

The acute effects of 3,4-methylenedioxymethamphetamine and *d*-methamphetamine on human cognitive functioning

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Abstract

Rationale This study investigated the acute (3-h) and 24-h post-dose cognitive effects of oral 3,4-methylenedioxymethamphetamine (MDMA), *d*-methamphetamine, and placebo in a within-subject double-blind laboratory-based study in order to compare the effect of these two commonly used illicit drugs on a large number of recreational drug users.

Methods Sixty-one abstinent recreational users of illicit drugs comprised the participant sample, with 33 females and 28 males, mean age 25.45 years. The three testing sessions involved oral consumption of 100 mg MDMA, 0.42 mg/kg *d*-methamphetamine, or a matching placebo. The drug administration was counter-balanced, double-blind, and medically supervised. Cognitive performance was assessed during drug peak (3 h) and at 24 h post-dosing time-points. Blood samples were also taken to quantify the levels of drug present at the cognitive testing time-points.

Results Blood concentrations of both methamphetamine and MDMA at drug peak samples were consistent with levels observed in previous studies. The major findings concern poorer performance in the MDMA condition at peak concentration for the trail-making measures and an index of working memory (trend level), and more accurate performance on a choice reaction task within the methamphetamine condition. Most of the differences in performance between the MDMA, methamphetamine, and placebo treatments diminished by the 24-h testing time-point, although some performance improvements subsisted for choice reaction time for the methamphetamine condition.

Conclusions Further research into the acute effects of amphetamine preparations is necessary to further quantify the acute disruption of aspects of human functioning crucial to complex activities such as attention, selective memory, and psychomotor performance.

Keywords MDMA · Ecstasy · Methamphetamine · Cognition · Memory · Psychomotor · CDR

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The acute effects of ecstasy and *d*-methamphetamine on human cognitive functioning

In Australia, drugs in the amphetamine class are the most widely used illicit substances after cannabis (Degenhardt et al. 2004). The types of amphetamine most commonly used for recreational purposes are 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (Degenhardt et al. 2007). Data analysed from the 2001 National Drug Strategy Household Survey found that, in 2001, 6.1% of Australians aged 14 years or older reported long-term amphetamine use, and 2.9% reported recent amphetamine

use (Degenhardt et al. 2007). Furthermore, at age 24 years, 12% of the sample had used amphetamines in the past year, with 1–2% using at least weekly (Degenhardt et al. 2007). In a population study focusing solely on recreational MDMA use, Degenhardt and colleagues (2007) found that one in ten of 20–29-year-olds and 5% of 14–19-year-olds had used MDMA recently, with current MDMA users more likely to have used a range of other drugs compared with those who had not used MDMA recently. Experimental research into the acute effects of amphetamines on human attention, memory, and psychomotor processes, however, has been limited and inconsistent (Bosker et al. 2010), with some studies employing quasi-experimental or between-subject designs and within-subject designed studies utilising relatively small samples. With the increasing prevalence of amphetamine use, there is a need for more research into the acute effects of amphetamine preparations such as methamphetamine and MDMA on human cognitive functioning in non-clinical populations. As such, the aim of the current study is to extend upon the limited amount of studies that have assessed the modulatory effects of methamphetamine and MDMA in a larger sample utilising a within-subject, randomised, placebo-controlled design in order to directly compare the acute effects of these two common amphetamine preparations.

Amphetamines are commonly abused for their central nervous system stimulant properties and have the ability to enhance mood, energy and alertness, and as such are widely used in the ‘rave’, ‘club’, and ‘all-night party’ scene (Winstock et al. 2001). This massive release of monoamines leads to temporary deficit or depletion of monoamine stores that may take days to replenish—hence, the oft-reported ‘3-day dip’ following a weekend of heavy use of these substances (Clemens et al. 2007) and the associated cognitive deficits. Methamphetamine and MDMA have similar actions in the brain, elevating levels of the monoamine neurotransmitters dopamine, noradrenaline and serotonin (5-HT; Clemens et al. 2007). The major difference is that MDMA primarily inhibits 5-HT uptake and stimulates 5-HT release, while methamphetamine primarily inhibits dopamine reuptake and stimulates dopamine release (Clemens et al. 2007). Further to this, repeated recreational use of amphetamines is thought to have a cumulative effect on cognition from damage to dopaminergic and serotonergic neurons (White 2002).

A large literature exists concerning the detrimental effects of MDMA on cognitive and psychomotor performance and has been the subject of meta-analysis (Kalechstein et al. 2007). The authors noted that, across 33 reviewed studies of abstinent MDMA users (ranging from recreational to dependant), MDMA exposure was associated with poorer attention/communication, verbal learning and memory, non-verbal learning and memory, motor/psychomotor speed and

executive systems functioning (Kalechstein et al. 2007). Whilst neuro-cognitive impairment relative to controls in recreational MDMA users has not been a constant finding in the literature (e.g. Back-Madruga et al. 2003), probable contributors to the variability in the findings in this area include: inconsistent approaches to the definition of recreational use versus abuse of MDMA; poly-drug use of participants and inconsistent study methodology and analyses (Zakzanis et al. 2007). Acute administration of MDMA in controlled doses allows selective observation of the neuro-cognitive effects of MDMA consumption in isolation, which should reduce the impact of any differences in MDMA use patterns, use of other drugs or other variables, such as diagnosis with a drug abuse disorder, may also explain some of the differences in cognitive function (Cole et al. 2002; Fernández-Serrano et al. 2011). Acute doses of MDMA amongst samples of regular MDMA users have been associated with impaired performance on measures of neuro-cognitive function (McCann et al. 1999), such as spatial memory, decision-making and selective attention (Kuypers and Ramaekers 2007; Ramaekers and Kuypers 2006) and on measures of verbal recall and executive function (Thomasius et al. 2006). Studies of recreational users have also returned results such as, stimulating effects on mood, arousal and improved performance on information processing tasks (Bosker et al. 2010), and other studies have reported improved psychomotor speed, but not accuracy, at 100-mg doses (Dumont et al. 2010).

In regards to research concerning methamphetamines, chronic usage of methamphetamine has been associated with moderate impairments of neuropsychological functioning, specifically working memory, episodic memory, executive functioning, learning, information processing and motor skills (Cruickshank and Dyer 2009). In contrast, acute methamphetamine consumption has been found to improve sustained and divided attention (Silber et al. 2006), reasoning ability (Johnson et al. 2000), pattern recognition (Shappell et al. 1996) and motor coordination (Hart et al. 2008), although it is important to note that these improvements do not subsist for chronic users (Kalechstein et al. 2003). Again, issues surrounding polysubstance use exist, with substance users often consuming more than one type of illicit substance, multiple times, and often in combination with alcohol. For one, there is notable difficulty in definitively attributing deficits in cognition to the use of individual substances (methamphetamine in this case) when users have a history of polysubstance use or abuse this can cloud findings from pure substance users (Fernández-Serrano et al. 2011). The definition of abuse and recreational use is another concern, as is the length of defined abstinence when examining non-pure amphetamine users on cognitive measures ostensibly modulated by metham-

phetamine consumption. For example, when considering short-term, mid-term and longer-term abstinence of people who have ‘abused’ or were ‘dependent’ upon methamphetamines in comparison to non-users, short-term (mean, 2.6 months) abstinent users have been observed to perform worse than both long-term abstinent and non-users on response inhibition tasks (Salo et al. 2009). In comparison, long-term abstinent users (mean, 1.79 years) have been found to be impaired on a visual memory task, but not on a verbal memory task in comparison to non-drug users (Moon et al. 2007).

In summary, the literature demonstrates that the effects of various types of amphetamine on human behaviour are complex. The research indicates that at therapeutic doses amphetamine improves performance on cognitive processes, such as attention, psychomotor function and perceptual speed. For other aspects of cognitive functioning such as risk-taking, visual scanning proficiency and efficient use of the visual field, there is evidence to suggest that low doses of amphetamine impair performance. Likewise, the effects of MDMA on human cognitive functioning are also complex. Small acute doses (59–100 mg) of MDMA have been shown to affect various domains of human cognitive functioning, including spatial working memory (Kuypers and Ramaekers 2007), attention and executive function (McCann et al. 1999). Subtle psychomotor deficits have been observed, though mainly in terms of less accurate performance on certain tasks rather than speed or reaction time (Lamers et al. 2006). The current study aimed to utilise computerised tasks that measure sustained and divided attention, spatial and numeric working memory and psychomotor skills to directly compare the peak acute effects of both methamphetamine and MDMA consumption and any residual effects 24 h post-consumption in a randomised repeated-measures placebo-controlled study for the first time. These time-points and assessments were selected on the basis of assessing important cognitive functions at both peak drug concentration and a day later to identify any discrepancies in performance attributable to drug consumption. Given the rising prevalence of illicit drug usage and the reported long-term consequences of amphetamine usage on cognitive processes important to everyday functioning, assessment of performance under the effect of illicit drugs in controlled settings is necessary to illustrate the consequences of illicit drug use.

Based on the findings in the literature reviewed so far, the following hypotheses were generated. It was expected based on the work of Silber and colleagues (2006) that an acute 0.42-mg/kg dose of methamphetamine would improve reaction times on cognitive tasks measuring psychomotor performance and attention compared with performance under placebo, with these improvements subsisting at the 24-h time-point. It was expected that a

single 100-mg dose of MDMA would result in impairments in psychomotor speed for the computerised tasks but not affect the accuracy of responding in line with previous findings (e.g. Dumont et al. 2010). Again, any effect of MDMA during intoxication was expected to subsist at the 24-h testing time-point in line with studies that have observed cognitive and psychomotor performance returning to normal 24 or more hours after consumption of MDMA (Kuypers and Ramaekers 2005, 2007).

Methods

Participants

The sample comprised 61 individuals, 33 females and 28 males aged between 21 and 34 (mean age, 25.45; SD 3.25 years). All participants had previously consumed amphetamine-type stimulants and underwent a medical examination prior to participation to ensure that they had no: history of cardiac disorders; current or past substance abuse; mental health problems; allergies to drugs and no other medical illness. The study was approved by the Swinburne University Human Research Ethics Committee, and all participants completed a consent form outlining the details of their participation, and all were informed that they were free to discontinue their participation at any time. Participants who consented to participate in the trial agreed not to consume alcohol for at least 24 h prior to each session, and no other drugs for at least 7 days prior to each session, with adherence to this being checked with a saliva sample (Securetec Drugwipe Twin) at the beginning of testing days and via telephone prior to booking participants into testing sessions. Participants received \$500 (AUD) for their participation in the study.

Lifetime drug usage

All participants completed a survey concerning their lifetime drug usage covering drugs previously consumed, frequency of consumption and the time since last drug usage. A sub-set of this data has been previously reported (see, Parrott et al. 2011) as part of related study concerning the acute mood effects of MDMA and methamphetamine in a laboratory setting. Past MDMA/ecstasy use indicated that 59 of the 61 participants had prior MDMA usage, similarly, 60 of 61 participants reported prior amphetamine usage. The frequency of drug use is summarised in Table 1 below, which illustrates that the participants were moderate alcohol, cannabis and stimulant users. Thirty-seven of the participants were tobacco smokers, who were allowed to smoke normally during the three testing sessions in order to avoid any nicotinic deprivation and associated cognitive or mood decrements (Parrott 1999).

Table 1 Frequency of self-reported recreational drug use: figures are total number of participants and percentage of whole sample (in brackets)

	Alcohol	Cannabis	Amphetamines	MDMA	Cocaine	Heroin	Inhalants
Daily	8 (13.1)	3 (4.9)	0	0	0	0	0
1–2 times a week	43 (70.5)	9 (14.8)	0	0	0	0	0
2–3 times a month	8 (13.1)	6 (9.8)	3 (4.9)	3 (4.9)	0	0	0
Once a month	2 (3.3)	8 (13.1)	13 (21.3)	10 (16.4)	4 (6.6)	0	0
Once every 2 months	0	0	4 (6.6)	8 (13.1)	1 (1.6)	1 (1.6)	0
Few times a year	0	17 (27.9)	20 (32.8)	19 (31.1)	8 (13.1)	0	0
Rarely/once	0	18 (29.5)	20 (32.8)	19 (31.1)	32 (52.5)	9 (14.8)	6 (9.8)
Never	0	0	1 (1.6)	2 (3.3)	16 (26.2)	51 (83.6)	55 (90.2)

Acute drug administration

The three sessions were double-blind and placebo-controlled, and the treatment order counter-balanced to avoid any confounding effects. The study consisted of three experimental sessions that involved the consumption of 100 mg of MDMA, 0.42 mg/kg *d*-methamphetamine and placebo that have been previously described in detail (see, Parrott et al. 2011). In short, 100 mg of MDMA was selected as a moderate dose that has been previously administered (e.g. Dumont et al. 2010). Weight-related *d*-methamphetamine doses were made from a combination of capsules, with 0.42 mg/kg being utilized to replicate previous research at the Brain Sciences Institute (Silber et al. 2006) where the study took place. The lactose placebo capsules were virtually indistinguishable from the treatment capsules, and each participant took the same number of capsules in each condition. The MDMA and *d*-methamphetamine were purchased from Lipomed, Arlesheim, Switzerland.

Cognitive assessment

Participants completed a battery of cognitive tests from the Cognitive Drug Research (CDR) computerised assessment system (Wesnes et al. 2000). The CDR assessment battery has previously been found to be a particularly sensitive measure for the detection of changes to cognitive function associated with chronic nutraceutical and dietary interventions (Ryan et al. 2008; Stough et al. 2008; Wesnes et al. 2000) as well as acute changes in cognitive function with illicit (Silber et al. 2006) substances. This test battery took approximately 20 min to complete, with the primary outcome measures being three cognitive factors ‘Quality Working Memory’, ‘Power of Attention’ and ‘Continuity of Attention’ (Wesnes et al. 2000).

Simple reaction time The participant was instructed to press the YES response button as quickly as possible every time the word YES was presented on the screen. Thirty stimuli were presented with a varying interstimulus interval of

between 1 and 4 s. The measure was the average reaction time to the stimuli (milliseconds).

Digit vigilance A target digit was randomly selected and displayed to the right of the screen. A series of digits were presented in the centre of the screen at the rate of 2.5 digits per second. The participant was required to press the YES button as quickly as possible every time the digit in the series matched the target digit. The measures were the percentage of targets detected, the average reaction time (milliseconds) and the number of false-positives (false alarms) made.

Choice reaction time Either the word YES or the word NO was presented on the screen, and the participant was instructed to press the corresponding button as quickly as possible. There were 30 trials with a varying inter-stimulus interval of between 1 and 4 s. The measures were the percentage of correct responses and the average reaction time to the stimuli (milliseconds).

Spatial working memory A picture of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorize the positions of the lit windows. For each of the subsequent presentations of the house, the participant had to decide whether the one window which was lit was also lit in the original presentation. Participants recorded their response by pressing the YES or NO button as appropriate. The measures were the percentage of correctly identified stimuli and the average reaction time (milliseconds).

Numeric working memory A series of five digits was presented for the participant to hold in their memory. This was followed by a series of 30 probe digits for each of which the participant was required to decide whether the digit was from the original series and indicate their choice by pressing either the YES or NO button. The measures were the percentage correctly identified stimuli and the average reaction time (milliseconds). The Trail-Making Task (forms A

and B) were also included to measure visual–conceptual and visual–motor tracking (Giovagnoli et al. 1996). Alternate parallel forms of the Trail-Making tasks A and B were used for the three treatment and post-treatment conditions to minimize practice effects. All participants completed a training session prior to the actual testing sessions in order to familiarize them with the cognitive tests and to eliminate any possible practice effects.

Procedure

Upon arrival at the Brain Sciences Institute (BSI) laboratory at Swinburne University, participants were shown to the medical room where a registered nurse took physical observations and a baseline blood sample. All subsequent assessments were undertaken under the supervision of a research assistant. Under double-blind supervision, participants then ingested an oral dose of MDMA, *d*-methamphetamine, or placebo at either 10:00 AM or 12:00 midday and maintained the same testing schedule for each session, all of which were separated by a 2-week washout period. Participants were monitored during the following 3-h rest period, and then a second blood sample was taken (180 min post-dose). Participants then completed the CDR and trail-making cognitive tests; they also completed driving simulation tasks either before or after the cognitive tests, the results of which are being presented elsewhere (Stough et al. 2011). Participants also completed a short questionnaire covering perceived drug side effects and a self assessment of their performance on the cognitive tests. Taxis were provided for transport home. The following morning, the participants returned to the laboratory by taxi for the 24-h post-drug administration session.

There, a final blood sample was taken, which was analysed for the presence of methamphetamine, MDMA and THC to confirm the presence of the administered treatment and absence of any other illicit drugs. Parallel forms of the cognitive tests were then completed. A sub-set of participants ($N=52$) also completed baseline mood measures at 3-, 4.5- and 24-h post-dose time-points; the findings of these measures are reported elsewhere (Parrott et al. 2011).

Statistical analysis

Cognitive variables were analysed by repeated-measures ANOVA with treatment (MDMA, methamphetamine, placebo) and time (3, 24 h) being the two factors. Where significant time, treatment or treatment $\times$ time effects were observed, post hoc Bonferroni-corrected comparisons were undertaken to determine the significance of differences between treatments at the two time-points. The statistical analyses were conducted using SPSS V18 for Windows.

Results

Prior to examination of the cognitive variable outcomes, all data was examined with regards to drug order and gender to identify any moderating effects; no significant effects of either were observed. Cognitive data is summarised in Table 2, and the significant time, treatment and time $\times$ treatment effects are reported in the text below; non-significant effects are not reported for the sake of brevity. The mean (M) and standard deviations (SD) of blood

Table 2 Mean ($\pm$ SD) scores for cognitive measures for 3- and 24-h time-points for three treatment conditions

	Meth 3 h	Meth 24 h	MDMA 3 h	MDMA 24 h	Placebo 3 h	Placebo 24 h
Quality of working memory	1.83 $\pm$ 0.14	1.85 $\pm$ 0.14	1.80 $\pm$ 0.20	1.85 $\pm$ 0.14	1.87 $\pm$ 0.09	1.86 $\pm$ 0.11
Power of attention	1076.65 $\pm$ 102.30	1091.51 $\pm$ 105.68	1089.58 $\pm$ 103.15	1074.91 $\pm$ 97.28	1095.96 $\pm$ 108.99	1081.56 $\pm$ 100.18
Continuity of attention	91.49 $\pm$ 2.95	91.05 $\pm$ 3.16	90.79 $\pm$ 3.23	90.80 $\pm$ 3.43	91.08 $\pm$ 2.57	90.26 $\pm$ 3.68
Simple reaction time (RT)	264.61 $\pm$ 29.83	268.11 $\pm$ 33.50	264.74 $\pm$ 30.94	257.00 $\pm$ 26.12	264.38 $\pm$ 35.76	262.46 $\pm$ 28.51
Choice reaction time (RT)	410.82 $\pm$ 47.89	415.85 $\pm$ 58.31	414.23 $\pm$ 49.90	410.54 $\pm$ 45.21	423.34 $\pm$ 51.64	416.35 $\pm$ 58.31
Choice reaction time (%)	96.63 $\pm$ 2.96	96.70 $\pm$ 3.24	95.86 $\pm$ 3.46	95.58 $\pm$ 3.58	95.61 $\pm$ 3.37	95.54 $\pm$ 3.38
Digit vigilance (RT)	401.21 $\pm$ 40.85	407.55 $\pm$ 38.21	410.61 $\pm$ 36.40	407.37 $\pm$ 42.05	408.23 $\pm$ 42.39	402.75 $\pm$ 35.83
Digit vigilance (%)	97.66 $\pm$ 3.84	96.88 $\pm$ 5.04	97.43 $\pm$ 3.84	97.23 $\pm$ 4.08	97.97 $\pm$ 2.83	97.16 $\pm$ 3.61
Digit vigilance false alarms	0.77 $\pm$ 0.93	0.89 $\pm$ 1.06	0.98 $\pm$ 1.29	0.74 $\pm$ 1.13	0.81 $\pm$ 1.11	1.23 $\pm$ 2.13
Numeric working memory (RT)	628.08 $\pm$ 184.78	597.24 $\pm$ 150.70	627.93 $\pm$ 159.27	596.83 $\pm$ 148.27	613.46 $\pm$ 195.69	577.36 $\pm$ 139.83
Numeric working memory (SI)	0.91 $\pm$ 0.08	0.92 $\pm$ 0.07	0.89 $\pm$ 0.08	0.91 $\pm$ 0.06	0.92 $\pm$ 0.06	0.91 $\pm$ 0.08
Spatial working memory (RT)	623.46 $\pm$ 182.00	566.31 $\pm$ 125.94	631.75 $\pm$ 191.90	552.99 $\pm$ 132.21	624.03 $\pm$ 193.08	550.99 $\pm$ 104.21
Spatial working memory (SI)	0.92 $\pm$ 0.11	0.93 $\pm$ 0.12	0.91 $\pm$ 0.18	0.94 $\pm$ 0.12	0.95 $\pm$ 0.05	0.95 $\pm$ 0.06
Trail-making A (time)	21.18 $\pm$ 6.00	20.14 $\pm$ 5.91	24.44 $\pm$ 7.00	21.77 $\pm$ 5.92	20.17 $\pm$ 5.71	18.80 $\pm$ 5.64
Trail-making B (time)	51.05 $\pm$ 16.70	48.39 $\pm$ 25.44	51.13 $\pm$ 15.71	48.14 $\pm$ 17.68	45.92 $\pm$ 14.40	40.81 $\pm$ 12.11

concentrations of MDMA and *d*-methamphetamine for each time-point are presented in Fig. 1.

Quality of working memory

There was a trend towards significance for the time $\times$ treatment interaction ($F_{2,112}=3.88$, $p=0.080$) for the quality of working memory factor. Post hoc Bonferroni-adjusted comparisons revealed this interaction was due to poorer performance by participants in the MDMA condition in comparison to placebo ($p=0.027$) at the 3-h time-point. No significant time or treatment effects were observed.

Choice reaction time (percent accuracy)

There was a significant main effect for treatment ($F_{2,55}=5.32$, $p=0.006$) for the accuracy of responses in the choice reaction time task. Post hoc Bonferroni-adjusted comparisons revealed this effect was due to greater accuracy in the *d*-methamphetamine condition in comparison to both MDMA ($p=0.019$) and placebo ($p=0.002$).

Spatial working memory (RT)

A significant main effect for time (3 to 24 h time-points) was observed for spatial working memory reaction time ($F_{1,55}=39.70$, $p<0.001$) with performance at the 24-h time-point being significantly faster across all treatments.

Numeric working memory (RT)

A significant main effect for time (3- to 24-h time-points) was observed for numeric working memory reaction time ($F_{1,55}=2.18$, $p<0.001$) with performance at the 24-h time-point being significantly faster across all treatments.

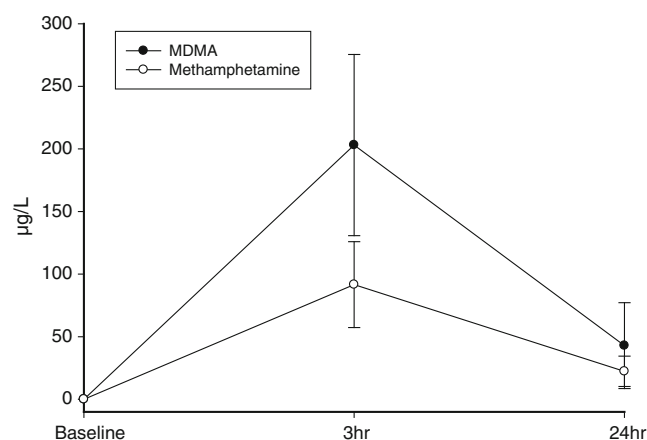


Fig. 1 Blood levels in micrograms of 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine as determined by gas chromatography-mass spectrometry following 100 mg oral MDMA and 0.42 mg/kg oral methamphetamine

Trail-making A (time)

Significant main effects were observed for time ($F_{1,55}=37.41$, $p<0.001$) and treatment ($F_{2,55}=14.27$, $p<0.001$) for the trail-making A task. Post hoc Bonferroni-adjusted comparisons revealed the treatment effects were due to slower completion of the task in the *d*-methamphetamine ($p<0.001$) and MDMA ($p<0.001$) conditions in comparison to placebo. Performance in the MDMA condition was also significantly slower than in the *d*-methamphetamine condition ($p=0.013$). In regards to the time effect, the difference was due to faster completion of the task at the 24-h time-point in the MDMA ($p<0.001$) and placebo ($p=0.046$) conditions.

Trail-making B (time)

Similarly, significant main effects were observed for time ($F_{1,58}=6.29$, $p<0.015$) and treatment ($F_{2,55}=8.35$, $p<0.001$) for the trail-making B task. Post hoc Bonferroni-adjusted comparisons revealed the treatment effects were due to faster completion of the task in the placebo condition in comparison to both the *d*-methamphetamine ($p<0.001$) and MDMA ($p=0.001$) conditions. The main effect for time was due to the faster completion of the task at the 24-h time-point in the placebo condition ($p=0.006$).

Discussion

The current study examined the acute effects of a 100-mg dose of MDMA and 0.42 mg/kg of *d*-methamphetamine in comparison to placebo on cognitive measures assessing attention, psychomotor function, perceptual speed and working memory at peak concentration (3 h post-administration) and 24 h post-drug administration. The major findings concern poorer performance in the MDMA condition at peak concentration for the trail-making measures and an index of working memory (trend level), and more accurate performance on a choice reaction task within the *d*-methamphetamine condition. Peak concentration levels of MDMA were observed to be consistent with previous acute work (e.g. 202.5 µg/L at 150 min post-drug administration: Dumont et al. 2010), with the average MDMA concentration at the 3-h time-point being 203.11 µg/L (SD=72.36 µg/L), dropping to 42.91 µg/L (SD=26.23 µg/L) at the 24-h post-dose time-point. This level of MDMA concentration has previously been observed to generate the stimulating and mood-elevating effects desired by recreational MDMA users, which is attributed to the release and reversal of re-uptake of 5-HT, increasing the levels of 5-HT at postsynaptic receptors (e.g. Liechti and Vollenweider 2000), and the associated release of noradrenaline and dopamine (Green et al. 2003). For *d*-

methamphetamine, average concentration at peak was 91.65 $\mu\text{g/L}$ (SD=34.31 $\mu\text{g/L}$), dropping to 22.36 $\mu\text{g/L}$ (SD=12.13 $\mu\text{g/L}$) at the 24-h post-dose time-point; this average was somewhat higher than the Silber and colleagues (72 $\mu\text{g/L}$) study utilising the same dosage schedule of 0.42 mg/kg (Silber et al. 2006).

In regards to the factor scores generated from the CDR cognitive tests, a trend-level time by treatment interaction was observed for the quality of working memory factor. This difference reflected poorer performance in the MDMA condition in comparison to the placebo condition at the 3-h time-point for the quality of working memory factor. This factor is a composite score of the sensitivity index scores for numeric and spatial working memory tests, which assesses attentional performance in relation to the accuracy of responding related to both spatial and numeric probes. This disruption in selective attention performance at the 3-h time-point is consistent with the findings of Kuypers and Ramaekers (2007) who observed that a 75-mg dose of MDMA impaired performance on word learning and spatial memory tasks at maximal drug concentration (1.5 h) and also with participants' performance returning to equivalent levels to placebo performance after 25.5 h (withdrawal phase) when blood concentrations were low. This result is consistent with the suggestion that the release of dopamine following MDMA consumption is more likely to improve psychomotor speed (e.g. Lamers et al. 2003) but less likely to improve accuracy (Dumont et al. 2010).

A significant main effect for treatment for the accuracy of responses in the choice reaction time task was also observed. This effect was due to greater accuracy in the *d*-methamphetamine condition in comparison to both MDMA and placebo. This result is consistent with findings that acute administration of *d*-methamphetamine improves psychomotor functioning transiently (e.g. Silber et al. 2006); however, participants' more accurate performance on the task was maintained at the 24-h post-dose testing time-point in contrast to expectations. It was expected that, in line with the metabolism (half-life 8–13 h) of the treatment (Busto et al. 1989) and previous findings (Hart et al. 2008), any improvement in psychomotor functioning would subside before the 24-h testing time-point. The concentration of methamphetamine (22.36 $\mu\text{g/L}$) still present in the blood of participants at the 24-h post-drug session may still provide some residual activation of attentive mechanisms or focus on the choice reaction time task, although replication of this result in another healthy population is necessary. Interestingly, findings from our study concerning mood changes across the same 24-h period indicated that no difference existed in the experience of negative moods in the *d*-methamphetamine condition (baseline, 3 h, 4.5 and 24 h post-dose). The experience of positive moods, however, was significantly

greater than in the MDMA and placebo conditions at peak concentration (3 h) matching the improvements in choice reaction time performance, but contrastingly, significantly lower than in the MDMA and placebo conditions at the 24-h time-point (Parrott et al. 2011), not corresponding to the still more accurate performance on the cognitive task.

For both the trail-making tasks, significant main effects were observed for time and treatment. The treatment effects were due to faster completion of the task in the placebo condition in comparison to both the *d*-methamphetamine and MDMA conditions. Performance in the *d*-methamphetamine condition was also significantly faster than in the MDMA condition for the trail-making-A task. Performance on the trail-making tasks in the MDMA condition were observed to improved significantly between the 3- and 24-h time-points, supporting previous work showing that the performance impairments of a single dose of MDMA are transient (e.g. Kuypers and Ramaekers 2007). This pattern of results was mostly in line with expectations, given that MDMA seemed to impair performance in completion of both forms of the trail-making task (at peak concentration) and that *d*-methamphetamine consumption did not enhance performance in comparison to placebo as has been observed previously in healthy volunteers (Silber et al. 2006). Unexpectedly, improvements in performance for both trail-making tasks, along with spatial working memory and numeric working memory reaction time were observed between the two testing time-points for each treatment condition. This may have been a function of practice effects, despite all participants having received training (four investigator supervised practice sessions) in the completion of all the cognitive tasks prior to the testing sessions (Wesnes and Pincock 2002). A second explanation may lay in the psychosocial environment of the laboratory testing experience which we have discussed elsewhere (Parrott et al. 2011) in regards to potentially explanatory factors that need to be empirically investigated or controlled for in future laboratory studies of illicit substances. Any disruptions in sleep (McCann et al. 2007) or sleep quality (Pirion and Morgan 2010) that the active drug preparations contributed to, through their stimulating effects, may also have prevented a return to performance levels equivalent to placebo performance at the 24-h post-dose testing time-point.

In summary, an acute dose of MDMA impaired performance on measures of attention, selective memory and psychomotor performance in comparison to *d*-methamphetamine and placebo. Acute dosage of *d*-methamphetamine resulted in task-specific improvement in psychomotor functioning, with accuracy in a speeded choice task, being significantly better in the methamphetamine condition. These results augment extant research and our series of studies concerning the acute effects of various

amphetamine preparations on mood (Parrott et al. 2011), cognition (Silber et al. 2006) and simulated driving (Silber et al. 2005), and in the case of the current study, to directly compare commonly used recreational drugs to placebo on a range of assessments that evaluate cognitive indices that are affected acutely by amphetamine type stimulants and that are reported to be compromised in chronic amphetamine users and dependents (Fernández-Serrano et al. 2011; Parrott 2000; Scott et al. 2007).

Some possible limitations to this study should be mentioned. Baseline performance on the cognitive tasks was not assessed at each experimental session, possibly limiting the ability to detect drug-dependent changes in cognitive performance. Performance was only assessed at 3- and 24-h post-drug administration (utilising a within-subjects design), which may have limited our conclusions concerning the time profile of the cognitive effects of the drugs. Finally, our findings are based upon a single dosage of both drug treatments, and different kinetic profiles across different dosages may have affected cognitive performance in a dose-dependent manner, with these three issues certainly requiring further research. The findings from this study do, however, have implications for the further understanding of the components of cognition differentially affected by methamphetamine and MDMA and how these can impact individuals who take illicit drugs.

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