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ORIGINAL INVESTIGATION

The acute effects of *d*-amphetamine and methamphetamine on attention and psychomotor performance

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Abstract
Rationale It is not clear how the deleterious effects of amphetamines on driving performance are mediated in terms of select cognitive processes.
Objectives The current three separate experiments assessed the acute effects of an oral dose of either 0.42-mg/kg *d*-amphetamine, *d*,*l*-methamphetamine and *d*-methamphetamine on driving-related cognitive functions in a total of 60 healthy non-fatigued adults.
Materials and methods Three separate repeated measures counterbalanced, double-blind, placebo-controlled designs were employed in which 20 volunteers completed two treatment conditions, either *d*-amphetamine, *d*,*l*-methamphetamine or *d*-methamphetamine and placebo. Performance was assessed on a range of attentional, psychomotor and perceptual speed tasks.
Results Mean blood concentrations at 120-, 170- and 240-min postdrug administration were 83, 98 and 96 ng/ml, respectively, for *d*-amphetamine, 90, 95 and 105 ng/ml, respectively, for *d*,*l*-methamphetamine and 72, 67 and 59 ng/ml, respectively, for *d*-methamphetamine. The amphetamines, in general, improved various aspects of attention (Digit Vigilance, Digit Symbol Substitution Test and Movement Estimation Performance) with some evidence to suggest possible enhancement in psychomotor functioning (Tracking ability) and perceptual speed (Inspection Time).
Conclusions The current series of studies primarily provides evidence of low-level amphetamine-related enhancement of function; however, it also provides evidence of less conservative movement estimation that might contribute to amphetamine-related road fatalities.

Keywords *d*-amphetamine · Methamphetamine · Attention · Psychomotor Performance · Perceptual Speed

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Introduction

Research has indicated that over the last decade, the number of drug-related road accidents in Australia is steadily increasing (Drummer et al. 2003a,b), with the most recent published report finding that 31% of Australian road fatalities are drug related (TAC 2005). Amphetamines are an important contributor to this statistic, with recent research finding that 4.1% of Australian drivers, in general, and 23% of truck drivers killed on the roads tested positive to stimulants (Drummer et al. 2003b). However, it is not clear whether amphetamine use has a direct causal role in the accident rate or whether there are specific cognitive processes that are impaired in driving after acute amphetamine use. Although it is acknowledged that low amphetamine doses generally improve cognitive functioning, it is the purpose of this paper to explore aspects of driving that may be impaired after acute amphetamine use which may subsequently lead to road fatalities.

Amphetamines are sympathomimetic amines with central nervous system (CNS) stimulant activity that have both therapeutic properties and a tremendous potential for abuse. The pharmacological effects of amphetamines have been attributed to their effects on central catecholamine neurotransmission, where they block the reuptake from the synapse,

inhibit the action of monoamine oxidase and facilitate the release of dopamine and noradrenaline (Laruelle et al. 1995; Breier et al. 1997; Feldman et al. 1997; Drevets et al. 2001). In terms of the behavioural effects, it is hypothesised that amphetamines enhance monoamine function, and consequently, increase signal to noise ratio, particularly in the cortex (Mattay et al. 2000).

Empirical investigations of performance in non-fatigued healthy adults on neurocognitive measures vary, with reports of no effects (Foltin and Evans 1993; Kelly et al. 1993; Pickworth et al. 1997; Comer et al. 2001), improved performance (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; Wachtel and de Wit 1999; Cami et al. 2000; de Wit et al. 2000, 2002; Johnson et al. 2000; Mattay et al. 2000; Asghar et al. 2003; Barch and Carter 2005) and impaired performance (Hurst 1962, 1967; Weiner et al. 1988; Solomon et al. 1981; Kennedy et al. 1990; Bakshi et al. 1995; Kumari et al. 1998; Hutchison and Swift 1999; Swerdlow et al. 2003), after low amphetamine consumption (doses ranging from 5 to 30 mg). These inconsistencies may be related to a number of factors including individual differences in catecholamine genes and function (Mattay et al. 2000), baseline cognitive capacity (Mattay et al. 2000), drug use history and differences in tasks and/or task complexity.

Amongst the cognitive domains modulated by amphetamines, the most consistent findings are of amphetamine-related improvements on tasks of attention, psychomotor function and perceptual speed, all processes important in driving. In terms of attention, although there have been some null findings (Comer et al. 1996, 2001; Pickworth et al. 1997), in general, significant improvements have been observed in vigilance tasks (both in accuracy and speed) after 5- to 15-mg *d*-amphetamine (Comer et al. 1996; Koelega 1993; Kelly et al. 1991). de Wit et al. (2002) also reported an enhancement of attention after *d*-amphetamine (10 and 20 mg) 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 10 mg/70 kg to 20-mg *d*-amphetamine and 40 mg *d*,*l*-amphetamine (Wachtel and de Wit 1999; Kelly et al. 1991; Ward et al. 1997; Cami et al. 2000). Finally, Johnson et al. (2000) also reported improved attention and accuracy of reasoning ability after the administration of 0.42-mg/kg *d*-methamphetamine.

Furthermore, in DSST performance, improvements on other psychomotor tasks, such as motor speed and coordination, have also been observed with low dose amphetamine use (Kennedy et al. 1990). Comer et al. (1996) reported improvement in tracking ability on a divided attention task after 10-mg *d*-amphetamine. Performance on tracking tasks has also been examined with sleep-deprived volunteers (Magill et al. 2003; Belleville et al. 1979), in which a dose of either 10- or 20-mg *d*-amphetamine significantly improved tracking performance.

Although there have been some null findings (Comer et al. 1996, 2001), amphetamines have been shown to enhance aspects of perceptual speed. Kennedy et al. (1990) reported increases in perceptual speed performance after 10-mg *d*-amphetamine. Speeded reaction time has also been consistently reported after *d*-amphetamine administration (Fillmore et al. 2005; Asghar et al. 2003; McKetin et al. 1999; Kumari et al. 1997; Halliday et al. 1994; Fleming et al. 1995; Johnson et al. 2000; Rapoport et al. 1980).

Contrary to the reported amphetamine-related improvements on attention, psychomotor function and perceptual speed, amphetamine has been shown to impair performance on visual scanning tasks (Kennedy et al. 1990; Silber et al. 2005). Kennedy et al. (1990) explored the effects of 10-mg *d*-amphetamine on a range of cognitive processes and found amphetamine to impair performance on a visual search task; whereas, performance on all other cognitive tasks showed improvements with amphetamine. It has been argued that sympathetic arousal can induce perceptual narrowing or tunnel vision which results in a perceptual restriction to the focal point (Easterbrook 1959), with a corresponding loss of acuity peripherally. "Tunnelling" is thought to occur when attentional processes become overwhelmed, such as during high task demands and stress (Mills et al. 1999; Williams 1988, 1995a,b), producing a decrease in an individual's ability to gather information efficiently. This mechanism may, thus, explain these apparently discrepant effects of amphetamine on cognition, with recent *d*-amphetamine research findings consistent with this thesis (Mills et al. 2001).

In addition, research has shown amphetamine to have negative effects on prepulse inhibition and latent inhibition (Kumari et al. 1998; Hutchison and Swift 1999; Swerdlow et al. 2003; Solomon et al. 1981; Weiner et al. 1988; Bakshi et al. 1995), measures of sensorimotor gating, reflecting deficits in the ability to filter out irrelevant or intrusive stimuli, which subsequently caused an overload of information (Blumenthal et al. 1996; Swerdlow 1996; Swerdlow and Geyer 1998). The literature, thus, highlights the complex nature of the effects of stimulants on human behaviour. The findings indicate that at therapeutic doses, amphetamine improves performance on cognitive processes such as attention, psychomotor function and perceptual speed. However, for other aspects of cognitive functioning, such as those requiring visual scanning or the ability to filter out irrelevant information, low doses of amphetamine appears to impair performance.

The aim of the present series of studies was to investigate the acute effects of *d*-amphetamine and isomers of metham-

phetamine on cognitive processes relevant to driving in healthy, stimulant-using, non-fatigued adults. These forms of amphetamine were administered orally, as they are commonly used recreationally by young adult drivers and occupationally by truck drivers, respectively. Methamphetamine is considered to be a more potent central psychostimulant than *d*-amphetamine. Methamphetamine exists in two isomeric forms, dextro (*d*-) and levo (*l*-) (Logan 2002), with the *d*-isomer having greater CNS potency than the *l*-isomer in terms of increasing dopamine and norepinephrine activity (Logan 2002). Racemic mixtures (*d*,*l*-) also produce less dopamine and norepinephrine activity than the *d*-isomeric form and are, thus, less potent. To simulate real-life amphetamine-induced effects, these studies administered oral doses of 0.42 mg/kg, as it is one of the highest doses administered to humans for controlled experimental research purposes, and the amphetamine levels in the blood are representative of the low range found in apprehended and fatally injured drivers (Logan et al. 1998; Drummer et al. 2003a). Studies 1, 2 and 3, thus, compared the effects of *d*-amphetamine, *d*,*l*-methamphetamine and *d*-methamphetamine, respectively, to the placebo.

Study 1: *d*-amphetamine

Materials and methods

Participants

Twenty healthy stimulant users (ten males; ten females) aged between 21 and 32 years (M=25.4 years, SD=3.2 years), with an average male weight of 82.1 kg (SD=10.6) and an average female weight of 62.2 kg (SD=10.4), were recruited through community 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). The Swinburne University Human Research Ethics Committee approved the research, and all participants provided written informed consent.

All participants were screened by a medical practitioner to ensure that they had no history of substance abuse, had no preexisting 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 illicit stimulants were permitted to participate.

Drug

Dexamphetamine sulphate (5-mg dexamphetamine tablets, Sigma Pharmaceuticals, Victoria, Australia) was prepared by mixing a 0.42-g/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).

Experimental design

A repeated measures, counterbalanced (drug), double-blind, placebo-controlled design was employed. Participants completed the two treatment conditions: 1) placebo and 2) 0.42-mg/kg *d*-amphetamine separated by a 1-week washout period to reduce residual effects of the drug from the first session. All participants consented to refrain from consuming alcohol for at least 24 h before each session and illicit drugs for at least 7 days before each session.

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 and to assess CNS functions influenced by amphetamines. The battery consisted of a combination of pen and paper tests and computerised tasks. In addition, a mood questionnaire was administered to determine whether there were any differences in mood at the start of the two testing conditions.

The Profile of Mood Scale (POMS) (McNair, Lorr, Droppleman 1992) is a 65-item self-administered questionnaire that provides an index of six mood dimensions over the preceding 7-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.

Digit Span (DS) (Wechsler 1997) involves the immediate verbal recall of numbers. It is a measure that loads heavily on working memory and efficiency of attention (i.e. freedom from distractibility). 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. Brief practice trials were given immediately before administration of the tasks to ensure that the instructions were clearly understood.

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 ability to focus and sustain attention, Digit Vigilance also provides a measure of simple reaction time. This computer task required participants 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/s for 5 min. Three measures of vigilance were computed: accuracy, reaction time and number of false alarms.

The Movement Estimation Task is an attention task that assesses the estimation of movement speed and "time to contact". The task is based on 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), which has been implicated in impaired traffic safety. The present task consisted of two 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, 14-cm diameter). The speed at which the target travelled also varied across trials (10, 5, or 2.5 cm/s). 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. "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 before administration of the tasks. The total duration of this task was 15 min.

Digit Symbol Substitution Test (DSST) (Wechsler 1997) 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. Participants are 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 s. A practice trial was given immediately before administration of the task to ensure that the task requirements were clearly understood.

The Tracking Task (Baddeley and Logie 1986) measures visual–motor coordination. This computerised task had two difficulty levels. The first level required the participant to follow a moving stimulus (2×2 cm white square) that randomly changed 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, 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 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 before administration of the task.

The Trail-Making Task 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 allocated 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 (e.g. 1–A–2–B–3–C, etc.). 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 before administration of the tasks to verify that the instructions were clearly understood.

The Inspection Time (IT) task (Deary and Stough 1996) is a measure of perceptual speed. This task assesses the presentation time that a subject requires to discriminate between two possible stimuli. The objective is 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 when this occurs is taken as the measure

of IT. Practice trials were given immediately before administration of the task.

Blood and saliva samples

Three blood and three saliva samples were taken from each participant during each session. As *d*-amphetamine has a peak blood concentration between 120 and 180 min (Angrist et al. 1987; Kupietz et al. 1985), the first blood and saliva sample was obtained 120 min after drug administration, the second sample, 170 min after drug administration and the third sample, 240 min after drug consumption. A 10-ml blood sample was obtained using a syringe, by venipuncture from the antecubital vein, and a 1-ml saliva sample was obtained using a collection swab. Blood and saliva samples were immediately stored in a −20°C freezer and subsequently transported to a −70°C freezer after 5–7 days. Blood and saliva samples were analysed for amphetamine levels using the gas chromatography/mass spectroscopy method (Moeller and Kraemer 2002).

Procedure

For the two 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 h before each session. In addition, participants were not permitted cigarettes throughout 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 the 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 before 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. For example, administering the POMS before drug consumption controlled the misinterpretation of differences in cognitive performance due to preexisting mood rather than the drug administration itself. The research nurse then administered the drug orally.

The first blood and saliva sample was obtained 120 min after drug administration and the second sample, 170 min after drug administration. The battery of neuropsychological tests was administered between 3 and 4 h after drug consumption as *d*-amphetamine blood concentrations remain relatively constant during this period (Angrist et al. 1987; Brauer et al. 1996). Practice trials for the cognitive tasks were only given immediately before administration of the corresponding test. 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. Upon completion of the cognitive tests, the third and final blood and saliva sample was obtained 240 min after drug consumption. The only reported adverse reaction to *d*-amphetamine consumption was difficulty with falling asleep and/or disturbed sleep on the night after that session.

Statistical analyses

A Wilcoxon signed-rank test was conducted for the POMS Total Mood Disturbance Score to determine whether there were any significant differences in mood between the placebo and *d*-amphetamine conditions (where the independent variable was drug condition and the dependent variable was the Total Mood Disturbance Score; a composite of the tension–anxiety, depression–dejection, anger–hostility, vigour–activity, fatigue–inertia, and confusion–bewilderment dimensions). This nonparametric test was employed because we were unable to normalise the data.

All cognitive variables were analysed using repeated measures analyses of variance (ANOVAs) 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 drug sessions, suggesting possible carryover effects (see results for full description). If an interaction was found between "session order" and drug ($p<0.05$), paired *t* test comparisons were employed to explore the effects of *d*-amphetamine on performance separately for each of the two groups (i.e. *d*-amphetamine administered in first session and *d*-amphetamine administered in second session). Outliers were removed from analyses where appropriate (greater than three standard deviations from the mean).

One-way ANOVAs tested for effects of *d*-amphetamine on the DSST, three Digit Vigilance indices (accuracy, reaction time and number of false alarms) and Inspection Time, separately. A series of 2×2 ANOVAs tested for effects of *d*-amphetamine on Digit Span (forward/backward), number of errors made on the Tracking Task (easy/

Table 1 Demographics and recreational drug use are shown for participants for each of the three studies

	d-Amphetamine				*d,l*-Methamphetamine				*d*-Methamphetamine			
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Age (years)	25.4	3.2	21	32	24.3	3.4	21	34	25.4	3.3	21	32
Years of education	15.1	1.8	11	20	14.2	1.8	11	18	14.4	2.1	12	18
Current amphetamine use (per year)	4.2	8.8	0	40	3.6	4	0	12	3.3	4.8	0	20
Amphetamine use when consumed most (per year)	7.4	12	0	40	10	11.5	0	40	9.1	12	0	40
Period of time using amphetamine (years)			0	10			0.5	7			0.5	7
Current ecstasy use (per year)	5.3	5.7	0	12	8.9	7.1	1	20	4.2	3.8	0	12
Ecstasy use when consume most (per year)	15.2	17.4	0	40	19.7[a]	14.6	1	40	20.3	16	0	40
Period of time using ecstasy (years)			0	6			2	7			0.5	10
Current marijuana use (per year)	13.2	17.7	0	50	26.6	66.2	0	300	24.4	65.7	0	300
Marijuana use when consume most (per year)	72.8	117.9	0	300	100.4	134.6	1	300	132	141.3	0	300
Period of time using marijuana (years)			0	10			1	12			0	12
Current cocaine use (per year)	0.5	0.8	0	2	1.5	2.6	0	12	0.7	0.7	0	2
Period of time using cocaine (years)			0	5+			0	6			0	5
Alcohol per week (units)	8.9	10.3	0	40	8.8	6.2	3	30	13.6	10	2	40

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

difficult), total time spent in error on the Tracking Task (easy/difficult) and the Trail-Making Test (trail A/trail B). A 2×2×3×3 ANOVA tested for effects of *d*-amphetamine on the Movement Estimation Task (easy/difficult), Occlusion Size (small/medium/large), Speed (slow/medium/fast), and their interactions. For each significant interaction (or main effect where degrees of freedom were greater than 1), a Bonferroni adjustment was employed to reduce alpha by the number of post hoc comparisons to decrease Type 1 error. All *p*-values reported are corrected *p*-values.

In addition, analyses were performed to examine the relation between individual blood amphetamine levels (determined by the average blood levels obtained 170 and 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 scores were subtracted from *d*-amphetamine performance scores for each individual across all tasks) with a series of Spearman's rho measures of association. Alpha was reduced to 0.01 to reduce Type I error.

Results

Demographic characteristics of the participants are summarised in Table 1. The level of *d*-amphetamine detected in blood and saliva at 120 min after drug administration was 83 and 236 ng/ml, respectively, at 170 min after drug administration, 98 and 242 ng/ml, respectively, and at 240 min after drug administration, 96 and 260 ng/ml, respectively.

POMS

Before drug administration, participants in the placebo condition reported more negative moods than before the *d*-amphetamine condition (T=29.5, p<0.02). The mood dimensions that loaded most strongly on this Total Mood Disturbance Score were vigour–activity (p<0.05), depression–dejection (p<0.05), confusion–bewilderment (p<0.05) and fatigue–inertia (p=0.06).

To further explore why these differences were evident "before" any drug administration, the data were divided into two groups, according to whether *d*-amphetamine was administered in the first or second session. Wilcoxon's signed-rank tests showed that those who received *d*-amphetamine in their first session reported more negative moods before their subsequent placebo session (T=6, p<0.05), whereas, those who received the placebo in their first session scored similarly on the POMS before their subsequent *d*-amphetamine session. This suggests that there may have been residual psychological effects of *d*-amphetamine that were related to performance on the subsequent placebo condition, and so, to account for any session-order effects in the analyses, the session that *d*-amphetamine was administered (first or second) was employed as a between subject factor for all statistical analyses.

Neuropsychological measures

Details of results for all main effects and interaction for the cognitive tasks, including means and standard errors, are

Table 2 Overview of main effects of *d*-amphetamine on cognitive and psychomotor performance

		d-Amphetamine; 1st session		*d*-Amphetamine; 2nd session				
		Mean (std error)		Mean (std error)				
Test	Factor	Placebo	*d*-Amphetamine	Placebo	*d*-Amphetamine	*df*	F	*p* value
Digit span	T × Ses					1, 17	2.06	NS
	T	6.4 (0.2)	6.4 (0.2)			1, 17	0.13	NS
(Forward)	T × Task	7.6 (0.2)	7.8 (0.1)			1, 17	1.05	NS
(Backward)		5.3 (0.3)	5.5 (0.3)					
DSST	T × Ses	73.8 (3.1)	67.3 (3.8)	63.0 (3.1)	67.4 (3.8)	1, 18	5.54	0.03
	T					1, 18	0.21	NS
DV/accuracy	T × Ses					1, 18	0.93	NS
	T	98.5 (0.5)	97.9 (0.5)			1, 18	0.48	NS
DV/reaction time	T × Ses					1, 18	0.08	NS
	T	396.8 (7.8)	384.5 (6.0)			1, 18	4.07	0.06 ↑
DV/false alarms	T × Ses					1, 18	0.15	NS
	T	1.3 (0.5)	0.7 (0.3)			1, 18	1.35	NS
Track/no. of errors	T × Ses					1, 15	4.3	NS
	T	32.2 (3.0)	28.8 (2.1)			1, 15	1.76	NS
(Tracking only)	T × Task	29.0 (3.7)	28.2 (2.6)			1, 15	1.59	NS
(Dual tracking)		35.4 (3.3)	29.4 (2.3)					
Track/time in error	T × Ses	2,990.7 (706.4)	3,368.8 (584.2)	5,103.8 (576.8)	3,531.8 (477.0)	1, 13	4.47	0.05
	T					1, 13	1.68	NS
(Tracking only)	T × Task × Ses	2,336.7 (845.0)	3,429.5 (505.8)	4,178.8 (690.0)	2,703.6 (413.0)	1, 13	0.4	NS
(Dual tracking)		3,644.7 (992.6)	3,308.2 (819.1)	6,028.8 (810.5)	4,360.0 (668.8)			
Movement est.	T × Ses	−0.16 (0.06)	0.04 (0.08)	−0.08 (0.06)	−0.21 (0.08)	1, 18	13.45	0.002
	T					1, 18	0.69	NS
(Easy task)	T × Task × Ses	−0.13 (0.09)	0.17 (0.13)	−0.00 (0.09)	−0.24 (0.13)	1, 18	5.13	0.04
(Difficult task)		−0.19 (0.08)	−0.1 (0.06)	−0.16 (0.08)	−0.17 (0.06)			
(Small occlusion)	T × Occl × Ses	−.1 (0.04)	0.01 (0.04)	−0.03 (0.04)	−0.11 (0.04)	1, 18	4.21	0.06
(Medium occlusion)		−0.19 (0.06)	0.01 (0.08)	−0.08 (0.06)	−0.2 (0.08)			
(Large occlusion)		−0.19 (0.1)	0.09 (0.14)	−0.15 (0.1)	−0.31 (0.14)			
(Slow speed)	T × Speed × Ses	−0.06 (0.1)	0.28 (0.14)	0.01 (0.1)	−0.16 (0.14)	1, 18	6.02	0.03
(Medium speed)		−0.24 (0.07)	−0.08 (0.08)	−0.19 (0.07)	−0.29 (0.08)			
(Fast speed)		−0.17 (0.05)	−0.09 (0.05)	−0.07 (0.05)	−0.17 (0.05)			
Inspection time	T × Ses	67.3 (3.9)	68.9 (3.8)	68.6 (3.9)	59.6 (3.8)	1, 18	7.76	0.01
	T					1, 18	3.69	0.07 ↑
Trail-making A and B	T × Ses	3,431.2 (352.9)	3,800.0 (389.6)	4,269.8 (352.9)	4,027.1 (389.6)	1, 18	4.36	0.05
	T					1, 18	0.16	NS
(Trail A)	T × Task × Ses	2,087.8 (203.7)	2,176.6 (251.9)	2,654.5 (203.7)	2,606.3 (251.9)	1, 18	1.0	NS
(Trail B)		4,774.6 (580.9)	5,423.3 (591.2)	5,885.1 (580.9)	5,447.9 (591.2)			

Note that 1) All *p*-values for main effects of treatment exceeding 0.10 are shown as NS (not significant) and the arrows indicate improvement (↑) and impairment (↓) relative to placebo condition. 2) *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. 3) 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 the first session and subjects who consumed *d*-amphetamine in the second session (however, where the interaction was not significant, the means for both sessions combined are displayed in the '1st session' column). 4) Tests in brackets represent the subsets of the preceding test. 5) *DV* Digit vigilance, *T* treatment main effect, *Ses* session order, *Occl* occlusion

given in Table 2. Results for all post hoc tests are given in the text below. The number of outliers excluded from analyses can be determined by the degrees of freedom reported in Table 2.

In the Digit Vigilance task, there was a trend-level reduction of reaction time in the *d*-amphetamine condition (p=0.06). 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=0.002). 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 the placebo [$t(9)$=4.17, p<0.01]. 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=0.50]. In addition, a significant interaction was found between session order and task (p=0.04). 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<0.05]. No further significant differences were found. A trend-level interaction was also noted for session order and occlusion (p=0.06). 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 the placebo for the small [$t(9)$=4.18, p<0.01], medium [$t(9)$=3.40, p<0.05] and large [$t(9)$=3.62, p<0.05] occlusions. However, it should be noted that in *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=0.03). 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<0.01] and underestimated significantly less for the fast speed [$t(9)$=3.28, p<0.05] compared to the 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 the placebo [$t(9)$= 2.98, p=0.08].

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=0.05). However, post hoc tests revealed no significant differences between drug conditions for the two groups (*d*-amphetamine consumed in the first session [$t(9)$=1.56, p=0.31]; *d*-amphetamine consumed in the second session [$t(9)$=1.21, p=0.52]). Similarly, for the DSST, a significant interaction was found for session order and drug (p=0.03); however, paired sample *t* tests yielded no significant differences between drug conditions for the two groups (*d*-amphetamine consumed in the first session [$t(9)$=1.70, p=0.12]; *d*-amphetamine consumed in the second session [$t(9)$=1.69, p=0.13]).

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=0.05). 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 the placebo [$t(8)$=2.36, p=0.09]. No significant drug effects were found when *d*-amphetamine was administered in the first session [$t(5)$=0.74, p=0.99]. Finally, *d*-amphetamine improved Inspection Time performance at a trend level (p=0.07). In addition, an interaction was found with session order (p=0.01), with post hoc tests indicating that when *d*-amphetamine was consumed in the second session, *d*-amphetamine significantly improved inspection time performance compared to the placebo [$t(9)$= 3.54, p<0.01]. This difference in performance between drug conditions was not observed when *d*-amphetamine was consumed in the first session [$t(9)$=0.58, p=0.58].

Exploratory analyses

No significant relations were found between *d*-amphetamine levels in blood and performance, with the strongest, an inverse association with reaction time in the Digit Vigilance task [r (19)=−0.44, p=0.06].

Study 2: *d,l*-methamphetamine

Materials and methods

The measures, procedure and statistical analyses for study 2 were the same as those reported in study 1, with the only exceptions being the different drug used, the participants involved and that there was a 2-week rather than 1-week washout period (based on the possibility of carryover effects described in study 1 Results section).

Participants

Twenty healthy stimulant users (ten males; ten females) aged between 21 and 34 years (M=24.3 years, SD=3.4 years), with an average male weight of 81.2 kg (SD=12.6) and an average female weight of 59.7 kg (SD=6.9) were recruited. All participants had a minimum

Table 3 Overview of main effects of *d,l*-methamphetamine on cognitive and psychomotor performance

Test		*d,l*-methamphetamine 1st session		*d,l*-methamphetamine 2nd session				
		Mean (Std Error)		Mean (Std Error)		*df*	F	*p* value
	Factor	placebo	*d,l*-meth	placebo	*d,l*-meth			
Digit span	T × Ses					1, 17	3.61	NS
	T	6.7 (0.2)	6.5 (0.2)			1, 17	1.86	NS
(Forward)	T × Task	7.7 (0.1)	7.5 (0.2)			1, 17	0.04	NS
(Backward)		5.8 (0.3)	5.5 (0.4)					
DSST	T × Ses	70.0 (2.4)	67.4 (3.2)	64.0 (2.3)	71.4 (3.0)	1, 17	23.7	0
	T					1, 17	5.6	0.03 ↑
DV/accuracy	T × Ses					1, 17	4	NS
	T	97.6 (0.6)	97.7 (0.9)			1, 17	0.00	NS
DV/reaction time	T × Ses					1, 17	1.06	NS
	T	395.0 (8.8)	379.4 (8.7)			1, 17	5.17	0.04 ↑
DV/false alarms	T × Ses					1, 17	3.23	NS
	T	1.5 (0.4)	1.3 (0.2)			1, 17	0.37	NS
Track/no. of errors	T × Ses					1, 17	1.83	NS
	T	29.1 (2.0)	27.3 (2.0)			1, 17	0.72	NS
(Tracking only)	T × Task	26.7 (1.7)	27.4 (3.0)			1, 17	2.12	NS
(Dual tracking)		31.4 (2.7)	27.3 (2.1)					
Track/time in error	T × Ses					1, 15	0.72	NS
	T	4,376.6 (567.9)	3,520.8 (338.3)			1, 15	4.82	0.04 ↑
(Tracking only)	T × Task	4,079.4 (539.3)	3,486.3 (486.8)			1, 15	0.71	NS
(Dual tracking)		4,673.8 (677.6)	3,555.2 (373.6)					
Movement est.	T × Ses					1, 16	1.43	NS
	T	−0.11 (0.05)	−0.06 (0.05)			1, 16	0.77	NS
(Easy task)	T × Task	0 (0.07)	0.05 (0.08)			1, 16	0.00	NS
(Difficult task)		−0.22 (0.06)	−0.17 (0.05)					
(Small occlusion)	T × Occl	−0.11 (0.04)	−0.06 (0.02)			1, 16	0.03	NS
(Medium occlusion)		−0.12 (0.06)	−0.09 (0.05)					
(Large occlusion)		−0.1 (0.07)	−0.04 (0.07)					
(Slow speed)	T × Speed	0.01 (0.09)	0.05 (0.08)			1, 16	0.01	NS
(Medium speed)		−0.21 (0.05)	−0.14 (0.04)					
(Fast speed)		−0.12 (0.04)	−0.1 (0.03)					
Inspection time	T × Ses					1, 17	2.47	NS
	T	72.8 (3.3)	71.9 (3.3)			1, 17	0.02	NS
Trail-making A and B	T × Ses	3,614.4 (239.1)	4,132.3 (204.4)	3,759.9 (226.9)	3,568.8 (194.0)	1, 17	5.8	0.03
	T					1, 17	1.24	NS
(Trail A)	T × Task × Ses	2,044.4 (177.2)	2,432.3 (152.3)	2,568.9 (168.1)	1,999.6 (144.5)	1, 17	0.69	NS
(Trail B)		5,184.4 (391.1)	5,832.3 (328.2)	4,950.9 (371.0)	5,137.9 (311.3)			

Note that 1) All *p*-values for main effects of treatment exceeding 0.10 are shown as NS (not significant) and the arrows indicate improvement (↑) and impairment (↓) relative to placebo condition. 2) *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. 3) 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 the first session and subjects who consumed *d*,*l*-methamphetamine in the second session (however, where the interaction was not significant, the means for both sessions combined are displayed in the '1st session' column). 4) Tests in brackets represent the subsets of the preceding test

d,l-methd,*l*-Methamphetamine, *DV* digit vigilance, *T* treatment main effect, *Ses* session order, *Occl* occlusion

of 11-years education. 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). The Swinburne University Human Research Ethics Committee approved the research, and all participants provided written informed consent. All participants completed a medical examination and the exclusion criteria was the same as that for study 1.

Drug

d,*l*-Methamphetamine (Lipomed, Arlesheim, Switzerland) was prepared by mixing *d*,*l*-methamphetamine with magne-

sium 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 2-, 5- or 10-mg *d*,*l*-methamphetamine. Each participant was administered 0.42-mg/kg *d*, *l*-methamphetamine.

Experimental design

A repeated measures, counterbalanced (drug), double-blind, placebo-controlled design was employed. Participants completed the two treatment conditions: 1) placebo and 2) 0.42-mg/kg *d*,*l*-methamphetamine, 2 weeks apart to reduce any residual effects of the drug from the first session.

Results

Data from one participant were omitted from all statistical analyses, as high level amphetamines were found in their blood during the placebo session due to participant-confirmed self-administration of amphetamines before the experimental session. Demographic characteristics of the participants are summarised in Table 1.

The level of *d*,*l*-methamphetamine detected in blood and saliva at 120 min after drug administration was 90 and 343 ng/ml, respectively, at 170 min after drug administration, 95 and 475 ng/ml, respectively, and at 240 min after drug administration, 105 and 568 ng/ml, respectively.

POMS

There was no significant difference between drug conditions on the Total Mood Disturbance Score (T=82.5, p=0.90). Although no effect was found, the session that *d*,*l*-methamphetamine was administered was used as a between subject factor in all analyses, as the results from the *d*-amphetamine study suggested possible learning effects indicated by the interactions found between drug and session order.

Neuropsychological measures

Details of results for all main effects and interaction for the cognitive tasks, including means and standard errors, are given in Table 3. Results for all post hoc tests are given in the text below. The number of outliers excluded from the analyses can be determined by the degrees of freedom reported in Table 3.

In the Digit Vigilance task, there was a significant reduction of reaction time in the *d*,*l*-methamphetamine condition (p=0.04). A significant overall improvement in DSST performance was observed in the *d*,*l*-methamphetamine condition relative to the placebo condition (p=0.03). In addition, a significant interaction was found with session order (p<0.001). Post hoc tests revealed that when *d*,*l*-methamphetamine was consumed in the second session, *d*,*l*-methamphetamine significantly improved DSST performance compared to the placebo [t(9)=5.72, p<0.001]. However, this was not observed when *d*,*l*-methamphetamine was consumed in the first session [t(8)=1.59, p=0.15]. Although no main effect of drug was found on the Trail-Making tasks, there was an interaction of session order with drug (p=0.03). 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=0.19] or when *d*,*l*-methamphetamine was consumed in the second session [t(9)=1.47, p=0.35]. Finally, participants in the *d*,*l*-methamphetamine condition spent significantly less time in error on the Tracking tasks compared to the placebo condition (p=0.04).

Exploratory analyses

No significant relations were found between *d*,*l*-methamphetamine levels in blood and performance, with the strongest, a positive associated with reaction time in the Digit Vigilance task [r (19)=0.54, p=0.02].

Study 3: *d*-methamphetamine

Materials and methods

The measures, experimental design, procedure and statistical analyses for study 3 were the same as those reported in study 2, with the only exceptions being the different drug administered and the participants involved.

Participants

Twenty healthy stimulant-users (ten males; ten females) aged between 21 and 32 years (M=25.4 years, SD=3.3 years), with an average male weight of 75.6 kg (SD=11.5) and an average female weight of 62.9 kg (SD=4.5) were recruited. All participants had a minimum of 12-years education. All participants were consumers of caffeine with an average daily intake of 1.6 cups of coffee (range 0–3). Of the 20 participants, eight were self-assessed smokers, averaging 3.7 cigarettes a day (range 0–20). The Swinburne University Human Research Ethics Committee approved the research, and all participants provided written informed consent. All participants completed a medical examination and the exclusion criterion was the same as those for study 1 and study 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-, 10-, 5- or 2-mg *d*-methamphetamine. Each participant was administered 0.42-mg/kg *d*-methamphetamine.

Experimental design

A repeated measures, counterbalanced (drug), double-blind, placebo-controlled design was employed. Participants completed two treatment conditions: 1) placebo and 2) 0.42-mg/kg *d*-methamphetamine, 2 weeks apart to reduce any residual effects of the drug from the first session.

Results

Demographic characteristics of the participants are summarised in Table 1. The level of *d*-methamphetamine detected in blood and saliva at 120 min after drug administration was 72 and 285 ng/ml, respectively, at 170 min after drug administration, 67 and 223 ng/ml, respectively, and at 240 min after drug administration, 59 and 190 ng/ml, respectively.

POMS

Before 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=0.07). Although only a trend level finding, the session that *d*-methamphetamine was administered was used as a between subject factor in all analyses to clarify any effects that session order may have had.

Neuropsychological measures

Details of results for all main effects and interaction for the cognitive tasks, including means and standard errors, are given in Table 4. Results for all post hoc tests are given in the text below. The number of outliers excluded from analyses can be determined by the degrees of freedom reported in Table 4.

In the Digit Vigilance task, there was an improvement in accuracy (p=0.01) and a trend-level reduction of reaction time (p=0.1) 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=0.02). Furthermore, in the *d*-methamphetamine condition, participants underestimated "time to contact" less for all occlusions relative to the placebo condition (p=0.02). This difference increased as a function of occlusion size.

A significant interaction of session order with drug was found in the DSST (p<0.001). 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 that of the placebo [t(8)=5.22, p<0.01]; however, when *d*-methamphetamine was consumed in the second session, participants performed significantly better in the *d*-methamphetamine condition compared to that of the placebo [t(10)=3.65, p<0.01]. Square root transformations were conducted on the Tracking Task data. Although no main effect for drug was found in 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=0.04) and total time spent in error (p=0.05). 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=0.40; t(7)=1.34, p=0.44, respectively] or in the second session [t(9)=2.00, p=0.15; t(9)=1.73, p=0.24, respectively].

Exploratory analyses

No significant relations were found between *d*-methamphetamine levels in the blood and performance, with the strongest, an inverse association with performance on the Tracking task [r (19)=−0.44, p=0.06].

Summary of results

In summary, *d*-amphetamine improved performance on measures of attention [i.e. Movement Estimation Task (when *d*-amphetamine was consumed in the first session) and reaction time on the Digit Vigilance task at a trend level], psychomotor performance (i.e. Tracking task; when *d*-amphetamine was consumed in the second session) at a trend level and perceptual speed (i.e. Inspection Time task; when *d*-amphetamine was consumed in the second session). *d*,*l*-methamphetamine improved performance on measures of attention and psychomotor performance, specifically reaction time was reduced in the Digit Vigilance task, and performance improved on the DSST (when *d*,*l*-methamphetamine was consumed in the second session) and the Tracking tasks.

Finally, compared to the placebo, *d*-methamphetamine improved performance on measures of attention (i.e. accuracy and reaction time (trend) on the Digit Vigilance task and Movement Estimation Task). Furthermore, when *d*-methamphetamine was administered in the first session, *d*-methamphetamine decreased DSST performance; howev-

Table 4 Overview of main effects of *d*-methamphetamine on cognitive and psychomotor performance

Test		*d*-methamphetamine 1st session		*d*-methamphetamine 2nd session		*df*	F	*p* value
		Mean (std error)		Mean (std error)				
	Factor	Placebo	*d*-meth	Placebo	*d*-meth			
Digit span	T × Ses					1, 16	0	NS
	T	6.5 (0.2)	6.5 (0.2)			1, 16	0	NS
(Forward)	T × Ses Task	7.3 (0.2)	7.3 (0.2)			1, 16	0.2	NS
(Backward)		5.7 (0.2)	5.6 (0.3)					
DSST	T × Ses	73.9 (3.1)	66.6 (2.6)	65.5 (2.8)	72.4 (2.4)	1, 18	33.9	0
	T					1, 18	0.05	NS
DV/accuracy	T × Ses					1, 14	0.67	NS
	T	98.3 (0.6)	100.0 (0.0)			1, 14	8.22	0.01 ↑
DV/reaction time	T × Ses					1, 16	1.38	NS
	T	396.7 (6.0)	387.6 (6.6)			1, 16	3.03	0.1 ↑
DV/false alarms	T × Ses					1, 17	4.16	NS
	T	0.5 (0.2)	0.4 (0.1)			1, 17	0.03	NS
Track/no. of errors	T × Ses	25.44 (3.1)	30.1 (2.6)	27.3 (2.8)	22.1 (2.4)	1, 16	5.27	0.04
	T					1, 16	0.002	NS
(Tracking only)	T × Ses Task × Ses	25.6 (3.6)	34.4 (4.4)	25.8 (3.3)	20.2 (3.9)	1, 16	2.46	NS
(Dual tracking)	Ses	25.3 (3.9)	25.7 (2.9)	28.8 (3.6)	23.9 (2.6)			
Track/time in error	T × Ses	3,164.2 (472.2)	4,020.7 (574.4)	3,289.1 (427.1)	2,596.7 (519.6)	1, 16	4.72	0.05
	T					1, 16	0.09	NS
(Tracking only)	T × Ses Task × Ses	3,176.6 (460.3)	5,266.8 (989.8)	2,754.5 (416.3)	2,397.8 (895.3)	1, 16	1.46	NS
(Dual tracking)	Ses	3,151.9 (689.6)	2,774.7 (428.7)	3,823.8 (623.8)	2,795.6 (387.8)			
Movement est.	T × Ses					1, 17	0.98	NS
	T	−0.22 (0.04)	−0.1 (0.04)			1, 17	6.11	0.02 ↑
(Easy task)	T × Ses Task	−0.16 (0.06)	−0.05 (0.06)			1, 17	0.36	NS
(Difficult task)		−0.28 (0.04)	−0.16 (0.04)					
(Small occlusion)	T × Ses Occl	−0.09 (0.02)	−0.06 (0.02)			1, 17	6.98	0.02 ↑
(Medium occlusion)		−0.24 (0.05)	−0.13 (0.04)					
(Large occlusion)		−0.33 (0.07)	−0.15 (0.07)					
(Slow speed)	T × Ses Speed	−0.23 (0.06)	−0.06 (0.08)			1, 17	0.47	NS
(Medium speed)		−0.28 (0.05)	−0.16 (0.04)					
(Fast speed)		−0.16 (0.03)	−0.1 (0.02)					
Inspection time	T × Ses					1, 18	3.17	NS
	T	65.0 (3.2)	63.9 (3.4)			1, 18	0.05	NS
Trail-making A and B	T × Ses					1, 16	2.71	NS

Table 4 (continued)

	T	3,433.6 (123.9)	3,529.2 (194.9)	1, 16	0.48	NS
(Trail A)	T × Ses Task	2,125.4 (112.3)	2,181.0 (129.8)	1, 16	0.05	NS
(Trail B)		4,741.8 (202.2)	4,877.3 (314.6)			

Note that 1) All *p*-values for main effects of treatment exceeding 0.10 are shown as NS (not significant) and the arrows indicate improvement (↑) and impairment (↓) relative to placebo condition. 2) *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. 3) 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 the first session and subjects who consumed *d*-methamphetamine in the second session (however, where the interaction was not significant, the means for both sessions combined are displayed in the '1st session' column). 4) Tests in brackets represent the subsets of the preceding test

d-meth d-Methamphetamine, *DV* digit vigilance, *T* treatment main effect, *Ses* session order, *Occl* occlusion

er, when *d*-methamphetamine was administered in the second session, *d*-methamphetamine improved DSST performance. Exploratory analyses failed to identify any significant relations between amphetamine levels found in the blood and changes in cognitive performance after amphetamine administration.

Discussion

The current three studies examined the effects of 0.42-mg/kg *d*-amphetamine, *d*,*l*-methamphetamine and *d*-methamphetamine on cognitive measures relevant to driving performance, including attention, psychomotor function and perceptual speed. The major finding was improvements in aspects of attention across the three amphetamine conditions and some evidence to suggest possible improvements in psychomotor functioning and perceptual speed. These findings are consistent with previous *d*-amphetamine research that have similarly shown an improvement in attention (de Wit et al. 2002; Wachtel and de Wit 1999; Cami et al. 2000; Kelly et al. 1991; Ward et al. 1997; Comer et al. 1996), psychomotor performance (Comer et al. 1996; Kennedy et al. 1990) and perceptual speed (Kennedy et al. 1990; Fillmore et al. 2005; Asghar et al. 2003; Kumari et al. 1997; Halliday et al. 1994; Fleming et al. 1995; Rapoport et al. 1980), with doses ranging from 5 to 30 mg. It is difficult to relate the present methamphetamine results to previous research, as the literature is scarce. The findings are, however, consistent with Johnson et al. (2000) who reported improvements in attention after 0.42-mg/kg *d*-methamphetamine.

In terms of the Digit Vigilance task, the present *d*-methamphetamine results are consistent with previous research where *d*-amphetamine has been shown to have no effect on false alarm rates but improve accuracy (Koelega 1993; Kelly et al. 1991). Although only trend level findings, it is worth noting that response speed was faster in the vigilance task across all three amphetamine conditions, which is consistent with previous research (Koelega 1993; Comer et al. 1996; Kelly et al. 1991).

As no previous studies have examined the effects of amphetamine on movement estimation, it is difficult to compare the present results with other research. Recently, however, Lamers et al. (2003) reported on 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 amphetamine, MDMA does share some general central nervous system activation effects with amphetamine. In light of the limited amphetamine research, these MDMA findings will be discussed.

Unlike in the present study, Lamers et al. (2003) found MDMA to impair "time to contact" performance. The

authors argued that this reflected impairment in the ability to perceive and predict motion, which subsequently may have compromising effects on traffic safety. This discrepancy in results may be understood in several ways, such as differences in drug type, dose, time of task administration (in the present study the task was administered 3–4 h after drug consumption, whereas, in Lamers et al. 2003, study the task was administered 4–5 h after drug consumption) and differences in the tasks.

In contrast, the present findings revealed that subjects in the *d*-amphetamine condition (when *d*-amphetamine was administered in the first session) and *d*-methamphetamine improved "time to contact" relative to the placebo condition. Interestingly, participants in the *d*-amphetamine condition consistently overestimated "time to contact", whereas, participants in the *d*-methamphetamine condition consistently underestimated "time to contact". This estimated difference from actual "time to contact" was, however, always smaller in the amphetamine condition compared to the placebo. A difficulty with interpreting these results is that it was also shown that those participants who received *d*-amphetamine in the first session reported more negative moods before the subsequent placebo session, thus, suggesting that there may have been residual psychological effects of *d*-amphetamine that may have consequently affected performance in the movement estimation task during the placebo condition. Furthermore, inspection of the means reveals that across all three drug studies, participants generally underestimated "time to contact" irrespective of drug condition, with the exception of participants who consumed *d*-amphetamine in the first session. Due to these incongruities, it is difficult to interpret the movement estimation results from the *d*-amphetamine study. Therefore, further discussion will only relate to *d*-methamphetamine.

The *d*-methamphetamine results can be understood in several ways, and we do not believe that there is currently enough evidence to support one interpretation over the others. The first interpretation is that *d*-methamphetamine merely improved movement estimation. The second is that *d*-methamphetamine increased risk-taking behaviour. It is possible that in the amphetamine condition, participants became more confident and took greater risks to perform well, and thus, responded earlier than under normal conditions (placebo). This is consistent with previous research where increases in risk taking behaviour have been noted after *d*-amphetamine administration (Hurst 1962; Hurst et al. 1967). The driving literature also argues that many amphetamine-related road fatalities are associated with risk taking behaviours (Logan 1996; Logan et al. 1998). The third interpretation is that amphetamine may have decreased impulsive responding. This is consistent with research showing that *d*-amphetamine can improve the ability to inhibit responses (de Wit et al. 2002, 2000), where inhibition and delay of response have been argued to be important aspects of movement estimation (Lamers et al. 2003).

Consistent with the literature, the present results indicated that amphetamine enhanced psychomotor ability, specifically DSST and tracking performance in healthy adults (de Wit et al. 2002; Wachtel and de Wit 1999; Cami et al. 2000; Kelly et al. 1991; Ward et al. 1997; Comer et al. 1996). However, surprisingly, the present findings revealed that when *d*-methamphetamine was consumed in the first session, participants performed significantly worse on the DSST. This inconsistency in results appears to be attributable to practice effects. The results of the present three experiments also support the notion that amphetamine levels in the blood and amphetamine effects are generally dissociable in healthy subjects (Angrist et al. 1987; Brauer et al. 1996; Asghar et al. 2003), as no relations were found between blood amphetamine levels and performance in any of the studies.

The present findings, thus, shed little light as to how amphetamine may detrimentally affect driving performance, with the only possible link being the results from the movement estimation task which "may" suggest increases in risk taking behaviours. This possibility is supported by the driving literature which argues that many amphetamine-related road fatalities are associated with risk taking behaviours (Logan 1996; Logan et al. 1998); however, further research is needed to clarify this issue. The Trail-Making task was included in the present study to assess possible visual scanning deficits which have been previously reported with amphetamine (Kennedy et al. 1990), but this, too, was not impaired in the present studies, suggesting that amphetamine-related visual scanning deficits of the type tested here, do not explain the fatalities (however, it should be noted that this Trail-Making task was not as pure a measure of visual scanning as that employed by Kennedy et al. leaving open the possibility that a visual scanning deficit may have been obscured by the choice of task in the present study). Another possibility is that the reported driving deficits are attributed to impairments in other functions not assessed in the present studies, such as early information processing deficits, which we are currently testing with electrophysiological techniques. However, given that no strong evidence of impairment is emerging within the lower end of the amphetamine levels found in road fatalities, this suggests that factors other than amphetamine should also be considered as possible causes. For example, given that professional truck drivers often abuse amphetamines to fight fatigue, this suggests that their fatigue, itself, may play a causal role in the fatalities, with the amphetamines found in the blood masking this.

It should be noted that: 1) baseline performance for each experimental session was not assessed, which may lower the sensitivity of the study to detect drug-related changes; 2) brief practice sessions were employed immediately before administration of the tasks rather than on an extensive practice session before the first testing session, which may have increased learning effects through the studies, and thus, increased type II error; 3) only a single dose was administered of each drug, which limits the interpretation of the results due to possible confounding of the performance/dose "Inverted U" function.

In summary, consistent with previous research, the results of the present three studies indicate that overall, low-dose amphetamine tends to improve aspects of attention with some evidence to suggest enhancement in psychomotor functioning and perceptual speed. The findings also indicated that measures of movement estimation are generally improved with amphetamine, but it was not clear whether this relates to improved functioning per se, or an increase in "risk taking" and/or impulsive behaviour. In terms of driving, the present results shed little light as to how amphetamine may contribute to driving fatalities, as there were no direct demonstrations of amphetamine-related impairments.

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