamphetamine did not affect the ability to automatically detect change in auditory stimulation. With the exception of Experiment 4 (Chapter 10), there have been no other studies that have examined the acute effects of amphetamine on this early pre-attentive comparative process. However, there is limited research that has examined the effects of other dopamine agonists, namely methylphenidate and apomorphine, on the MMN response.
Unlike the present results, Experiment 4 (Chapter 10) reported a trend for $d$-amphetamine to improve the speed at which changes in auditory stimulation were automatically detected, indexed by a decrease in MMN latency. The discrepancy in results between the present experiment, and Experiment 4 (Chapter 10), may be attributed to slight differences in task administration. In Experiment 4 (Chapter 10), during the MMN task, attention was directed away from the tones by implementing a reading task, whereby participants were instructed to read self-selected text while tones were presented (refer to Section 10.2.4.2.3 for full details). In contrast, in the present experiment, attention was directed away from the tones by implementing a simple secondary task, which involved pressing a response button as quickly as possible every time a face with a nose flashed on the computer screen (refer to Section 11.2.4.2 for full details).

Although these are considerable differences in task administration, the reported means for MMN amplitude and latency for the placebo conditions, were similar for the present experiment and Experiment 4 (Chapter 10), thus suggesting that differences in task demands do not appear to elucidate the inconsistency in results. In contrast, during the active drug conditions, there were differences in mean amplitude and latency between the two studies, therefore suggesting that the discrepancy in results appears to be attributed to differences in drug type or differences in amphetamine blood concentrations (the blood data was not available to address this latter point). Furthermore, it has previously been established that the MMN response can be evoked in the absence of attention (Näätänen, 1990), thus suggesting that differences in attentional demands should not modulate MMN (for review see Muller-Gass & Campbell, 2002). However, as Experiment 4 (Chapter 10) reported only trend-level findings, further research is required to clarify the effects of amphetamine on MMN.

Consistent with the present findings, previous research has generally shown that dopamine agonist drugs, such as methylphenidate and apomorphine, do not modulate MMN (Hansenne et al., 2003; Winsberg et al., 1997). Although $d$-methamphetamine and dopamine agonist drugs have similar effects on dopamine activity, $d$-methamphetamine also influences other neurotransmitter activity, namely norepinephrine and serotonin. However, the present results suggest that this difference in neurotransmitter activity does not appear to produce different effects to MMN. Although the present results support previous dopamine research, the trend-level enhancement in MMN latency noted in
Experiment 4 (Chapter 10), following the administration of \(d\)-amphetamine, warrants further research to clarify whether amphetamine does in fact modulate MMN, or whether the findings reported in Experiment 4 were a chance finding.

In terms of driving, the present results indicate any indications of decrements to driving performance associated with a acute therapeutic dose of amphetamines are unlikely to be associated with disruptions to MMN response. The present findings indicate that a low \(d\)-methamphetamine dose does not modulate a driver’s ability to automatically discriminate auditory changes within the traffic environment. The results from Experiment 4 (Chapter 10) substantiate this, as there was a trend for \(d\)-amphetamine to improve the speed in which auditory changes in traffic information are automatically detected. Thus, the results from the present thesis, in addition to previous dopamine agonist research, highlight that low dose amphetamine-related driving impairments are unlikely to be associated with disruptions to the MMN response.

In summary, the present results indicate that 0.42mg/kg \(d\)-methamphetamine does not modulate MMN. Although these findings are inconsistent with those reported in Experiment 4 (Chapter 10), in terms of driving, the ERP results from the present thesis suggest that any amphetamine-related decreases in driving performance are unlikely to be associated with disruptions in the ability to automatically discriminate auditory changes within the traffic environment. This is substantiated with previous dopamine agonist research which similarly has failed to report disruptions to MMN following drug administration.

11.4.2.2 Effect of \(d\)-methamphetamine on Pre-Pulse Inhibition of the Acoustic Startle Reflex

The present experiment found that an acute dose of \(d\)-methamphetamine improved sensorimotor gating, at 150-180 min following drug ingestion (indexed by an increase in PPI amplitude of the startle response), in healthy adults. Unlike much of the preclinical work, the present experiment did not find that an acute dose of \(d\)-methamphetamine reduced PPI response after drug ingestion (Mansbach et al., 1988; Swerdlow et al., 1994, 2003; Bakshi et al., 1995; Wan et al., 1995). Furthermore, in terms of previous research using humans, the present results are also inconsistent, as no modulations to PPI have been
shown to occur 150-180 minutes following $d$-amphetamine ingestion (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2002a; Alessi et al. 2003; Swerdlow et al., 2003).

Although the bulk of preclinical and human experimental research indicates that amphetamine either attenuates or has no effect on PPI, recently Swerdlow et al. (2002a) reported a trend towards an increase in PPI, at 90 min following 20 mg $d$-amphetamine. Moreover, the authors reported a moderate effect size, suggesting adequate power to detect significant increases in PPI at alpha = .05 with a sample size of only 11-13 (Swerdlow et al., 2002a). Consistent with this, the present experiment found $d$-methamphetamine to significantly increase PPI with a sample size of 19. However, there have been no other studies that have reported improvements to sensorimotor gating following amphetamine consumption.

The present findings are inconsistent with the results from Experiment 4 (Chapter 10), which indicate that $d$-amphetamine had no effect on sensorimotor gating. This discrepancy in results between the present experiment and that of Experiment 4 (Chapter 10) may be attributed to differences in task administration. During the presentation of the startle tones in Experiment 4 (Chapter 10), participants were instructed to fixate gaze straight ahead and ignore the loud startle tones. However, in the present experiment, during the presentation of the startle tones, participants were required to complete a simple secondary task while asked to ignore the startle tones. These differences in task administration may elucidate the incongruent effects amphetamines had on sensorimotor gating.

However, it is also possible that the discrepancy in results may be attributed to differences in amphetamine blood concentrations, however, the blood data was not available to address this. Furthermore, this inconsistency may be attributed to differences in drug type. Particularly as the present findings are also inconsistent with previous $d$-amphetamine research, which, similar to Experiment 4 (Chapter 10), have consistently failed to demonstrate $d$-amphetamine (doses ranging from 5 mg to 20 mg $d$-amphetamine) to modulate PPI, 150-180 minutes after drug ingestion, in healthy adults (Kumari et al., 1998; Hutchison & Swift, 1999; Swerdlow et al., 2002a; Alessi et al. 2003; Swerdlow et al., 2003). As, to the author’s knowledge, there have been no previous studies that have
examined the acute effects of methamphetamine on PPI, further research exploring the effects of methamphetamine on sensorimotor gating is necessary to clarify the discrepancy.

Although there are limited reports suggesting that amphetamine modulates PPI in healthy adults at 150-180 minutes after drug ingestion (Swerdlow et al., 2002a), it has previously been reported that \textit{d}-amphetamine disrupts PPI in healthy adults at 90 min (Hutchison & Swift, 1999) and 25-40 min (Swerdlow et al., 2003) following the administration of 20 mg \textit{d}-amphetamine. Although differences in the time that PPI was assessed may explain why a \textit{d}-methamphetamine disrupted PPI effect was not observed in the present experiment, as compared with the findings reported by Hutchison and Swift (1999) and Swerdlow et al. (2003), there are also other factors that could elucidate the discrepancy. These include differences in drug type, experimental design, stimulus characteristics, response ranges, and other design features (refer to Section 10.4.2.2 for full details).

Consistent with the findings from Experiment 4 (Chapter 10), \textit{d}-methamphetamine did not modulate PPI in a subgroup of smokers. Therefore, these results do not support previous research that has shown \textit{d}-amphetamine to disrupt PPI in smokers, 150 min following drug consumption (Kumari et al., 1998). This discrepancy in results may be attributed to differences in drug type, drug dose, and drug condition comparisons (refer to Section 10.4.2.2. for full details). However, as the present experiment and Experiment 4 (Chapter 10) similarly observed no modulations to PPI in smokers following an average dose of 30 mg \textit{d}-amphetamine, it seems unlikely that 5 mg \textit{d}-amphetamine would produce PPI-disruptive effects in only 6 smokers. To clarify this discrepancy in results, further research examining the effects of 5 mg amphetamine on PPI need to be assessed in smokers.

In terms of driving, the present findings indicate that any reductions to driving performance observed 120-180 min following amphetamine consumption is unlikely to be associated with disruptions to PPI. The present results indicate that following a low dose of \textit{d}-methamphetamine, the ability to automatically ‘screen out’ irrelevant or intrusive sensory stimuli is enhanced at 150-180 min following drug consumption. This suggests that \textit{d}-methamphetamine improves driver’s ability to regulate environmental inputs and selectively allocate attention to relevant stimuli, which, in terms of driving, would not negatively impact driving performance. The results from Experiment 4 (Chapter 10) substantiate this, as \textit{d}-amphetamine was not found to affect PPI at all.
In summary, the results of the present experiment suggest that an acute dose of 0.42mg/kg of d-methamphetamine improves PPI (denoted by an increase in PPI amplitude of the startle response), 150-180 min after drug administration. Although, these results are inconsistent with Experiment 4 (Chapter 10), and previous preclinical and experimental human research, this may be attributed to differences in drug type or amphetamine blood concentrations. However, in terms of driving, the results from the present thesis indicate that a driving impairment, observed 120-180 min following amphetamine consumption, is unlikely to be related to disruptions to sensorimotor gating, as amphetamines were shown to improve or have no effect (Experiment 4) on this early inhibitory mechanism. Furthermore, previous research has consistently failed to report decrements to PPI 150-80 min after the consumption of d-amphetamine, therefore, further substantiating the claim that disruptions to PPI are unlikely to affect driving performance.

11.4.2.3 Effect of d-methamphetamine on the Auditory Oddball Task

The present experiment found that an acute dose of d-methamphetamine decreased N200 amplitude, suggesting a reduction in selective attention. However, d-methamphetamine was not found to modulate the P300 component. These results are inconsistent with Experiment 4 (Chapter 10), which reported an improvement in the speed at which information was evaluated and processed with d-amphetamine (indicated by a decrease in P300 latency).

It is difficult to interpret the discrepancy in results between the present experiment and Experiment 4 (Chapter 10), although differences in amphetamine type or amphetamine blood concentrations may have contributed to the inconsistency in results. However, interestingly, the discrepancy in results becomes less apparent when the d-amphetamine and d-methamphetamine results from the visual field task are also addressed (refer to Section 10.4.1.2 for d-amphetamine results and Section 11.4.1.2 for d-methamphetamine results). Specifically, for the visual field task, d-methamphetamine improved the speed at which visual information was evaluated and processed (denoted by a decrease in P300 latency), whereas, d-amphetamine was found to produce decrements to indices of selective attention, specifically for information presented in the periphery (denoted by a decrease in N200 amplitude). Although the visual field task and the auditory oddball task vary considerably, particularly in terms of modality, both tasks similarly involved the random
occurrence of an infrequent stimulus presented among frequently occurring stimuli. Furthermore, both tasks required the participant to attentively discriminate the rare stimulus from the frequent one, by noting the occurrence of only the target stimuli. Based on this, it seems suitable that the results from the visual field task be included in the present discussion.

Thus, following from this, the results from the two oddball tasks indicate a reduction in N200 amplitude (suggesting a decrease in selective attention) and a decrease in P300 latency (indicating improvements in the speed at which information is evaluated and processed) following the consumption of d-amphetamine and d-methamphetamine. This suggests that amphetamines appear to impair selective attention, however, enhance speed of information processing, irrespective of the modality that information is presented in.

It is difficult to relate the present results to previous research, as the literature is devoid of studies investigating the effects of amphetamine on the N200 component, in healthy adults. For the majority of studies in which the acute effects of stimulants on the P300 are examined, data on the earlier wave forms (i.e. N200) are not reported. The limited research that has examined the effects of stimulants, predominantly methylphenidate, on the N200 component, has involved ADHD patients. Although these studies have generally reported N200 component to be insensitive to methylphenidate, in ADHD patients (Halliday et al., 1993; Taylor et al., 1993; Winsberg et al., 1997; Jonkman et al., 1999), there have been some studies that have reported stimulant-induced modulations to the N200 waveform (Verbaten et al., 1994; Ozdag et al., 2004).

Contrary to the present findings, Verbaten et al. (1994) noted an increase in N200 amplitude following 10 mg dose of methylphenidate in children with ADHD. In contrast, Ozdag et al. (2004) demonstrated that methylphenidate normalised several ERP indices in children with ADHD except for N200 amplitude, suggesting that methylphenidate appears to be effective in improving impaired information processing in ADHD but not effective in receiving and discriminating information. These latter results are to some extent consistent with the present results. However, due to extensive differences in the population samples tested, it is difficult to make direct comparisons. Therefore, further research is necessary that examines the acute effects of amphetamine on this attention-dependant component, using healthy adults.
Few studies have shown amphetamine to modulate the P300 component (Halliday et al., 1994; McKetin et al., 1999). Consistent with the present findings, Halliday et al. (1994) and McKetin et al., (1999) failed to report any \(d\)-amphetamine effects on P300 amplitude when assessed at the Pz scalp site. Also consistent with the present experiment, McKetin et al., (1999) did not find \(d\)-amphetamine to modulate the latency of the P300. Although Halliday et al. (1994) reported a speeding of the P300 with \(d\)-amphetamine, this was evident only when latency estimates were based on single-trial epochs. To the author’s knowledge, there are no other studies that have examined the acute effects of amphetamine on the P300 component.

However, numerous studies have examined the effects of other stimulants, namely methylphenidate, on the P300. However, the results are contradictory. Some reports are consistent with the present results, which fail to observe any effects following drug administration (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Halliday et al., 1987; Fitzpatrick et al., 1988). In contrast, other reports have found similar effects to those reported in Experiment 4 (Chapter 10), where decreases in P300 latency have been observed following methylphenidate consumption (Brumaghim et al., Study 2, 1987; Cooper et al., 2005).

In addition, it has previously been argued that stimulants act on neurotransmitter systems that mediate response processing and not stimulus evaluation (Coons et al., 1981; Callaway, 1983, 1984; Halliday et al., 1983; Naylor et al., 1985; Brumaghim et al., Study 1, 1987; Halliday et al., 1987; Fitzpatrick et al., 1988; McKetin et al., 1999). However, the present results do not support this notion, as decreases in neither reaction time nor P300 latency were observed following \(d\)-methamphetamine consumption. Furthermore, the results from Experiment 4 (Chapter 10) also failed to support this hypothesis, as \(d\)-amphetamine was shown to improve the speed at which information was processed (indexed by decreases in P300 latency), which was positively associated with improvements in reaction time. Thus, contrary to previous reports, the results from the present thesis suggest that response processing and stimulus evaluation are related.

The \(d\)-methamphetamine-induced decrease in N200 amplitude may negatively impact driving, as this attenuated component suggests a reduction in a driver’s ability to selectively attend to relevant information within the traffic environment. Consequently,
this impairment is likely to result in an overload of information. Previous reports have indicated that deficits to attentional mechanisms, such as selective attention, can increase crash risk (for review see Anstey et al., 2005), as drivers may not appropriately attend to important information. The present results, therefore suggest that driving impairments attributed to therapeutic amphetamine concentrations may be associated with decrements in selective attention.

This notion is further supported with the findings from Experiment 4 (Chapter 10), which indicate that the ability to efficiently discriminate information presented in the periphery is impaired following \( d \)-amphetamine consumption (indexed by decreases in N200 amplitude for stimuli presented in the peripheral visual field). Although the cognitive (Experiment 1, Experiment 2, and Experiment 3) and ERP (Experiment 4 and the present experiment) results of the present thesis, indicate that any low dose amphetamine-related driving impairments are unlikely to be attributed to deficits to various aspects of attention, the attenuation of the N200 component observed in the present experiment and Experiment 4, suggest that attention, in terms of stimulus discrimination, may negatively affect driving ability.

In summary, the present findings indicate that an acute dose of 0.42mg/kg \( d \)-methamphetamine attenuates the N200 component, suggesting a reduction in selective attention. Although these results are inconsistent with the findings reported in Experiment 4 (Chapter 10), similar decrements in selective attention (N200) were found following \( d \)-amphetamine consumption during the visual field oddball task. In terms of driving, the results from the present thesis indicate that possible amphetamine-related driving impairments associated with low amphetamine concentrations may be associated with decrements to the attention-dependant component (N200), thus reflecting disruptions in the ability to efficiently discriminate information. However, as there have been no previous studies that have examined the effects of amphetamine on this ERP component further research is warranted to support these findings.

**11.4.3 Summary of the Effect of \( d \)-methamphetamine on Visual and Auditory Cognitive Processes and its Implications to Driving Performance**

In summary, the present results indicate that a low dose of \( d \)-methamphetamine generally improves aspects of cognitive functioning assessed with indices of visual and auditory
processes. Specifically, the present results demonstrate that an acute dose of \( d \)-methamphetamine improved the speed at which information was processed within the magnocellular and parvocellular visual pathways (denoted by a decrease in the latency of the P100 component for the visual pathways combined). Furthermore, there was a trend for \( d \)-methamphetamine to differentially affect the speed at which information was processed by the visual pathways, which was indexed by a more pronounced decrease in P100 latency for the magnocellular visual pathway. This suggests that \( d \)-methamphetamine has a more marked effect on the processing speed of motion, coarse details, and overall stimulus organisation (magnocellular), than the processing of high contrast, pattern, colour, and fine-detailed stimulus information (parvocellular). This enhancement in visual attention is consistent with the ERP results reported in Experiment 4 and the cognitive results reported in Experiment 1, Experiment 2, and Experiment 3. Thus, the results of the present thesis provide some evidence to suggest that possible amphetamine-related driving impairments associated with therapeutic amphetamine doses are unlikely to be associated with deficits to aspects of visual attention.

The present experiment did not find that \( d \)-methamphetamine differentially affected different regions of the visual field. However, \( d \)-methamphetamine improved the speed at which information presented to the central and peripheral visual fields was evaluated and processed (denoted by a decrease in P300 latency for the visual fields combined). This improvement in information processing speed was supported with corresponding improvements in reaction time. Although these results are inconsistent with the visual field task results reported in Experiment 4, which revealed a trend for \( d \)-amphetamine to differentially affect the different regions of the visual field in terms of selective attention (N200), the present thesis is the first investigation that has explored this issue using EEG. Therefore, further research is warranted.

However, overall, the results of the present thesis provide evidence to suggest that a single acute therapeutic dose of various forms of amphetamines improves the processing speed of visual information, which in terms of driving, suggests that possible driving impairments attributed to low amphetamine concentrations are unlikely to be associated with the early and late processing of visual information. However, the results from Experiment 4, do suggest that low-dose amphetamine-related driving impairments may be attributed to
decrements to peripheral visual field processing (in terms of selective attention), and possibly even ‘tunnel vision’ effects.

In terms of auditory processing, the present results indicate that \( d \)-methamphetamine does not modulate MMN. Although these findings are inconsistent with those reported in Experiment 4, in terms of driving, the ERP results from the present thesis suggest that any therapeutic-dose amphetamine-related driving impairments are unlikely to be associated with disruptions in the ability to automatically discriminate auditory changes within the traffic environment. In addition, the present experiment found that \( d \)-methamphetamine improved the ability to automatically ‘screen out’ irrelevant and intrusive auditory information (indexed by an increase in PPI amplitude of the startle response), 150-180 min after drug administration. Although, these results are inconsistent with Experiment 4 and previous research, in terms of driving, these results provide evidence to suggest that any amphetamine-related driving impairments observed 120-180 min following a therapeutic dose of amphetamine, are unlikely to be associated with disruptions to sensorimotor gating, as amphetamines were shown to improve or have no effect (Experiment 4) on this early inhibitory mechanism.

The present experiment found that \( d \)-methamphetamine reduced N200 amplitude during an auditory oddball task, indicating a decrease in selective attention. This suggests that any amphetamine-related driving impairments attributed to low amphetamine concentrations, may be associated with a reduction in the ability to selectively attend to and discriminate relevant information within the traffic environment. Although these results are inconsistent with the findings reported in Experiment 4, similar decrements in selective attention (N200) were found following \( d \)-amphetamine consumption during the visual field oddball task. These ERP results thus suggest that, at low levels, amphetamines may be producing decrements to the association level of cognitive processing, which consequently may result in drivers not selectively attending to and discriminating changes within the traffic environment. However, as there have been no previous studies that have examined the effects of amphetamine on this ERP component further research is warranted to support these findings.
Chapter 12. Limitations

There were several limitations that emerged from the present thesis that will be addressed in the present chapter.

An important limitation was that the baseline performance (for driving, neuropsychological and ERP measures), in each experimental session, was not assessed. Consequently, this may have lowered the sensitivity of the study to detect drug-related changes. Similar to the rationale adopted in controlling for mood differences between sessions (assessed with the POMS), baseline performance for driving, neuropsychological and ERP performance, obtained prior to drug administration, may have improved the study, as it would control for possible differences in performance between sessions prior to drug administration. This would have ensured that the interpretation of differences in performance across sessions were due to the drug itself, rather than differences in baseline performance (prior to drug administration). Furthermore, obtaining baseline performance data may have provided additional information as to the acute effects of amphetamines on performance, as further analyses, comparing pre- and post-drug administration, could have been conducted.

A further limitation of the present thesis was that only a single therapeutic drug dose was administered in each experiment, where each participant received one placebo and one amphetamine dose (either d-amphetamine, d,l-methamphetamine, or d-methamphetamine). This limits the interpretation of the results, as changes in performance in response to amphetamine, may have reflected different dose-response curves, rather than ‘general’ amphetamine effects. Specifically, by including a second drug condition in each experiment, performance following amphetamine consumption can be compared to a different drug dose, in addition to no drug (placebo). Thus, differences in performance can be attributed to amphetamine effects specifically, rather than participant’s response to a drug. Therefore, including a second drug dose in each experiment would enable a more meticulous evaluation of the effects of amphetamines on performance.

In addition, no baseline blood or saliva samples were obtained prior to drug administration to ensure participants had not consumed any amphetamines recently. Although participants were instructed to refrain from consuming illicit drugs for at least 7 days prior to each
session, participants may have forgotten or failed to inform the experimenter of recent drug use, from fear of being excluded from the study. This limitation was clearly manifested in the \(d,l\)-methamphetamine experiment (Experiment 2; Chapter 8), where data from one participant was omitted from analyses as the participant self-administered amphetamines prior to the experimental session. This was realised only because blood analyses from the placebo session revealed considerably high amphetamine levels in the blood. Recent amphetamine use prior to experimental sessions would compromise the results, as performance on tasks could not be attributed to the effects of the drug administered specifically during the experimental sessions, but a combination of recent amphetamine use and the drug administered in the study (amphetamine/placebo).

However, it is important to note that all blood samples obtained during the experimental sessions were screened for the seven major drug classes (opiates, amphetamines, benzodiazepines, cannabinoid, barbiturates, cocaine and methadone) using ELISA/EMIT screens. Subsequently, blood and saliva samples were analysed for specific amphetamine levels using the GC/MS method. Therefore, all participants were screened for recent use of drugs other than amphetamines. Although blood and saliva data were not available for Experiment 4 and Experiment 5, baseline saliva samples, using a saliva drug testing device, were obtained prior to drug administration to ensure no recent drug use. However, as the efficiency of the drug testing device is still being validated, the baseline results provided only an indication of recent drug use.

As a result of research ethic restrictions, the amphetamine doses administered in the present thesis was considerably low in comparison to ‘general’ recreational use. Therefore, no direct inferences with the results from the present thesis can be made to real-life amphetamine-related driving incidences of apprehended and fatally injured drivers. Although this is a fundamental difficulty in attempting to address this serious problem, the present results do indicate that single acute therapeutic doses of various preparations of amphetamines do affect performance, and this in itself is an important finding. Furthermore, the present results also demonstrate that a dose of 0.42mg/kg amphetamine has no serious adverse side effects.

Further to the drug dosing method used in the present study, a minor limitation was that different drug fillers (flour, magnesium carbonate, and lactose) were used for Experiments
1, 2, and 3, as different pharmacists prepared the drugs for the research. However, it is unlikely that this small variation in drug preparation would have affected the results as it is well recognized that these fillers do not modulate absorption, metabolism, or the pharmacodynamic effects of most drugs in general (hence why they are so commonly used). These fillers are also commonly used in drug research, such as with amphetamines. Thus, although to the author’s knowledge, there is no research that has assessed whether differences may be seen in drug effects due to different fillers being used, there is no evidence at present that this would occur. However, for consistency it would be more appropriate to maintain similar fillers across all drug conditions.

In terms of the simulated driving task, a brief amount of time was spent on each of the four driving tasks (i.e. five minutes). Although some, albeit weak, driving decrements were found with amphetamines, following a total of 20 minutes driving time, more robust and representative effects may have been observed with additional driving time. For instance, ten minutes driving time for each of the four driving tasks would be more representative of a ‘real life’ car trip, as rarely are car trips only five minutes in duration. However, it is also possible that administering longer driving tasks may result in amphetamines improving performance relative to placebo due to improvements in sustained attention, which was shown both significantly and at trend-level across the three amphetamine doses administered in the present thesis. A further limitation was that the simulated driving tasks were not randomised, as these computer-based tasks were pre-programmed and not amendable. That is, the night freeway driving task was always completed after the day time freeway task, and the night city task was always completed following the day time city driving task, which introduces the possibility of practice and fatigue effects. However, as no significant differences were found between the day and night driving conditions, this appears to have had little effect on the results.

Finally, as was discussed in Section 7.4.1, the loading factors assigned to some of the driving variables were questionable, and consequently may have produced some misleading results. For instance, according to the driving simulator analysis manual, signalling errors are assigned loading factors of 4 and 5, while straddling the solid line, exceeding the speed limit, and straddling the barrier line are assigned loading factors of 2. Yet, it is these latter driving behaviours that are most commonly reported in the amphetamine driving literature. The loading factors used in the present thesis were in
accordance with the standard loading factors provided by the driving simulation software used in our research laboratory (CyberCAR™ LITE driving simulator manual; Thoroughbred Technologies Pty. Ltd.). Although there may be limitations, in order to avoid reducing the reliability and validity of the driving assessment, performance was analysed according to the driving simulation software manual. Therefore, although using the standard loading factors suggested possible driving decrements with \( d \)-amphetamine, this may be somewhat misleading as the significant reduction in driving performance noted in the \( d \)-amphetamine condition may have resulted, for example, from excessive signalling (due to the high loading). Therefore, caution should be applied to the interpretation of the present results.

In terms of the neuropsychological measures used, brief practice sessions were employed immediately prior to the administration of each task. Including an extensive practice session, on a separate day, prior to the first experimental session, may have reduced learning effects throughout the studies, and decreased the likelihood of Type II error. This limitation was illustrated in the results, as for some cognitive tasks, differences in performance between sessions were notably attributed to learning effects over sessions, rather than drug effects. Although including session order as a factor reduced the misinterpretation of practice effects for drug effects, it also reduced the probability of finding a significant effect. Specifically, including a between-subject factor increased the number of comparisons, therefore, stronger Bonferroni adjustments were employed to correct for Type I error. Thus, as the alpha was divided by the number of post hoc comparisons, the small alpha values made it difficult to report significant amphetamine effects.
Chapter 13. Future Directions

The present thesis is the first set of investigations to examine the acute effects of various forms of amphetamine on simulated driving performance, movement estimation, driving-related cognitive functions assessed using EEG, and performance on the SFSTs, in healthy adults. For this reason, the present thesis will disseminate valuable information, pertaining to the effects of single acute therapeutic doses of various preparations of amphetamines on performance, to the scientific and general community. Specifically, the present thesis demonstrates that a single acute therapeutic dose of various preparations of amphetamines has minimal and inconsistent effects on driving ability and cognitive functioning. Furthermore, the present thesis indicates that the degree of impairment produced with the low amphetamine dosing conditions was below the sensitivity threshold of the SFSTs (which were designed to detect gross impairment associated with considerably higher amphetamine concentrations). However, as no considerable impairments in other psychomotor and cognitive functions were observed with amphetamines either, the present SFSTs findings highlight the point that these tests are unlikely to produce false positive results during police drug evaluation procedures for amphetamine-related impairments. This has important implications for law enforcement agencies currently using, or considering using, the SFSTs to test drivers for impairment associated with drugs other than alcohol.

The results from the present thesis provide direction for future research. Specifically, future research should endeavour to replicate and extend the present findings, by examining the acute effects of amphetamine on the ability to perceive and predict motion, risk taking behaviour, aspects of visual field processing, tunnel vision effects, and selective attention. Currently the literature is devoid of studies that address the acute effects of amphetamine on these indices. However, the results of the present thesis provide some evidence to suggest that therapeutic amphetamine doses have some minimal impairing effects on these indices. Therefore, to further understand the complex nature of amphetamine on human functioning, such as driving performance, the effects of amphetamine on these cognitive functions need to be further assessed.
In addition, it would be useful for future research to address the limitations discussed in the present thesis. Specifically, it would be beneficial for future research to obtain baseline performance measures for all experimental sessions, as this will control for possible differences in performance between sessions prior to drug administration. Employing baseline measures will enable the investigator to be confident that changes in performance across sessions are due to the drug itself, rather than differences in baseline performance (prior to drug administration). Furthermore, obtaining baseline performance data will provide additional information as to the acute effects of amphetamine on performance, as further analyses, comparing pre- and post-drug administration, may be conducted.

Furthermore, it would be useful for baseline bodily fluid samples to be obtained prior to drug administration and screened for all major drug classes, to ensure that recent drug use does not compromise the results. Specifically, screening for recent drug use prior to drug administration will control for the misinterpretation of performance due to the drug administered for research purposes (amphetamine/placebo), with the effect of recent drug use combined with the drug administered for research purposes (amphetamine/placebo). Furthermore, obtaining baseline bodily samples will deter participants from consuming drugs throughout the duration of the study for fear of being exposed. Consequently, this will also reduce the likelihood of residual psychological effects resulting from self-administration of drugs, which subsequently, would also affect study performance.

In addition, comparing the effects of several drug doses, or drug classes, on performance will avoid possible dose-response curves. Including a second drug condition in the study will enable a more meticulous evaluation of the effects of amphetamine on performance, as differences in performance can be attributed to specific drug effects, rather than participant’s response to a drug.

It would also be useful if future amphetamine research administer higher amphetamine doses to humans. The results of the present thesis provide support for research ethic committees to increase the approved amphetamine dose that can be administered to humans for controlled experimental research purposes. Assessing the effects of amphetamine on driving performance following the administration of higher amphetamine doses will extend the findings of the present thesis by expanding the representative sample.
Chapter 14. Summary of Major Findings

In summary, the results of the present thesis indicate that a single acute therapeutic dose of various preparations of amphetamines does not produce considerable driving impairments in recreational stimulant users, 2-3 hour post-drug administration. Although overall driving performance was found to be significantly impaired with d-amphetamine, it is important to highlight that only few specific driving behaviours were found to be significantly reduced with d-amphetamine. These included reductions in signalling adherence and driving too fast for the traffic conditions. d,l-methamphetamine and d-methamphetamine were not shown to significantly impair performance on any of the individual driving behaviours. Thus, the present results indicate that in general, therapeutic doses of amphetamines produce minimal driving effects. Moreover, the driving behaviours that were found to be impaired (d-amphetamine) do not reflect the typical driving behaviours that are most commonly seen in real-life amphetamine impaired drivers. This inconsistency in results between the present thesis and the epidemiological reports are likely to be attributed to substantial differences in the amphetamine blood concentrations. Interestingly, during all three amphetamine conditions, drivers travelled at a slower speed on the freeway at the time that an emergency situation occurred, relative to the placebo condition. This was the only driving behaviour that was observed across all three amphetamine conditions. It is argued that this may result from more cautious driving, or that the reduction in speed acted as a compensatory mechanism to permit drivers to attend to other aspects of driving.

The cognitive results indicate that a therapeutic dose of amphetamines has minimal effects on driving-related cognitive functioning, with only some suggestions of improvements, assessed using both standard cognitive tasks and EEG. Overall, the results highlight that low-dose amphetamines enhance various aspects of attention (ranging from early to late processing), psychomotor functioning, information processing, and early pre-attentive functions, such as MMN and PPI. Thus, overall, the present results provide little indication as to how a single acute therapeutic amphetamine dose may impair driving performance. However, as no considerable driving impairments were found with amphetamines, it is not surprising that no robust decrements to cognitive functioning were observed following a similar dose. This lack of significant decrement to performance appears to be attributable
to the low amphetamine doses administered. However, research examining the effects of considerably higher amphetamine doses on performance is required to ascertain this.

However, the noted improvement in movement estimation performance following \textit{d}-amphetamine and \textit{d}-methamphetamine consumption was interpreted as an impairment, as the smaller difference found between estimated and actual ‘time to contact’ may reflect less safe driving, as there is less time to respond appropriately to sudden changes in traffic conditions. Further support for this was manifested with the results from the driving simulator results, which indicated that amphetamines specifically affected driving behaviours associated with movement estimation, such as, driving too fast, driving too slow, and the notably smaller stopping distance between the vehicle and other objects during emergency situations. However, further research is required to corroborate this hypothesis.

In addition, the ERP analyses, which provided more sensitive measures of neural function underlying driving-related cognitive processes, indicated particularly subtle impairing effects of amphetamines on specific cognitive functions that are not readily observable using standard cognitive tasks. Specifically, the ERP results suggested a trend for \textit{d}-amphetamine to improve indices of selective attention for information presented to the central visual field, but impair indices of selective attention for information presented to the peripheral visual field. In terms of driving, these findings suggest the possibility that drivers dosed with low amphetamine concentrations may not efficiently attend to and discriminate objects in the periphery. Furthermore, the noted improvement in selective attention for stimuli presented in the fovea, suggests that drivers may be restricting attention to their focal point, which consequently may be impairing attentional mechanisms available for peripheral processing, such as responding to traffic lights. These results thus provide some support for an amphetamine-related ‘tunnel vision’ hypothesis.

Although impairments to the peripheral visual field were not similarly observed following the administration of \textit{d}-methamphetamine, decrements to indices of selective attention were found, following the consumption of \textit{d}-methamphetamine, during the auditory oddball task. In terms of driving, the consistent deficit to indices of selective attention following \textit{d}-amphetamine and \textit{d}-methamphetamine administration, suggests that drivers dosed with low amphetamine doses may not selectively attend to and discriminate changes
in the traffic environment. This decrement is likely to result in an overload of information, which can result in important information to be neglected, for example, responding to traffic lights.

In terms of the SFSTs, the present thesis demonstrates that following the administration of 0.42mg/kg d-amphetamine, 0.42mg/kg d,l-methamphetamine, and 0.42mg/kg d-methamphetamine, performance on the SFSTs was not impaired. Using the SFSTs, impairment associated with low dose d-amphetamine was identified in only 5% of cases, d-methamphetamine in 5% of cases, and d,l-methamphetamine in 0% of cases. These findings indicate that the degree of impairment produced with the low amphetamine dosing conditions was below the threshold of sensitivity of the SFSTs. However, as no considerable impairments in other psychomotor and cognitive functions were observed with amphetamines, the present SFSTs findings highlight the point that these tests are unlikely to produce false positive results during police drug evaluation procedures for amphetamine-related impairments.
References


Hurst, P.M. (1987), Amphetamines and driving. *Alcohol, Drugs, and Driving, 3*(1), 13-16.

Hurst, C. M. F. (2004). The hurst model of vision balances. *Clinical, 40*-44.


Appendix A  Patient Medical Questionnaire

PATIENT QUESTIONNAIRE

Name: ______________________  D.O.B.: __________
Address: ______________________  Date: __________
                                            Phone: ______

Instructions: These questions are designed to help us understand any medical problems
that you may have. All information given will be treated in the strictest confidence. Please
tick all relevant boxes. Please ask for assistance if you unsure about any of the questions.

Medical History:
Are you allergic to anything that you know of?
Medications? □ Yes  □ No
Foods? □ Yes  □ No
Surgical Tapes? □ Yes  □ No
Any other substances? □ Yes  □ No
If yes, please give details: _______________________________________________________

Do you take any medications (prescription or over-the-counter)? □ Yes  □ No
If yes, please fill in the details in the table below:

<table>
<thead>
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<th>Name of medication</th>
<th>Dose</th>
<th>Number of times taken each day</th>
<th>Date of commencement</th>
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</tbody>
</table>

Do you have any of the following problems?
Heart Problems? □ Yes  □ No
High or low pressure? □ Yes  □ No
Respiratory problems? □ Yes  □ No
Stomach or intestinal problems? □ Yes  □ No
Liver problems? □ Yes  □ No
Kidney or urinary problems? □ Yes  □ No
Diabetes? □ Yes  □ No
Anaemia or blood disorders? □ Yes  □ No
Epilepsy or fitting? □ Yes  □ No
Eyesight problems or colour blindness? □ Yes  □ No
Cancer? □ Yes  □ No
Skin disorders? □ Yes  □ No
Anxiety or depression? □ Yes  □ No
Any other psychological problem? □ Yes  □ No

If you answered YES to any of the questions above, please give details:
Have you ever had any operations? □ Yes □ No
If yes, please give details:

When did you last consult a doctor? And for what reason?

Do you follow any special diet? □ Yes □ No
If yes, what type?

How much alcohol do you drink?
Number of glasses? ________/day Type
Number of glasses? ________/week Type
Do you smoke? □ Yes □ No Number of cigarettes/day? ________
Do you drink coffee? □ Yes □ No Number of cups/day? ________

Do you use glasses? □ Yes □ No
Do you use contact lenses? □ Yes □ No
Do you use a hearing aid? □ Yes □ No
Do you use any other type of prosthesis? □ Yes □ No

Additional questions for **FEMALES ONLY**:
Are you or could you be pregnant? □ Yes □ No
Are you breastfeeding □ Yes □ No
Are your periods regular? □ Yes □ No
Last period ended? (date) __________________
Do you take the contraceptive pill? □ Yes □ No
Brand name? ______________
## Appendix B  Medical Examination Sheet

**MEDICAL HISTORY**

Trial Name and Number: ____________________________

Participant Name: ____________________________ Number ____________________________

D.O.B: ________________________ Sex: ____________________________ Date: ______________________

Background and concurrent disease:

Medications:

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<th>No</th>
<th>If yes, give details below:</th>
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<tr>
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<tr>
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</table>

Signature: ____________________________
# PHYSICAL EXAMINATION

**Trial Name and Number:** _________________________________

**Participant Name:** _____________________________ **Number** __________________

**D.O.B.** __________ **Sex**: ____________ **Date**: ____________

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<thead>
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<th>Abnormal</th>
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<tr>
<td>Abdomen</td>
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<tr>
<td>Nervous System</td>
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<tr>
<td>Lymph Nodes</td>
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<tr>
<td>ENT and Eyes</td>
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<tr>
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<td>Skin</td>
<td></td>
<td></td>
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<tr>
<td>Other (specify)</td>
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<td></td>
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</tbody>
</table>

**Baseline Obs:**

- **BP Standing**
- **BP sitting**
- **Pulse**
- **T**
- **Height**
- **Weight**

**Urinalysis**

**Comments:**

- _______________________________________________________________________
- _______________________________________________________________________
- _______________________________________________________________________
- _______________________________________________________________________
- _______________________________________________________________________
- _______________________________________________________________________
- _______________________________________________________________________

*Signature: ________________________________*
Appendix C  Information Sheet

PARTICIPANT'S NAME:

SUBJECT CODE  CODE

The Effects of Methamphetamine on Cognition, Electrophysiological Activity, Driving Ability and Sobriety Test Performance

Research Investigators: Professor Con Stough, Katherine Papafotiou, and Beata Silber

This study aims to investigate the efficiency of Victoria Police sobriety tests (Standardised Field Sobriety Tests (SFSTs)) in detecting driving impairment associated with methamphetamine. In addition, the present study will examine and identify the acute effects of this drug on mental and physical performance and electrophysiological activity. This project is being undertaken to provide more information on the effects of amphetamines on performance and assess the efficiency of sobriety tests in detecting amphetamines in drivers. This investigation will provide essential data concerning the introduction of roadside sobriety testing in Victoria. This research is part of an ongoing investigation into the evaluation of sobriety tests by K. Papafotiou, C. Stough and B. Silber, and is a collaborative project between Swinburne University of Technology and VicRoads.

The investigation consists of two phases:

- Phase One: Methamphetamine: Driving, SFSTs and cognition (two randomised sessions)
- Phase Two: Methamphetamine: EEG and cognition (two randomised sessions)

Initially, you will be screened (short interview and medical examination) to ensure that you are deemed suitable to participate in the study. Informed consent will be obtained and you will be required to complete a Demographics Questionnaire and an Amphetamine Use Questionnaire. This should take approximately 15 mins.

Phase One
This phase comprises of two experimental sessions. You will be given either a 0.42mg/kg methamphetamine capsule or a placebo capsule upon arrival. You will be required to perform a driving simulator task, the Standardised Field Sobriety tests (SFSTs) and a variety of computerised and pen and paper cognitive tasks. The driving simulator task is a computerised driving test that assesses driving ability across a range of situations, including a freeway and city traffic scenario. The SFSTs consist of various tests that require balance and motor coordination. These tests include the Horizontal Gaze Nystagmus, the Walk and Turn and the One Leg Stand. The cognitive tasks that will be administered assess a wide range of cognitive variables including attention, executive processes, information processing speed, motor responsiveness and decision-making. These tests should take approximately 1.5 hours to complete. Blood and saliva samples will be taken throughout the sessions. Past research has not demonstrated that the presence of amphetamines in the blood is associated with increased road collisions and deaths. The blood samples taken in the study will be used to help understand the relationship between these variables. Taking a blood sample before and after the administration of performance tests, such as the driving task, SFSTs and cognitive tests, allows us to determine whether the impairment (if observed) is related to the specific levels of amphetamine found in the blood. Therefore, one sample will be taken before you begin the tasks (after two hours have elapsed since the administration of the methamphetamine), a
second sample will be obtained after the driving simulator task and SFSTs (at 160 min), and a final sample will be obtained after you have completed the cognitive tasks (at 220 min). These two sessions should take approximately 4 hours each to complete.

**Phase Two**

This phase consists of two experimental sessions. Participants will be randomly given either a placebo capsule or a 0.42 mg/kg active methamphetamine capsule upon arrival. These sessions will involve using electroencephalogram (EEG) measures to examine brain electrical activity after the administration of methamphetamine. While the drug is reaching its blood peak level (0 mins-2 hours), a close-fitting cap containing 64 electrodes will be placed over your scalp and a small quantity of water-soluble gel will be used to ensure a good contact between the electrodes and scalp. Electrodes will also be attached to your nose and earlobes. The electrodes are for recording the natural activity of the brain and cannot give you an electric shock. All equipment that will come into contact with you is sterile and strict health and safety guidelines will be followed. A number of simple tasks will be administered during EEG recording, such as sitting quietly with eyes open or closed, while auditory and visual stimuli will be presented. Blood and saliva samples will be taken throughout each session. One sample will be taken prior to EEG recording (after two hours have elapsed since the administration of the methamphetamine), and a final sample will be obtained after EEG is recorded (at 3 hours). After the EEG recording the cap and leads will be removed and hair will be washed. These two sessions should take approximately 4 hours each to complete.

Desoxyn is a stimulant that has been approved for use in USA and is commonly prescribed for treatment of Attention-Deficit Hyperactivity Disorder (ADHD), obesity, or Narcolepsy. The usual daily dose ranges from 5-25 mg for children suffering from ADHD. A total Desoxyn dose will contain 0.42 mg/kg of methamphetamine. Placebo (no methamphetamine) will contain 0.42 mg/kg of flour.

This is a double-blind study; therefore, neither you nor the researcher will know what dose has been taken until the completion of the trial. During those sessions where you will administer the active methamphetamine it is likely that you will feel the following effects: impairment of motor-coordination, loss of appetite, increased heart rate, rapid pulse rate, over stimulation, restlessness, and insomnia.

If you consent to participating in the trial, you must agree not to consume alcohol for at least 24 hours prior to each session, or no other drugs for at least 7 days before each session. Amphetamine is known to influence driving ability, therefore, taxi vouchers will be provided for those who cannot make alternative transport arrangements home from each session. In addition, you must agree not to drive or ride, operate any machinery, nor consume any alcohol, drugs or medications, for at least 24 hours after each experimental session.

Additionally, applicants must fulfil the following criteria: Participants must have no history of current or past substance abuse, non regular amphetamine users (less than once a month), have no pre-existing physical or neurological conditions, no history of psychiatric, cardiac, endocrine, gastrointestinal, or bleeding disorders, not pregnant or lactating, and not taking any medication. Participants must also be required to have experimented with amphetamines previously. All participants must have a full driver’s license (no probationary drivers).

Your participation in this study is entirely voluntary and you are free to withdraw from the study at any time. If you decide to withdraw, you are still required to abide by the safety restrictions advising you not to drive for at least 24 hours after the administration of methamphetamine, and not to consume alcohol, drugs or any other medications for at least 24 hours after each session.
You will be video taped while performing the SFSTs. This footage is likely to be used by Victoria Police officers and/or other professionals in SFSTs training sessions, only if you provide your consent (see attached SFSTs Footage Consent Form).

It is expected that the results of this study will be published in a peer-review journal and will be presented at national conferences. The identity of participants will not be disclosed and all data will be presented as group data.

Should you have any questions regarding the investigation titled “The Effects of Methamphetamine on Cognition, Electrophysiological Activity, Driving Ability and Sobriety Test Performance”, can be directed to Prof. Con Stough, Swinburne Centre for Neuropsychology, Swinburne University of Technology (ph: 9214 8167 email: cstough@swin.edu.au).

In the event you have a complaint regarding the way you were treated during the study or a query that Prof Con Stough was been unable to satisfactorily answer, please contact:

The Chair
Human Research Ethics Committee
Swinburne University of Technology
P.O. Box 218
HAWTHORN, VIC. 3122
Appendix D  Consent Form

SWINBURNE UNIVERSITY OF TECHNOLOGY

INFORMED CONSENT

The Effects of Methamphetamine on Cognition, Electrophysiological Activity, Driving Ability and Sobriety Test Performance

Research Investigators: Professor Con Stough, Katherine Papafotiou, and Beata Silber

This is a joint project between Swinburne University and VicRoads

<table>
<thead>
<tr>
<th>PARTICIPANT’S NAME:</th>
<th>SUBJECT CODE</th>
<th>CODE _ _</th>
</tr>
</thead>
</table>

I (the participant) have read and understood the information above and understand the general purposes, methods, and demands of the study. Any questions I have asked have been addressed to my satisfaction.

I have no history of current or past substance abuse, non regular amphetamine user (less than once a month), have no pre-existing physical or neurological conditions, no history of psychiatric, cardiac, endocrine, gastrointestinal, or bleeding disorders, not pregnant or lactating, and not taking any medication.

I agree that in the experimental sessions I may be administered a capsule that may contain either no methamphetamine or 0.42mg/kg of methamphetamine.

I agree that for the sessions in which I may possibly be administered methamphetamine, I will not drive or ride to or from the session. I agree that I will utilise the transport home provided for me by the researchers.

I agree that I should not consume alcohol for at least 24 hours or any medications or other drugs for at least 7 days prior to my sessions.

Amphetamine is known to influence driving ability, therefore, I agree to utilise the transport/taxi vouchers arranged to get home.

I agree that I should not drive or ride, operate any machinery, nor consume alcohol or any medication for at least 24 hours after my sessions.

I am satisfied with the explanation given in relation to the project, and my consent is freely given.

I agree to participate in this activity, and I understand that I am free to withdraw from the study at any time.

I agree that research data collected for the study may be published or provided to other researchers on the condition that anonymity is maintained and that I cannot be identified.

NAME OF PARTICIPANT..............................................................................…..……………………….
SIGNATURE...........................................................…….…………………….....DATE..........……..…...

NAME OF PRINCIPAL INVESTIGATOR/S............................................……………………..........……
SIGNATURE..........................................................……..……………………....DATE....………….......
SIGNATURE...........................................................……..……………………...DATE.........…………..

SWINBURNE UNIVERSITY OF TECHNOLOGY

INFORMED CONSENT
SFSTs FOOTAGE CONSENT FORM (b)
Swinburne University of Technology

The Effects of Methamphetamine on Cognition, Electrophysiological Activity, Driving Ability and Sobriety Test Performance

Research Investigators: Professor Con Stough, Katherine Papafotiou, and Beata Silber

This is a joint project between Swinburne University and Vicroads

<table>
<thead>
<tr>
<th>PARTICIPANT’S NAME:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECT CODE</td>
<td>CODE</td>
</tr>
</tbody>
</table>

Part of our research on the efficiency of the Standardised Field Sobriety Tests (SFSTs) involves the videotaping of participants while they perform the SFSTs. This video footage is likely to be presented during Police Officers and other professionals SFSTs training sessions ONLY.

I (the participant) have read and understood the information above and understand the general purposes, methods, and demands of the study. Any questions I have asked have been addressed to my satisfaction.

I (the participant) have seen/reviewed the footage of myself (the participant) and consent to the video footage of myself (the participant) to be shown to Police officers and other professionals in SFST training sessions.

NAME OF PARTICIPANT……………………………………………………………………………………………………..

SIGNATURE……………………………………………………………………………………………………………………..DATE………..

NAME OF PRINCIPAL INVESTIGATOR/S……………………………………………………………………………………………………..

SIGNATURE……………………………………………………………………………………………………………………..DATE………..

SIGNATURE……………………………………………………………………………………………………………………..DATE………..
Appendix E  Demographics Questionnaire

Demographics Questionnaire

Subject Code: ______________________

Age: ______

Gender: Female    Male

Marital Status? ______

Highest level of education attained:

(please circle)

1. Year 10
2. Year 11
3. Year 12
4. T.A.F.E

Please state what degree

5. University(Undergraduate)

Please state what degree


6. University (Postgraduate)

Please state what degree

7. Other (please State)

Do you have any history of physical, psychiatric, neurological, endocrine disorders, bleeding disorders or gastrointestinal disorders?  

(Including health problems, substance abuse, depression, etc.)

1. Yes
2. No

(Please State)

Are you pregnant or lactating?  

1. Yes
2. No

If female, when did you last menstruate?  

What is the status of your current employment?  

1. Full-time
2. Part-time
3. Casual
4. Unemployed

How many hours do you work in an average week? ______
Appendix F  Drug Use History Questionnaire

Drug Use History Questionnaire

Please provide the following information:
(If you do not want to answer a question please leave it blank.)

1. Age: years       months
2. Gender:  Female  Male
3. Females: How many days ago did your menstrual cycle end? ___________
4. Handedness (circle):  Left  Right  Both
5. Have you ever suffered an epileptic seizure? Yes / No
   If yes, please specify: ____________________________________________
6. Have you ever suffered any serious head injuries or periods of unconsciousness? Yes / No
   If yes, please specify: ____________________________________________
7. Do you have any hearing problems? Yes / No
   If yes, please specify: ____________________________________________
8. Are you currently taking any form of medication? Yes / No
   If yes, please specify: ____________________________________________
9. Have you ever had to see a psychologist or psychiatrist (or are you concerned about your psychological well-being)? Yes / No
   If yes, please specify: ____________________________________________
10. Has anyone in your family had any psychological or psychiatric illnesses? Yes / No
    If yes, please specify which family member and what illness:

11. Is English your first language? Yes / No

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.

12. Have you ever smoked tobacco? Yes / No

12.1 When was the last time you smoked tobacco? Please specify

   Hours  □   Days  □   More than 1 week ago  □   More than a month ago  □  Other  □
   (if today)  (if within last week)
12.2 How often do/did you smoke tobacco? Please specify approximately how many cigarettes per day/week etc.

<table>
<thead>
<tr>
<th>These Days (past year)</th>
<th>When you Smoked MOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Weekly</td>
<td>Weekly</td>
</tr>
<tr>
<td>Less than Weekly</td>
<td>Less than Weekly</td>
</tr>
<tr>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

12.3 What strength tobacco do you or did you smoke? (eg. <4mg, 4mg, 8mg, 12mg, 16mg)

12.4 How long have you or did you smoke tobacco for?

13. Have you ever consumed alcohol? Yes / No

13.1 When was the last time you consumed alcohol? Please specify

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 1 week ago</td>
<td>More than a month ago</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

13.2 How often do you consume alcohol? Please specify approximately how many times per day/week etc.

<table>
<thead>
<tr>
<th>Daily</th>
<th>Weekly</th>
<th>Less than Weekly</th>
<th>Monthly</th>
<th>Other</th>
</tr>
</thead>
</table>

13.3 How many standard drinks do you consume in a session?

13.4 How many standard drinks do you consume in a week?

13.5 How often during the last year have you needed a drink in the morning to get yourself going after a heavy drinking session? Please Specify

<table>
<thead>
<tr>
<th>Never</th>
<th>Less than monthly</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily or almost daily</th>
</tr>
</thead>
</table>

13.6 How long have you been drinking alcohol for?

14. Have you ever consumed caffeine (e.g. tea, coffee, coke)? Yes / No

14.1 When was the last time you consumed caffeine? Please specify

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 1 week ago</td>
<td>More than a month ago</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
14.2 How often do you or did you consume caffeine? Please specify approximately how many cups

These Days

Daily
Weekly
Less than Weekly
Monthly
Other

14.3 How long have you/did you drink caffeine for?

15. Have you ever had cannabis? Yes / No

15.1 When was the last time you had cannabis? Please specify

Hours [ ] Days [ ] More than 1 week ago [ ] More than a month ago [ ] Other [ ]
(if today) (if within last week)

15.2 How often and how much cannabis do you or did you consume?
Please specify approximately how many times and how much per session

These Days (past year):

Daily
Weekly
Less than Weekly
Monthly
Other

Quantity
eg. 1 joint, 3 bong

When you Smoked MOST
Daily
Weekly
Less than Weekly
Monthly
Other

Quantity
eg. 1 joint, 3 bongs, etc.

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

16. Have you ever had ecstasy? Yes / No

16.1 When was the last time you had ecstasy? Please specify

Hours [ ] Days [ ] More than 1 week ago [ ] More than a month ago [ ] Other [ ]
(if today) (if within last week)
16.2 How often do you or did you have ecstasy and how many tablets do/did you consume per session? Please specify approximately how many times and how much per session.

<table>
<thead>
<tr>
<th>These Days (past year);</th>
<th>Quantity eg. 1 tablet</th>
<th>When you Consumed MOST;</th>
<th>Quantity eg. 1 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td></td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>6-monthly</td>
<td></td>
<td>6-monthly</td>
<td></td>
</tr>
<tr>
<td>Yearly</td>
<td></td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

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

17. Have you ever had cocaine? Yes / No

17.1 When was the last time you had cocaine? Please specify.

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
<th>More than 1 week ago</th>
<th>More than a month ago</th>
<th>Other</th>
</tr>
</thead>
</table>

17.2 How often do you or did you use cocaine and how much do/did you consume per session? Please specify approximately how many times and how much per session.

<table>
<thead>
<tr>
<th>These Days (past year);</th>
<th>Quantity eg. 1 line, 1 point</th>
<th>When you Consumed MOST;</th>
<th>Quantity eg. 1 line, 1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td></td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>6-monthly</td>
<td></td>
<td>6-monthly</td>
<td></td>
</tr>
<tr>
<td>Yearly</td>
<td></td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

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

18. Have you ever had amphetamines? Yes / No

18.1. When was the last time you had an amphetamine? Please specify.

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
<th>More than 1 week ago</th>
<th>More than a month ago</th>
<th>Other</th>
</tr>
</thead>
</table>
18.2 How often do you or did you use amphetamine and how much amphetamine do/did you consume per session?

*Please specify approximately how many times and how much per session*

<table>
<thead>
<tr>
<th>These Days (past year); Quantity</th>
<th>When you Consumed MOST; Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily</strong></td>
<td><strong>Daily</strong></td>
</tr>
<tr>
<td><strong>Weekly</strong></td>
<td><strong>Weekly</strong></td>
</tr>
<tr>
<td><strong>Monthly</strong></td>
<td><strong>Monthly</strong></td>
</tr>
<tr>
<td><strong>6-monthly</strong></td>
<td><strong>6-monthly</strong></td>
</tr>
<tr>
<td><strong>Yearly</strong></td>
<td><strong>Yearly</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>

18.3 How long have you or did you use amphetamine for?

19. Have you ever had heroin? Yes / No

19.1 When was the last time you had heroin? *Please specify*

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
<th>More than 1 week ago</th>
<th>More than a month ago</th>
<th>Other</th>
</tr>
</thead>
</table>

19.2 How often did you or do you use heroin and how much heroin do/did you have per session? *Please specify approximately how many times and how much per session*

<table>
<thead>
<tr>
<th>These Days (past year); Quantity</th>
<th>When you Consumed MOST; Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily</strong></td>
<td><strong>Daily</strong></td>
</tr>
<tr>
<td><strong>Weekly</strong></td>
<td><strong>Weekly</strong></td>
</tr>
<tr>
<td><strong>Monthly</strong></td>
<td><strong>Monthly</strong></td>
</tr>
<tr>
<td><strong>6-monthly</strong></td>
<td><strong>6-monthly</strong></td>
</tr>
<tr>
<td><strong>Yearly</strong></td>
<td><strong>Yearly</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>

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

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

20.1 When was the last time you used an inhalant? *Please specify*

<table>
<thead>
<tr>
<th>Hours (if today)</th>
<th>Days (if within last week)</th>
<th>More than 1 week ago</th>
<th>More than a month ago</th>
<th>Other</th>
</tr>
</thead>
</table>
20.2 How often did you or do you use inhalants and how much do/did you inhale per session?

*Please specify approximately how many times and how much per session*

<table>
<thead>
<tr>
<th>These Days (past year);</th>
<th>Quantity eg. 1 inhale</th>
<th>When you Consumed MOST;</th>
<th>Quantity eg. 1 inhale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td></td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>6-monthly</td>
<td></td>
<td>6-monthly</td>
<td></td>
</tr>
<tr>
<td>Yearly</td>
<td></td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

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

________________________________________________________

306
Appendix G  The Profile of Mood States (POMS) Questionnaire

THE PROFILE OF MOOD STATES

Subject ID          Study Code          Test Session

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

1. Friendly
2. Tense
3. Angry
4. Worn out
5. Unhappy
6. Clear-headed
7. Lively
8. Confused
9. Sorry-for-things-done
10. Shaky
11. Limpers
12. Peeved
13. Considerate
14. Sad
15. Active
16. On edge
17. Greeneyed
18. Blue
19. Energetic
20. Panicky
21. Hopeless
22. Relaxed
23. Unworthy
24. Spurned
25. Sympathetic
26. Uneasy
27. Restless
28. Unable to concentrate
29. Fatigued
30. Helpful
31. Annoyed
32. Discouraged
33. Resentful

NOT AT ALL  A LITTLE  MARGINALLY QUITE  EXTREMELY

34. Nervous
35. Lonely
36. Miserable
37. Muddled
38. Cheerful
39. Bitter
40. Exhausted
41. Anxious
42. Ready-to-fight
43. Good-natured
44. Glossy
45. Desperate
46. Sluggish
47. Rebellious
48. Helpless
49. Weary
50. Bewildered
51. Alert
52. Deceived
53. Perturbed
54. Effervescent
55. Transfixed
56. Full of pep
57. Hot-tempered
58. Worthless
59. Forgetful
60. Carefree
61. Terrified
62. Guilty
63. Vigorous
64. Uncertain about things
65. Bushed

Appendix H  The Standardised Field Sobriety Test Score Sheet

Physical Impairment Test - Performance Record, Page 1

Horizontal Gaze Nystagmus

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspect wearing</td>
<td></td>
<td></td>
<td>Eye tracking normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>contact lenses</td>
<td></td>
<td></td>
<td>Eye disorder observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil size equal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signs Observed

- Eye does not pursue smoothly
- Distinct nystagmus at maximum deviation
- Nystagmus onset before 45 degrees

Left Eye

Right Eye

Other

Walk and Turn Test

Instruction Stage

- Cannot Keep Balance

Starts to Soon

Walking Stage

<table>
<thead>
<tr>
<th>Signs Observed</th>
<th>First Nine Steps</th>
<th>Second Nine Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misses heel to toe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps off line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raises arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual steps taken</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Improper Turn
(describe)

Cannot Perform Test
(explain)

Other

23 June 1999 - 22/02
Physical Impairment Test - Performance Record, Page 2

Interpretation Table

Nystagmus

<table>
<thead>
<tr>
<th>Walk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>and</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One Leg Stand Test

<table>
<thead>
<tr>
<th>Signs Observed</th>
<th>Left Leg</th>
<th>Right Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sways while balancing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uses arms to balance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puts foot down</td>
<td></td>
<td></td>
</tr>
</tbody>
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Other

Type of Footwear

23 June 1999 - 22:302
Appendix I Raw d-amphetamine Blood and Saliva Concentrations at 120, 170, and 240 Minutes After Drug Administration For All Subjects Separately

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<th>Subject No.</th>
<th>Blood 120 min (ng/mL)</th>
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Note that the blood concentrations presented in the above table have been rounded off to the nearest full integer. However, all means and Standard Deviations discussed in the thesis have been calculated with decimal places.
### Appendix J Raw d,l-methamphetamine Blood and Saliva Concentrations at 120, 170, and 240 Minutes After Drug Administration For All Subjects Separately

<table>
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<tr>
<th>Subject No.</th>
<th>Blood 120 min (ng/mL)</th>
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*Note that the blood concentrations presented in the above table have been rounded off to the nearest full integer. However, all means and Standard Deviations discussed in the thesis have been calculated with decimal places.*
Appendix K Raw d-methamphetamine Blood and Saliva Concentrations at 120, 170, and 240 Minutes After Drug Administration For All Subjects Separately

<table>
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