

MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study

Andrew C. Parrott · Amy Gibbs · Andrew B. Scholey ·
Rebecca King · Katherine Owens · Phil Swann ·
Ed Ogden · Con Stough

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Abstract

Rationale This study investigated the acute mood effects of oral MDMA, methamphetamine, and placebo in a double-blind laboratory study.

Methods Fifty-two healthy participants comprised abstinent recreational users of stimulant drugs, 27 female and 25 male, mean age 24.8 years. Three test sessions involved acute 100 mg oral 3,4-methylenedioxymethamphetamine (MDMA), 0.42 mg/kg oral methamphetamine, and matching placebo. Drug administration was counterbalanced, testing was double-blind, and medical supervision was present throughout. Car-driving performance on a laboratory simulator was assessed after 3 and 24 h, with the findings being presented elsewhere. Positive and negative moods (PANAS self-ratings) were completed before drug administration, 3, 4.5, and 24 h later. Blood samples were taken to monitor drug plasma levels.

Results Following MDMA, there were no significant increases in positive moods, whereas negative moods were significantly higher than under placebo. Methamphetamine led to significant increases in both positive and negative moods. The MDMA findings contrast with the elated moods, typically noted by dance clubbers on Ecstasy.

However, they are consistent with some previous laboratory findings, since a wide array of positive and negative mood changes have been demonstrated. One possible explanatory factor was the neutral environmental situation, particularly if a primary action of MDMA is to intensify ongoing psychological states. Other explanatory factors, such as dosage, gender, post-drug timing, neurohormonal aspects, and social factors, are also discussed.

Conclusions In the laboratory, acute methamphetamine led to significantly higher positive moods. However, against expectations, MDMA did not generate a significant increase in positive moods.

Keywords MDMA · Ecstasy · Methamphetamine · Mood · Environment · PANAS · Serotonin · Dopamine

Introduction

The ring-substituted methamphetamine derivative, MDMA (3,4-methylenedioxymethamphetamine), is a powerful CNS stimulant, which increases activity across several neurotransmitter and neurohormonal systems (Cadet et al. 2007; Degenhardt and Hall 2009; Dumont and Verkes 2006; Green et al. 2003). In recreational users, this powerful neurobiological activation can be strongly euphoric. Solowij et al. (1992) noted that the main effect of Ecstasy was a positive mood state encompassing feelings of euphoria, intimacy, and closeness. In a questionnaire survey of 466 recreational users, Verheyden et al. (2003) reported that 91% reported experiencing a 'euphoric rush' following Ecstasy. These positive moods are illustrated by quotations from individual users: 'I loved everything. Life was beautiful', and 'I felt utter bliss' (Cohen 1998), 'Imagine the best feeling you have ever felt, times it by ten and you're still not close to

A. C. Parrott · A. Gibbs · A. B. Scholey · R. King · K. Owens ·
P. Swann · C. Stough
Brain Sciences Institute, Swinburne University,
Melbourne, VIC, Australia

E. Ogden
Vicroads, Victorian Government, Kew,
Melbourne, VIC, Australia

A. C. Parrott (✉)
Department of Psychology, Swansea University,
Swansea SA2 8PP, UK
e-mail: a.c.parrott@swansea.ac.uk

how amazing you feel' (Parrott 2010). In laboratory trials also, MDMA can induce strong feelings of happiness and elation. Liechti et al. (2001) summarized three placebo-controlled trials, where oral doses of MDMA (mean 108 mg) were administered to 74 drug-naïve participants. Significant increases were found on every positive mood scale, including greater 'emotional excitation', and higher 'positive mood' (Liechti et al. 2001). Many other laboratory studies have similarly reported positive mood changes, following various dosage levels, and with different mood questionnaires (Cami et al. 2000; Bedi et al. 2009, 2010; Bedi and de Wit 2010; Dumont et al. 2009, 2010; Hernández-López et al. 2002; Kolbrich et al. 2008; Tancer and Johanson 2001, 2003, 2007).

Though less widely reported, negative moods can also be boosted by MDMA. Several placebo-controlled laboratory studies have reported significant increases in negative types of feeling state. Liechti et al. (2001) found significant increases in 'apprehensiveness–anxiety', 'depressiveness', and other negative mood scales, following an acute dose of 108 mg MDMA. They also observed women to report more intense subjective experiences whilst on drug, especially relating to disordered thought, perceptual changes, and fear of loss of body control; acute adverse MDMA reactions were also noted more frequently by females. Tancer and Johanson (2007) reported a significant increase in anxiety after 2 mg/kg oral MDMA. Bedi and de Wit (2010) found significantly higher self-ratings of feeling anxious in females than males, following both low and high doses of oral MDMA. They further noted that: 'Females also showed greater decreases in self-rated elation and positive mood after MDMA (0.75 mg/kg only) than males'. Negative mood experiences are not restricted to the laboratory. Ecstasy-using dance clubbers can also report negative moods, with occasional feelings of panic, overstimulation, or loss of personal control (Davison and Parrott 1997). Hence, the following quotation from a dance clubber: 'I had a bad experience. I felt like I was surrounded by water and drowning. It must have been panic' (Cohen 1998). Furthermore, positive and negative mood changes often occur in the same individual, with users feeling more sociable/extraverted and more reflective/introverted during the same drug experience. Hence, the overall mood effects of MDMA can often appear paradoxical, with self-rated introversion and extraversion, happiness and depressiveness, all significantly heightened post-MDMA (Liechti et al. 2001). Another of Cohen's recreational users reported 'I did experience mood fluctuations—ups and downs'. One potential explanation for this mixture of effects is that MDMA is essentially a mood intensifier. Its primary effect is to enhance neurobiological activation across several neurotransmitter and neurohormonal systems (Green et al. 2003; Parrott 2001, 2009). Hence, many different internal

psychobiological states can be intensified by MDMA, as illustrated by this quotation from a recreational user: 'Ecstasy is not a happy drug. It by itself does not do anything. The Ecstasy and joy must come from within you' (Cohen 1998).

The present study was one of a series of laboratory studies funded by the Victoria State of Australia, into the effects of recreational drugs on car driving skills (Silber et al. 2006; Papafotiou et al. 2005). The two drugs assessed here were the ring-substituted methamphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA), and the parent compound methamphetamine (Green et al. 2003; Cadet et al. 2007). Both drugs are powerful CNS stimulants, and used recreationally by dance clubbers worldwide (Yacoubian et al. 2003; M ter Bogt and Engels 2005; Clemens et al. 2007). The common street name for MDMA is 'Ecstasy' (Solowij et al. 1992; Parrott 2004a), while methamphetamine is often called 'Ice' (Clemens et al. 2007). In this study, every participant had previously used illicit stimulant drugs for recreational purposes. They were assessed on a car driving simulator, to investigate the performance effects of these drugs in a controlled laboratory setting. Mood self-ratings were assessed for four reasons. Firstly, to provide more empirical data on the mood effects of acute MDMA. Secondly, to generate comparative mood data for MDMA against its parent compound methamphetamine. Thirdly, to investigate potential gender differences. Finally, to study mood changes in a laboratory setting, since previous studies have suggested an important contributory role for the environmental conditions (Parrott 2004b; Greer and Tolbert 1990).

Methods

Participants The sample comprised 52 individuals from Melbourne, 27 female and 25 male, aged between 21 and 34 years (mean 24.8, SD 3.1). The first criterion for acceptance was previous consumption of any illegal stimulant drug from the amphetamine class for recreational purposes. Every volunteer underwent a formal medical examination by a medical practitioner, in order to ensure physical and mental health. Hence, each participant was free from any history of cardiac disorder, mental health problems, drug allergies, or other illnesses. Menstrual phase was not recorded. Each participant was provided with a written information sheet about the study. Any verbal questions were answered, and those who agreed signed the written consent form. They were informed that they were free to withdraw from the study at any time. The study was approved by the Swinburne University Human Research Ethics Committee. Participants received \$500 (AUD) on completion of the three testing sessions.

Lifetime drug usage Participants completed a Drug Use Questionnaire covering drugs ever consumed, frequency of consumption, and time since last usage. Past Ecstasy/MDMA usage ranged from 0 to 300 pills; only two participants had not used it before, but they had used other drugs in the amphetamine class. The overall mean lifetime consumption was 55 Ecstasy tablets, which represents a good estimate for prior MDMA usage, given the high concordance between Ecstasy and MDMA (Parrott 2004a; Scholey et al. 2010). The frequency of drug use for the various drug types is summarized in Table 1. This demonstrates a pattern of moderate alcohol use, moderate cannabis use, and moderate stimulant drug usage. None of the participants was a heavy stimulant drug user, with no reports of weekly or more frequent usage, for MDMA, cocaine, or amphetamines (Table 1). Heroin and inhalant usage were minimal. Of the 52 participants, 32 were tobacco smokers (mean 8.29 cigarettes/day). They were allowed to smoke normally, since nicotine maintenance allows mood and cognition to remain within normal bounds, whereas nicotine deprivation leads to significant mood and cognitive decrements (Parrott 1994, 1999).

Acute drug administration Drug administration was double-blind and placebo-controlled. MDMA (3, 4-methylenedioxymethamphetamine) was administered as a 100-mg dose, in four 25 mg gelatin capsules (weight-corrected range 0.8–2.0 mg/kg). Methamphetamine was given as a weight-related dose of 0.42 mg/kg, in a combination of capsules containing 0, 2, 5, 10, or 20 mg methamphetamine (mean weight-corrected dosage: 30 mg). The weight-corrected methamphetamine dose was selected to duplicate the dosage level employed in our earlier driving simulator study (Silber et al. 2006). The emergent group mean dose of 30 mg was equivalent to the typical oral dose cited in the methamphetamine review by Cruickshank and Dyer (2009; their Table 1). The MDMA dose of 100 mg was chosen to represent a moderate dose, identical to that used in previous laboratory trials (Dumont

et al. 2009; Farré et al. 2004), although lower and higher doses have also been employed safely (Bedi et al. 2010; Cami et al. 2000; Tancer and Johanson 2003). We selected a standard oral dosage as many studies have followed this practice (Dumont et al. 2009; Farré et al. 2004), although weight-corrected doses have also often been employed (Tancer and Johanson 2003, 2007). It may be noted that the only other group to directly compare MDMA with methamphetamine, employed a standard oral dose for methamphetamine, but weight-corrected doses for MDMA (Bedi et al. 2009, 2010). Oral MDMA has a shorter half-life than oral methamphetamine, with peak effects between 1–4 h for MDMA (Tancer and Johanson 2003; Bedi et al. 2010), and 3–5 h for methamphetamine (Cruickshank and Dyer 2009). This helped to determine the timing for the post-drug sessions, at 3 and 4.5 h (see below). Turning to the placebo condition, the lactose capsules were visually indistinguishable from the active drug conditions. Each participant was administered the same number of capsules every session. The methamphetamine and MDMA were purchased from Lipomed, Arlesheim, Switzerland.

Assessment measures As part of the initial screening, participants completed a Demographics Questionnaire, Medical History Questionnaire, and Physical Examination Questionnaire. These determined whether the participants met all the eligibility requirements. The Lifetime Drug Usage Questionnaire was completed prior to testing. Mood was assessed using the Positive Affect and Negative Affect Scale PANAS (Watson et al. 1988). This 20-item self-rating questionnaire provides separate indices for positive and negative affect, with ten mood adjectives covering each factor. Participants indicated how they were feeling at the moment, with five response choices ranging from ‘slightly’ (1) to ‘extremely’ (5). The other aim of the study was to assess the effects of MDMA and methamphetamine on car driving skills. The simulated driving task assessed basic steering accuracy, use of the pedals under different real life scenarios: day and night, in the city, and on the freeway

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	7 (13.46)	3 (5.77)	0	0	0	0	0
1–2 times week	36 (69.23)	7 (13.46)	0	0	0	0	0
2–3 times month	7 (13.46)	5 (9.62)	2 (3.85)	3 (5.77)	0	0	0
Once a month	2 (3.85)	6 (11.54)	10 (19.23)	8 (15.38)	4	0	0
Once every 2 months	0	0	2 (3.85)	7 (13.46)	1 (1.92)	1 (1.92)	0
Few times a year	0	15 (28.85)	17 (32.69)	16 (30.77)	5 (9.62)	0	0
Rarely/once	0	16 (30.77)	20 (38.46)	16 (30.77)	27 (51.92)	7 (13.46)	5 (9.62)
Never	0	0	1 (1.92)	2 (3.85)	15 (28.85)	44 (84.62)	47 (90.38)

(Papafotiou et al. 2005). Further details of the car driving simulator, along with the emergent findings, are being presented elsewhere.

Procedure Testing began at either 10 A.M. or 12 midday, and participants maintained the same testing schedule for each session, with a minimum of a 2-week washout period between drug conditions. 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. Participants completed a baseline PANAS mood scale. Under double-blind supervision, they then ingested an oral dose of MDMA, methamphetamine, or placebo. For the 3 h following drug administration, each participant engaged in quiet restful activities, with free access to videos, books, magazines, and the internet. Participants were monitored throughout this waiting period. They were allowed cigarettes only in the 'smoking' area. Three hours after drug administration, the participant accompanied the nurse to the medical room where a second blood sample was taken. Participants then completed the 3-hour PANAS mood scale. The four driving simulator scenarios were performed, followed by the cognitive tests, and standardized Field Sobriety Tests (SFSTs). Participants then completed a short questionnaire covering perceived drug side effects, a post-driving self-assessment, and the 4.5 h PANAS mood scale. Taxis were provided for transport home. The following morning, they returned to the laboratory by taxi for the 24-h post-drug administration session. There, a final blood sample was taken, the driving simulator task performed again, and the cognitive tests completed. The final 24-h PANAS was also given, along with a questionnaire on perceived drug side effects, and the driving self-assessment.

Statistical analysis

Initial one way analyses of variance (ANOVA) were conducted to ensure that there were no baseline differences between treatment conditions. Scores from the positive and negative scales of the PANAS were then analyzed by two-way repeated measures ANOVAs with treatment (placebo, MDMA, methamphetamine) and Time (baseline, 3 h, 4.5 h, 24 h) as the two factors. In the case of significant interactions, Sidak pairwise comparisons were conducted to determine the significance of differences between treatment conditions at each time point. Given the possibility of gender differences, a secondary analysis was conducted using three-way ANOVAs for treatment $\times$ time $\times$ gender, the last being a between-subjects

factor, for each PANAS scale. A further series of one-way ANOVA was undertaken within each drug condition, followed by Sidak pairwise comparisons between baseline and each post-drug test session. The statistical analyses were performed using SPSS for Windows v17.

Results

The drug usage histories are shown in Table 1. The blood levels of MDMA, 3,4-methylenedioxymphetamine (MDA), and methamphetamine are summarized in Table 2. The mood state changes are presented in Fig. 1. The initial one-way ANOVA of the baseline mood data showed no significant differences between treatments for either positive or negative PANAS scores ($F < 1$ in both cases). The two-way ANOVA of the positive mood data, revealed a significant time $\times$ treatment interaction, ($F(6,210)=8.39$, $p < 0.001$), a significant main effect of time ($F(3,105)=8.52$, $p < 0.001$), and a trend towards significance for the effect of treatment ($F(2,70)=2.93$, $p = 0.06$). Pairwise comparisons for each time point revealed significantly higher positive affect after methamphetamine, compared with placebo after 3 h ($p < 0.001$), and 4.5 h ($p = 0.005$), and significantly lower positive affect following methamphetamine than placebo at 24 h ($p = 0.01$). There were no significant differences between MDMA and placebo at any time point. There was, however, significantly higher positive affect under methamphetamine compared with MDMA after 3 h ($p = 0.003$). With respect to differences from baseline within each drug condition under placebo, there was a significant reduction in positive affect at 4.5 h ($p = 0.023$). For MDMA and methamphetamine, there were significant reductions in positive mood at 24 h ($p = 0.038$ and $p < 0.001$, respectively). In the three-way ANOVA, the main effect for gender was non-significant ($p = 0.973$), and there were no significant gender interactions with other factors.

For the negative PANAS mood scale, there was a significant ANOVA main effect for treatment ($F(2, 58)=3.30$, $p = 0.044$), and time ($F(3, 87)=6.72$, $p = 0.001$), also a significant time $\times$ treatment interaction ($F(6,174)=6.05$, $p = 0.001$). Pairwise comparisons at each time revealed that compared with placebo, there was significantly more negative affect under methamphetamine at 3 h ($p = 0.002$), 4.5 h ($p = 0.024$), and 24 h ($p = 0.036$). Pairwise comparisons also revealed that compared to placebo, there was significantly more negative affect following MDMA at 3 h ($p < 0.001$), and 4.5 h ($p = 0.024$). Furthermore, after 24 h, there was a significant difference between methamphetamine and MDMA ($p = 0.034$). With respect to the negative mood changes from baseline, under placebo, there were significant reductions at 3 h ($p = 0.003$), 4.5 h ($p = 0.004$), and 24 h ($p = 0.004$). Under MDMA, there was a significant reduction at 24 h ($p = 0.029$), while for methamphetamine, there were

Table 2 Blood levels in ug/L of 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), and methamphetamine as determined by gas chromatography-mass spectrometry following 100 mg oral MDMA and 0.42 mg/kg oral methamphetamine

Drug administration condition	Drug or metabolite sample level (ug/L)	Baseline	3 h	24 h
MDMA 100 mg oral 3,4-methylenedioxy- methamphetamine	MDMA	0	207.74 (69.68)	33.49 (28.72)
	MDA	0	4.30 (7.10)	1.40 (5.72)
METHAMPHETAMINE 0.46 mg/kg oral methamphetamine	METH	0	93.38 (34.41)	7.55 (10.56)
	METH	0	0	0
PLACEBO matched oral capsules	MDMA	0	0	0
	MDA	0	0	0
	METH	0	0	0

Blood samples were taken pre-drug (*baseline*), 3-h post-drug (immediately prior to the test phase), and 24-h post-drug (*recovery*). Note: MDA levels were also assessed since MDMA is directly metabolized into MDA

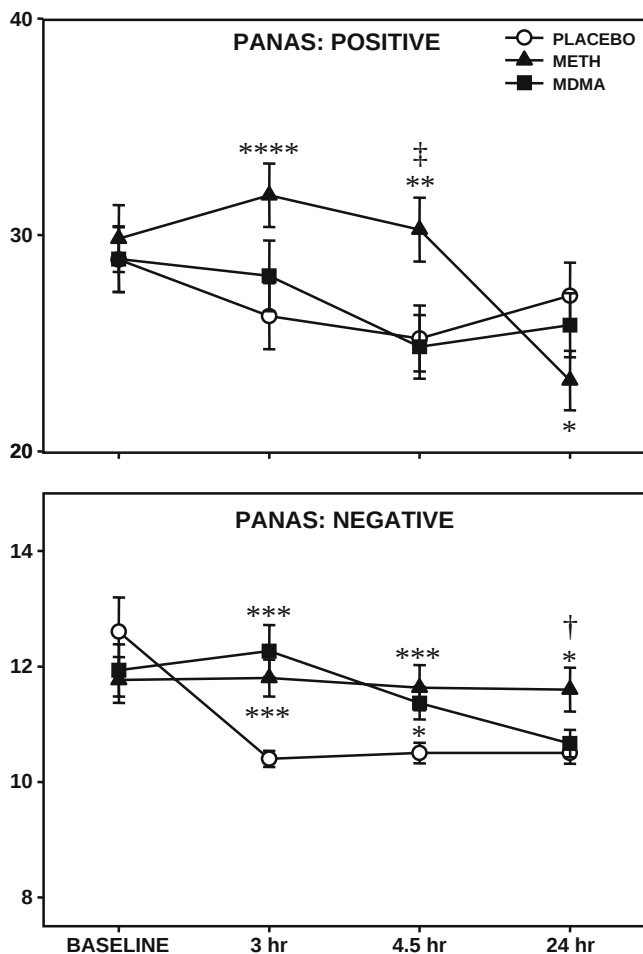


Fig. 1 Mean ($\pm$ SEM) positive (*top*) and negative (*bottom*) PANAS scores at baseline then 3, 4.5, and 24 h following placebo, 0.42 mg/kg oral methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). Asterisks denote significant differences between drug conditions and placebo (* p <0.05; ** p <0.01; *** p <0.005, **** p <0.001). Significant differences between MDMA and METH conditions are also indicated († p <0.05; ‡ p <0.01)

no significant differences from baseline. In the three-way ANOVA, there was a significant main effect for gender ($F(1, 28)=4.587$, $p=0.041$), with females reporting higher negative affect overall than males. There were no significant two-way interactions involving gender. The three-way time $\times$ treatment $\times$ gender interaction was however significant ($F(6, 28)=4.983$, $p=0.027$), due largely to two parallel but opposite changes in females only. Between baseline and the 3-h test session, females reported a stronger decrease in negative affect under placebo, together with a stronger increase in negative affect under MDMA, when compared with males. The methamphetamine drug values were similar between genders, with females reporting slightly higher negative affect at every time point.

Discussion

In this study, an acute dose of 100 mg MDMA did not generate a significant increase in positive moods. The PANAS positive mood score at 3 h was slightly higher than under placebo, but the difference was non-significant (Fig. 1). This contrasts with some previous laboratory studies where positive moods were significantly heightened, although it agrees with other studies where positive moods were *not* significantly improved. Amongst the studies reporting elevated mood, Cami et al. (2000) found significant increases in feelings of euphoria, stimulation, and good-drug effects, following oral doses of 75 and 125 mg MDMA. Farré et al. (2004) noted significantly increased levels of feeling high and feeling stimulated, after 100 mg oral MDMA. Liechti et al. (2001) reported significant gains across a wide range of positive mood scales, following an average dose of 108 mg oral MDMA. Tancer and Johanson (2007) found significant increases across a range of positive scales, including those for elation, positive mood, and vigor, after 1.5 mg/kg oral MDMA. Bedi et al. (2009) noted a significant increase in sociability,

and a statistically borderline increase in friendliness, following 1.5 mg/kg acute MDMA. Bedi and de Wit (2010) reported significant increases in feeling loving and feeling friendly, again after 1.5 mg/kg oral MDMA. Kolbrich et al. (2008) reported significant increases in self-rated energy, feeling high, closeness to others, and heightened senses, following 1.6 mg/kg oral MDMA. However, not every study has found significant mood improvements. Although Tancer and Johanson (2001) reported a significant increase in elation and friendliness after the comparatively low dose of 75 mg/70 kg MDMA, the effects of higher doses (110 and 145 mg/kg) on these positive mood scales were not statistically significant. Indeed, the only POMS scales to be significantly increased at these higher doses were for anxiety and mental confusion (see next paragraph). Furthermore, Bedi and de Wit (2010) reported *reductions* in positive moods after 0.75 mg/kg oral MDMA. They noted significantly greater ‘decreases in self-rated elation and positive mood’ in females compared to males. The equivalent positive mood scores for males were largely unchanged—with values close to placebo.

The PANAS negative mood scores were significantly higher after MDMA than placebo, at both 3 and 4.5 h (Fig. 1). This was consistent with many previous findings, since MDMA is a powerful sympathomimetic, and the emergent arousal typically includes negative mood elements. For instance, Tancer and Johanson (2001) reported a significant increase in anxiety after 110 mg/kg MDMA, and significant increases in anxiety and mental confusion after 145 mg/kg MDMA. In a later study, Tancer and Johanson (2003) again found significantly increased anxiety after 2 mg/kg oral MDMA, and this was replicated in Tancer and Johanson (2007). Bedi and De Wit (2010) noted that MDMA ‘dose-dependently increased ratings of anxiety’ for the overall sample, although these increases in anxiety were significantly greater for females than males after both dosage levels (0.75 and 1.5 mg/kg). Bedi et al. (2010) reported a significant increase in self-rated loneliness after 0.75 mg/kg MDMA, across a mixed-gender group. Liechti et al. (2001) noted significant increases in apprehension—*anxiety*, depressiveness, and fear of loss of body control. Other adverse drug experiences can include feelings of overstimulation, perceptual distortion, and panic (Cohen 1998). The adverse somatic effects of recreational Ecstasy/MDMA may include dizziness, numbness, blurred vision, unreal body, and occasional more severe abreacons (Baylen and Rosenberg 2006; Degenhardt and Hall 2009; Dumont and Verkes 2006; Parrott 2002, 2010; Topp et al. 1999). Davison and Parrott (1997) found that 25% of regular Ecstasy users had experienced adverse reactions, when unpleasant sensations and negative moods predominated. Greer and Tolbert (1986) described two clinical abreacons during MDMA-assisted psychotherapy, while in their overall

sample of 29 clients: ‘all subjects reported some undesirable experiences’ (review: Parrott 2006). Hence, the increase in negative moods with MDMA here (Fig. 1) was consistent with previous laboratory findings (Liechti et al. 2001; Bedi and de Wit 2010), the experiences of dance clubbers (Cohen 1998; Topp et al. 1999), and clients undergoing MDMA-assisted psychotherapy (Greer and Tolbert 1990). One important factor contributing to these findings was negative mood relief under placebo, since compared to baseline, there were significant reductions in negative affect at each time point in the placebo condition (Fig. 1). In contrast, negative moods during testing stayed close to baseline values, under both methamphetamine and MDMA. Hence, the significantly higher negative affect under the active drug conditions, largely reflected the absence of mood relief under placebo.

The methamphetamine condition led to significant differences from placebo, with both PANAS mood factors. Compared to placebo, positive moods were significantly heightened 3 and 4.5 h post-administration, and showed a significant rebound after 24 h. As noted above, negative moods fell significantly under placebo, but continued over time under methamphetamine, with the Sidak paired comparison tests between methamphetamine and placebo being significant (Fig. 1). The positive mood changes may be due to methamphetamine being primarily a dopaminergic agonist, while the mood rebound reflects neurochemical recovery. Many previous studies have shown positive moods with oral methamphetamine (Iversen 2006; Cruickshank and Dyer 2009). For instance, Bedi et al. (2010) noted significant increases in self-rated playfulness and sociability after 20 mg methamphetamine. On self-rated sociability, the time profile was very similar to that found with 1.5 mg/kg oral MDMA. Peak drug effects occurred at 120 min under both drugs, although only the increase with methamphetamine reached statistical significance. Sociability values at 150 min were raised to a similar extent with both drugs, and remained somewhat raised at 240 min under both drugs. On self-rated playfulness, the peak was higher and earlier with 1.5 mg/kg MDMA than methamphetamine, although from 150 to 240 min, the mean effects of both drugs were very similar. In their methamphetamine review, Cruickshank and Dyer (2009) noted that the peak effects of 30 mg of oral methamphetamine occurred 3–5 h post-drug, and our findings were consistent with this timescale (Fig. 1). (Hart et al. 2001) also found that 10 mg acute oral methamphetamine led to significant increases in a range of positive moods, including good-drug effect, feeling stimulated, and feeling high. In a sub-chronic study by the same group (Comer et al. 2001), repeated doses of self-administered methamphetamine led to an increase in positive moods, but only on the first day of administration. A range of negative reactions, such as ‘bad-drug effect’ were noted by day 3 of the repeated dosing regimen. There are also a number of studies reporting rapid

mood changes with intranasal methamphetamine, since that route is also used recreationally (Cruickshank and Dyer 2009; Hart et al. 2008), although our study was only involved with oral drug effects. In summary, the significantly higher positive and negative moods under methamphetamine compared to placebo here (Fig. 1) were consistent with the generalized emotional arousal found with many sympathomimetic drugs (Iversen 2006; Mendelson et al. 2006; Hart et al. 2001, 2008; Cruickshank and Dyer 2009).

Returning to the MDMA findings, a key question is why a drug called ‘Ecstasy’ did not generate a significant increase in positive moods (Fig. 1). Firstly, it should be noted that although this finding was unexpected, similar counterintuitive findings have been previously noted (Bedi and de Wit 2010). Several potential explanatory factors will be examined including dosage, post-drug timing, gender, the rating scale employed, also the wider psychosocial demands, and general test situation. In terms of dosage, several studies have found significant mood changes following similar or lower doses than that used here; namely, Farré et al. (2004) with 100 mg, Tancer and Johanson (2001) with 75 mg/70 kg MDMA, and Bedi et al. (2010) with 0.75 mg/kg MDMA. Hence, the current dosage of 100 mg MDMA should have been sufficient to generate positive moods. Although the overall effects of MDMA dosage are not simple or straightforward. Many studies have reported stronger mood changes following higher dosage levels (Cami et al. 2000; Johanson et al. 2006; Tancer and Johanson 2003; Bedi et al. 2009, 2010; Kolbrich et al. 2008). However, since this mood intensification occurs with both positive and negative moods, the overall effect can be difficult to predict. For instance, Tancer and Johanson (2001) compared the three doses of oral MDMA: 0.75, 110, and 1.45 mg/70 kg. They reported a significant positive drug effects for POMS elation and friendliness after the lower dose, but not after the two higher doses. Furthermore, whereas POMS anxiety was not affected by the lower dose, it was significantly increased by the two higher doses. Hence, their findings suggested that the lower dose was optimal for generating positive moods. Bedi and De Wit (2010) also reported significant difference between gender, with females reporting more anxiety under MDMA than males. The present findings partially support this, with females noting slightly stronger mood gains under placebo, and stronger mood deficits under MDMA. Although this only occurred on the PANAS negative affect scale. The influence of gender requires further study.

Another potentially important factor is the timing of the post-drug session. However, while some studies have reported a relatively rapid pharmacodynamic profile, others have described a more prolonged duration of action. Farré et al. (2004) reported a rapid time frame, with peak drug effects at 1 and 1.5 h, and values returning near to baseline

after 2 and 3 h. Cami et al. (2000) described a slightly longer time frame, with peak effects at 1 and 2 h, and mood values still comparatively raised at 3 h. Tancer and Johanson (2001) noted an even longer period of action. Self-rated stimulation was markedly raised at 1 h, increased slightly further to peak at 2 h, returned to the 1-h level at 3 h, but was still raised at 4 h. This pattern at the highest dose (145 mg/70 kg) was broadly replicated at the mid-dose (105 mg/70 kg). Johanson et al. (2006) noted high levels of drug-liking at 1, 2, 3, and 4 h after 1.5 mg/kg MDMA; furthermore, self-rated elation was slightly higher at 3 h than at 1 h. Bedi et al. (2010) similarly reported a prolonged time scale, with feeling-loving and feeling-friendly both raised from the 1.5 to the 4-h post-MDMA sessions. Two factors may be influencing this temporal variation: dosage, and the mood state under assessment. In general, higher doses seem to generate more prolonged effects (Cami et al. 2000; Johanson et al. 2006; Tancer and Johanson 2001; Kolbrich et al. 2008). The pharmacodynamic peak also seems to vary markedly according to the particular psychobiological variable. Tancer and Johanson (2003) reported peak effects at 1 h for feeling anxious, 2 h for positive moods, 3 h for feeling friendly, and 4 h for reduced feelings of hunger. This variation was confirmed in a later study, where different peak effects were noted across a similar range of dependent measures (Johanson et al. 2006). However, even closely related variables can show different pharmacodynamic profiles. Dumont et al. (2009) reported a significant ANOVA drug effect for feeling amicable, which peaked at 1 h, and returned near to baseline after 2.5 and 4 h. In contrast, self-rated gregariousness showed a different overall profile; the ANOVA drug effect was non-significant, whereas the drug $\times$ time interaction was significant. Gregariousness peaked at 1 h, but reversed at 2.5 and 4 h, when scores became *lower* under MDMA than placebo. In summary, the temporal profile for MDMA is complex and seems to vary between studies. It is another factor, which may have influenced the current findings, especially if our 3-h session had passed the peak for the particular positive mood states assessed here (Fig. 1).

This leads to a related issue, namely possible differences between mood assessment measures. Several well-established questionnaires have been employed, including the Profile of Mood States (POMS), the Positive and Negative Affect Scale (PANAS), the Addiction Research Center Inventory (ARCI), the Hallucinogen Rating Scale (HRS), and others. There have also been numerous visual analogue scales (VAS), covering further aspects of positive and negative mood. The many differences between these scales may contribute to the variance in findings. For instance, the current PANAS scale is probably weighted more towards intellectual arousal and alertness (e.g., feeling active, enthusiastic, inspired), whereas the POMS tends more towards hedonic tone and pleasure

(e.g., feeling friendly, lively, cheerful). Since the PANAS scale was used here (Fig. 1), it may be that the absence of positive moods reflects the particular types of questions on that scale. However, it should be noted that Bedi and co-workers used the POMS questionnaire, and found significant *decreases* in positive mood with acute MDMA (Bedi et al. 2010; Bedi and de Wit 2010). Future research could use multiple mood scales, followed by factor analysis to investigate mood linkages and groupings across drug types.

Another potential modulatory factor was the environmental situation. Given that MDMA is a powerful mood intensifier, the nature of any emergent psychological state may reflect the prevailing conditions (Parrott 2004b, 2006). The entactogenic psychotherapists Greer and Tolbert (1990) noted that MDMA could intensify both positive and negative feeling states. Hence, they noted it was crucial to engender positive expectations in potential clients and important to provide a supportive environment during MDMA-assisted psychotherapy. They also suggested that the effects of MDMA were *secondary* to the therapeutic ritual. Recreational Ecstasy/MDMA users have also noted the importance of positive expectations, as in the following quotation from a recreational user: ‘It is great stuff if you are in the right frame of mind for it’ (Cohen 1998). The emergence of positive moods in recreational users may be partially dependent on taking it in a supportive social situation, such as that provided at weekend dance clubs and parties (Parrott 2004b). It may be relevant that when it was first introduced as a recreational drug, MDMA was called ‘empathy’ rather than Ecstasy (Parrott 2004a). It should also be noted that not every recreational user experiences strong positive reactions to MDMA. For instance, novice users who quit after a few times, reported less positive reactions to their first Ecstasy/MDMA experience, than those novice users who continued to use the drug recreationally (Parrott 2010).

The psychosocial environment may also be important in laboratory studies. In particular, some mood studies involve participants who are undergoing parallel assessments, such as fMRI neuroimaging (Bedi et al. 2009), or psychological tasks (Bedi et al. 2010). In contrast, other laboratory mood studies involve participants who are resting quietly (Kolbrich et al. 2008). Hence, while some laboratory studies involve potentially stressful assessments, others provide a more experiential scenario. In our study, the core assessment task was to perform on a car driving simulator. Yet MDMA can impair attentional focus and reduce working memory (McCardle et al. 2004; Parrott 2006; Murphy et al. 2009), and hence make car driving more difficult. Blood samples were also taken. Participants also spent long periods in the rest area, and although magazines were provided, feelings of boredom may have occurred. Participants were also tested alone, and mild feelings of social isolation may have occurred. The following quotation from a recreational

Ecstasy/MDMA user illustrates the potential importance of social factors: ‘It is not the type of drug to do if you are alone’ (Cohen 1998). To summarize, various situational factors may have contributed to the absence of positive moods here. These and other potential explanatory factors need to be empirically investigated. Possible factors for future research might include: setting and expectancy (Greer and Tolbert 1990), being tested alone or in friendship groups (Irvine et al. 2006; Parrott et al. 2008), psychosocial perceptions (Clemens et al. 2007; McGregor et al. 2008; Bedi et al. 2010), concomitant exercise/dancing (Parrott and Lasky 1998; Parrott et al. 2006, 2008), past drug experience and chronic tolerance (Peroutka 1988; Parrott 2005; Scholey et al. 2004), gender and phase of the menstrual cycle (Bedi and de Wit 2010; Liechti et al. 2001; Lynch et al. 2002; White et al. 2006), and neurohormonal aspects—especially cortisol and oxytocin (Dumont et al. 2009; McGregor et al. 2008; Parrott 2009). Such studies might help explain the subtle variations in psychobiological response to MDMA.

To summarize, an acute dose of methamphetamine generated positive moods, whereas MDMA did not. The methamphetamine findings were largely as predicted, but the absence of significant mood gains with MDMA was rather unexpected. Our proposed explanation is that this may reflect the combination of two factors, namely the neurotransmitter system being stimulated and the environmental conditions. Currently, there is much emphasis on pharmacogenetics and the role genetic polymorphisms may play in susceptibility to drugs. The present results reinforce the contributory role the environment can sometimes play in human psychopharmacology. Methamphetamine is primarily a dopaminergic agonist, and its mood effects seem to be largely independent of situational influences. In contrast, MDMA is primarily a serotonin agonist, and its mood effects are strongly influenced by the environmental conditions (Greer and Tolbert 1986; Parrott 2004b, 2006). The absence of significant mood gains with MDMA here may therefore reflect the situational demands of being in a driving simulator study (Fig. 1). This may also explain why some other laboratory studies, which also involved potentially stressful task assessments, have also generated some unexpected mood changes (Bedi et al. 2009, 2010). This explanation is supported by another serotonergic drug, namely LSD. The mood effects of LSD are dependent on the prevailing conditions, with hippie folklore noting the importance of a supportive social environment for a ‘good’ trip, and environmental stressors for inducing a ‘bad’ trip. Serotonergic neurones in the raphe nuclei are important for stimulus integration and intensification, and they are affected by both drugs (Green et al. 2003; Iversen 2006; Parrott 2004a). Nevertheless, despite being able to offer a scientific explanation, we remain surprised by these mood findings. Under the right conditions, MDMA is a powerful

social euphoriant (Cohen 1998). Hence, it still seems rather paradoxical that positive moods did not emerge with a drug called 'Ecstasy'.

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