Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP

Manuel Tancer *, Chris-Ellyn Johanson

Department of Psychiatry and Behavioral Neurosciences, Substance Abuse Research Division, Addiction Research Institute, Wayne State University, 2761 E. Jefferson, Detroit, MI 48207, USA

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA) is a widely used drug of abuse chemically related to both the amphetamines and mescaline. Laboratory animal studies have shown that MDMA is a potent re-uptake inhibitor and releaser of dopamine and serotonin. Although the subjective and physiological effects of MDMA have been compared to d-amphetamine in humans, no direct comparison with a serotonin releasing agent has been reported and reinforcing effects have not been evaluated. In this paper we report a direct comparison of the reinforcing, subjective, and physiological effects of MDMA (1 and 2 mg/kg) to d-amphetamine (10 and 20 mg), to metachlorophenylpiperazine (mCPP—a serotonin releasing agent (0.5 and 0.75 mg/kg)), and to placebo using a within-subject design in 12 volunteers with moderate MDMA experience. Both the high dose of d-amphetamine and MDMA showed significant reinforcing effects as indicated by high crossover values on the multiple choice procedure compared to all other treatments. All three drugs showed dose-dependent changes in subjective effects whereas physiological effects were most pronounced for MDMA with almost no changes seen with mCPP. The subjective effects of MDMA were similar both to those of mCPP and d-amphetamine, suggesting that both dopamine and serotonin systems are involved in mediating these effects. In contrast, only the dopaminergic agents, d-amphetamine and MDMA, had reinforcing effects.

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1. Introduction

Use of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) has increased dramatically within the past few years (Strote et al., 2002). Unlike cocaine, heroin, and methamphetamine, MDMA is perceived by many users as a safe drug (Kalant, 2001). Despite this perception, results obtained from both animal and human studies indicate that MDMA use can be associated with both acute and possibly long-term deleterious consequences in brain structure and function (Croft et al., 2001; Dafters et al., 1999; Gouzoulis-Mayfrank et al., 2000; McCann et al., 2000; Obrocki et al., 2002; Parrott, 2000; Ricaurte et al., 2000; Verkes et al., 2001; Zakzanis and Young, 2001). Studies conducted with nonhumans indicate that MDMA, which is structurally similar to amphetamine and mescaline, is a releaser and reuptake inhibitor of both serotonin and dopamine as well as a potent releaser of norepinephrine (White et al., 1996). While chronic administration of MDMA produces signs of long-term neurotoxicity in rats and monkeys, especially in the serotonin system (Seiden and Sabol, 1996), the relative role of neurotransmitter systems in the acute reinforcing and subjective effects in humans is less clear, yet it is these effects that likely contribute to drug-taking.

In nonhuman primates, MDMA is an efficacious reinforcer as indicated by its ability to maintain intravenous self-administration behavior (Beardsley et al., 1986). However, even in that study one of the four rhesus monkeys tested did not self-administer MDMA. In contrast, d-amphetamine did serve as a positive reinforcer in all monkeys, suggesting a lower abuse liability for MDMA (Beardsley et al., 1986). Similarly,
although all monkeys self-administered intravenous MDMA in a study by Fantegrossi et al. (2002), rates were not as great as those for methamphetamine. That study also suggested that serotonin systems were important in MDMAs reinforcing effects because pretreatments with serotonin antagonists attenuated responding maintained by MDMA. However, the investigators did not evaluate whether dopamine systems were also important (Fantegrossi et al., 2002).

In humans, a variety of methods have been used to assess reinforcing effects, including the measurement of subjective effects (Griffiths et al., 2003). However, subjective and reinforcing effects do not always correspond (Fischman, 1989). For instance, while the anorectic drug mazindol produces subjective effects that are stimulant-like, mazindol is not a reinforcer in humans (Chait et al., 1986b, 1987). Unfortunately, while the subjective effects of MDMA have been evaluated in previous studies, the reinforcing effects of MDMA have not been assessed in humans, despite the view that reinforcing effects are the best predictor of abuse liability.

Nevertheless, the studies describing the subjective effects of MDMA indicate a high abuse liability. Descriptions of the subjective effects of MDMA have been obtained from two types of studies. The first type, represented by reports by Peroutka et al. (1988) and Curran and Travill (1997), are retrospective descriptions of symptoms experienced following purported but unconfirmed MDMA ingestion. Users in these retrospective studies describe a wide range of symptoms ranging from ‘altered time perception’ or a sense of ‘closeness’ with other people, increased alertness, luminescence of objects, and decreased ‘hostility’. In addition to the positive symptoms that may underlie its abuse, negative symptoms reported by MDMA users included insomnia, nausea, tight jaw muscles, dry mouth, diaphoresis, trouble concentrating, palpitations, tremor, and increased body temperature.

The second type of study designed to characterize the subjective effects of MDMA involves the administration of MDMA in a controlled laboratory setting. These laboratory-based reports of MDMA administration have described physiological, neuroendocrine, and psychological symptoms in addition to subjective drug effects (Cami et al., 2000; Grob et al., 1996; Harris et al., 2002; Lester et al., 2000; Mas et al., 1999; Tancer and Johanson, 2001; Vollenweider et al., 1998). The subjective effects of MDMA reported consistently across these studies were stimulant-like as well as effects that might be related to abuse liability more directly, e.g. Good Drug Effects (Cami et al., 2000; Tancer and Johanson, 2001). On the other hand, MDMA resulted in some reports of symptoms, such as confusion, sedation, dysphoria, and difficulty concentrating (Cami et al., 2000), that might limit its abuse liability. Most of the studies reported some perceptual changes, but only Vollenweider et al. (1998) reported any hallucinations.

While Cami et al. (2000) directly compared MDMA to d-amphetamine, no comparison to drugs affecting the serotonin system has been reported and, in addition, the testing of multiple doses has been rare. Comparing MDMA to both dopamine and serotonin-acting agents may help to elucidate the relative contribution of these two systems to the acute effects of MDMA that contribute to continued drug-taking. Although the reinforcing and subjective effects of the prototypical 5-HT releasing agent fenfluramine have been systematically studied (Brauer et al., 1996; Chait et al., 1986a) and would serve as the logical comparator, this drug was taken off the market by the FDA because of cardiovascular side effects. Since then, no single agent has been consistently used as a 5-HT releasing agent. Metachlorophenylpiperazine (mCPP), a metabolite of the antidepressant trazodone, has been used by many investigators as a probe for 5-HT function although it has both 5-HT releasing and post-synaptic effects (Kahn and Wetzler, 1992). McCann et al. (1999) have given intravenous mCPP to abstinent MDMA users as a probe for 5-HT responsivity. Interestingly, they reported a ‘euphoric’ response to mCPP in the MDMA users but not the non-drug using volunteers. This euphoric response to mCPP has been reported in both cocaine (Buydens-Branchez et al., 1997) and alcohol abusers (Benkelfat et al., 1991). Tancer and Johanson (2001) found a mixed response to oral mCPP in moderate MDMA users with both increased stimulant effects and drug liking as well as negative effects.

In the present study, the reinforcing effects of MDMA, mCPP and d-amphetamine were directly compared using a within-subject design. Subjective and physiological effects were also evaluated for comparison to previous studies. Salivary cortisol levels were also measured. Twelve, carefully screened, healthy, moderate MDMA-using participants received two doses of MDMA (1 and 2 mg/kg), two doses of mCPP (0.5 and 0.75 mg/kg), two doses of d-amphetamine (10 and 20 mg), and placebo under double-blind conditions with order of administration counterbalanced across participants.

2. Method

2.1. Participants

Participants were recruited who were between 18 and 35 years of age, had a minimum of a high school education, and had no psychiatric or medical conditions that precluded participation. In addition, they had to have a history of stimulant drug use (at least 6 times) including previous MDMA use (at least 3 times). No
candidate with a current or past Axis I diagnosis including drug or alcohol dependence disorder, other than Nicotine Dependence, was eligible. The exception was that drug or alcohol abuse disorder was not exclusionary if at least a year had passed since remission. Candidates were excluded if lifetime recreational drug use of psychomotor stimulants, opiates, phencyclidine or sedatives exceeded 50 times. Females could not be pregnant or lactating. The study was approved by the Wayne State University Human Investigation Committee and participants were reimbursed for their time and inconvenience.

Potential participants attended a screening interview so that the investigators could determine eligibility, explain the study, and obtain written informed consent. Participants were told that they might receive a stimulant, sedative, serotonin-acting drug, hallucinogen, empathogen, or a placebo. They were instructed not to take any drugs, including recreational drugs, between sessions and no alcohol for 12 h before a session. Participants were allowed to consume their usual amounts of caffeine and nicotine, but caffeine use was not allowed during the session. Smoking was allowed except for a 30-min period prior to drug ingestion and 30 min prior to each evaluation.

2.2. Procedures

When participants reported to the laboratory, breath alcohol levels were obtained to verify that they were alcohol-free (Alco-Sensor III, Intoximeters, Inc) and urine was tested for the presence of cocaine, amphetamines, opiates, benzodiazepines, and barbiturates using fluorescence polarization immunoassay (Abbott ADx® analyzer and standard reagents). Sessions were rescheduled if the breath or urine test detected recent drug use. Pregnancy tests were also performed on female participants.

The study utilized a within-subjects design, in which all participants were tested under seven drug conditions (placebo, 10 mg d-amphetamine, 20 mg d-amphetamine, 0.5 mg/kg mCPP, 0.75 mg/kg mCPP, 1 mg/kg MDMA and 2 mg/kg MDMA). Drugs were administered under double-blind conditions with order of administration counterbalanced across participants. Sessions were separated by at least 1 week to allow complete clearance of drugs between sessions. Sessions were 6 h in duration and conducted in a comfortable laboratory environment and began at approximately the same time each session. One to four individuals could participate at any one time. The other individuals may or may not have been participating in the same protocol.

At the beginning of each experimental session, vital signs (heart rate, blood pressure, oral temperature) were taken and participants completed baseline mood and subjective effect rating scales. Next, an opaque gelatin capsule containing the drug was administered with water. Physiological and subjective effect evaluations were obtained every hour. A saliva sample for the analysis of cortisol levels was also obtained 15 min prior to the capsule administration and every hour after. Five hours after drug administration, participants completed an end-of-session questionnaire and the multiple choice procedure form (MCP; see below). When participants were not completing mood questionnaires, they were free to relax in the laboratory and to engage in leisurely activities (e.g. watch television, read, play board games).

2.3. Reinforcing effects

The reinforcing effect of each drug was assessed using a modified version of the MCP (Griffiths et al., 1993). Participants completed one MCP form at the end of each session. Each form listed 20 drug (‘today’s drug’) vs. money choices (from ‘Give up $5’ to ‘Receive $5’) and they were numbered sequentially across sessions (e.g. session 1: 1–20, session 2: 21–40, etc.); volunteers circled drug or money for each independent choice on the list. The reinforcing value of drug was defined as the money amount (negative or positive) when the participant switched from choosing drug to choosing to give up or receive money (i.e. crossover point). On the eighth session, a blind ‘lottery’ was held in which one of the 140 choices previously made during the seven sessions was randomly selected. The purpose of this lottery session is to provide intermittent reinforcement of drug vs. money choices made on the previous sessions. If a drug had been randomly selected, it was administered at the usual time. Vital signs were collected over the next 5 h for safety purposes but no data for analyses were collected. Even if money was the selected choice, participants remained in the laboratory over the next 5 h. If the money selected was labeled ‘receive’, the amount was added to their earnings. If the money selected was labeled ‘give up’, the amount was subtracted from their earnings.

2.4. Subjective effects measures

The following questionnaires were filled out prior to capsule administration (except the hallucinogen rating scale, HRS) and for 5 h afterwards.

2.4.1. Addiction Research Center Inventory (ARCI)

Martin et al. (1971) have compiled a shortened version (49 true–false items) from the 550-item ARCI that is separated into five scales (amphetamine (A); benzodrine group (BG); lysteric acid diethylamide (LSD); morphine–benzodrine group (MBG); pentobarbital–chlorpromazine–alcohol group (Cam et al., 2000)). Participants indicate by circling T for true
2.4.2. Profile of Mood States (POMS)

This version (modified from McNair et al. (1971)) consists of 72 adjectives commonly used to describe mood states and has been factor analyzed into 8 scales (Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, Vigor). Two unvalidated scales have been derived as well (Arousal and Positive Mood). Participants indicate how they feel at the moment in relation to each of the adjectives from 0 (not at all) to 4 (extremely).

2.4.3. Visual Analog Scales (VAS)

The VAS consists of a series of 19 horizontal 100-mm lines, each labeled with an adjective (Alert, Anxious, Bad Drug Effect, Confusion, Down, Friendly, Good Drug Effect, High, Hungry, Irritable, Liking, Miserable, On Edge, Sedated, Self-Conscience, Social, Stimulated, Talkative, Tired). Participants are instructed to place a mark on each line indicating how they feel at the moment from ‘not at all’ to ‘extremely’.

2.4.4. Hallucinogen rating scale

This scale was developed and validated by Strassman et al. (1994) for measuring hallucinogenic symptoms following dimethyltryptamine administration. The HRS identifies six domains that purportedly describe hallucinogenic experiences. Each of the items is a phrase or single word and participants are asked to rate how or what they feel from 0 (not at all) to 4 (extremely). The six domains (and number of items per domain) include: (a) somaesthesia (13 items; e.g. ‘a rush’; ‘body feels different’; ‘feeling removed, detached, separated from body’); (b) affect (17 items; e.g. ‘anxious’; ‘awe’; ‘change in feelings of closeness of people in room’); (c) perception (17 items; e.g. ‘change in skin sensitivity’; ‘a sound or sounds accompanying the experiment’; ‘room overlaid with visual pattern’); (d) cognition (12 items; e.g. ‘new thoughts or insights’; ‘change in rate of thinking’; ‘change in sense of sanity’); (e) volition (8 items; e.g. ‘able to “let go”’; ‘able to focus attention’; ‘in control’; all of which are reversed scored); and (f) intensity (three items; e.g. ‘waxing and waning of the experience’; ‘intensity’; ‘high’). One of the items on the affect scale and six of the items on the volition scale are reversed scored. The characteristics of the questions proscribes its administration prior to any capsule administration.

2.4.5. End-of-session questionnaire

At the end of each session, participants were asked to rate their liking of the drug’s effects on a 100-mm line visual analog scale and to identify what drug they believed they received (i.e. stimulant, sedative, empathogen, hallucinogen, or placebo).

2.5. Cortisol assay

Saliva samples were collected in standard laboratory specimen cups, and then transferred to cryogenic tubes for storage at −4 °C. Cortisol levels in the samples were determined using a commercially available radioimmunoassay (RIA) kit, the Coat-A-Count Cortisol RIA kit (Diagnostic Products Corp.) that is capable of detecting levels as low as 0.02 μg/dl in saliva.

2.6. Data analyses

Physiological measures and salivary levels of cortisol as well as the POMS, VAS, ARCI, and HRS scales were analyzed using repeated measures two-way analysis of variance with drug condition and session time as repeated factors. Violations of sphericity were addressed using the Huynh–Feldt adjustment factor. Except for the HRS, which was not administered prior to capsule ingestion, predrug baseline measures were included in the analyses. When there was a significant drug × time interaction (P < 0.05), three simple effects tests were conducted comparing the high dose of each drug with placebo at time of peak drug effect. Peak effect was defined as the scale score averaged across participants that differed the most from placebo at the same time period. The drug identification questionnaire was not analyzed statistically whereas the MCP and end-of-session liking VAS were analyzed with a one-way ANOVA with drug condition as the factor. For these measures simple effects tests were conducted comparing each dose to placebo and for those found to be significantly different from placebo, a simple effects test was used to determine if they were different from each other. Binomial correlations between MCP cross-over values and end-of-session liking scores were obtained separately for each drug condition.

2.7. Drug supplies

MDMA was obtained from David Nichols and mCPP was purchased from Research Biochemicals International and then purified under cGMP by Murty Pharmaceuticals (Lexington, KY). Purity was confirmed using HPLC, IR spectroscopy, and NMR spectroscopy. Both were obtained in powder form so that it was possible to administer doses on a milligram per kilogram basis. The measured powder was placed in gelatin capsules and filled with dextrose. d-Amphetamine tablets (10 mg) were obtained commercially. One or two tablets were placed into capsules along with dextrose but it was not possible, given the small volume, to accurately reduce the tablets to powder in order to dose on a milligram per kilogram basis. Placebo capsules were filled with dextrose. All capsules were identical in color and size.
3. Results

3.1. Demographics

Fourteen participants began the study but two dropped out because of scheduling issues, yielding a total of 12 participants. Six of the participants were white females, four were white males, one male was Asian and one male was Native American. On average they were 22.3 years of age (range 18–31) and had taken a dose of MDMA 14.5 times (range 4–40). Ninety-two percent of the participants were both current cigarette and marijuana smokers. Use more than 50 times of stimulants, cocaine, opiates and sedatives was exclusionary but 25, 50, 42 and 67% had never used stimulants, cocaine, opiates and sedatives, respectively.

3.2. Reinforcing effects (MCP)

Fig. 1 (top panel) shows the results of the MCP across drugs. There was a significant effect of drug ($F(6, 66) = 4.2; P < 0.006$). Only 20 mg d-amphetamine ($F(1, 11) = 6.5; P < 0.03$) and 2 mg/kg MDMA ($F(1, 11) = 19; P < 0.0004$) had significantly higher crossover values than placebo. Although the crossover value was higher for MDMA, the difference compared to 20 mg d-amphetamine did not reach statistical significance ($F(1, 11) = 3.3; P < 0.09$).

3.3. Subjective effects

Table 1 is a summary of the significant drug × time interactions for each of the scales of the ARCI, POMS, VAS and HRS. Scales on which there were no significant drug × time interactions are not shown. This table also shows the results of the simple effects tests analyses of 20 mg d-amphetamine, 0.75 mg/kg mCPP, and 2 mg/kg MDMA, each in comparison to placebo at time of peak effects, which is also indicated.

3.3.1. Addiction Research Center Inventory

There were significant drug × hour interactions on all five scales (Table 1). All three drugs increased scores on A scale although the effects of MDMA peaked earlier in the session and were substantially greater (Fig. 2A). The effects of MDMA were similar in magnitude to the effects of d-amphetamine in increasing BG and decreasing PCAG but again the effects peaked an hour earlier compared to d-amphetamine. Only MDMA significantly increased MBG scores at peak effect. Unlike d-amphetamine and MDMA, mCPP decreased scores on BG and increased PCAG scores. MDMA was similar to mCPP on the LSD scale (increases) with a similar time of peak effects while d-amphetamine was without effect compared to placebo.

3.3.2. Profile of Mood States

There were significant drug × hour interactions on four of the POMS scales (Table 1). MDMA increased scores on the Positive Mood scale and both MDMA and d-amphetamine increased Elation with MDMAs effects substantially greater in magnitude and peaking an hour earlier than the effects of d-amphetamine (Fig. 2B). mCPP decreased Elation and Positive Mood. However, MDMA was similar to mCPP in increasing Anxiety and Confusion with a similar time course but for both scales, the effects of MDMA were lower in magnitude compared to mCPP.

3.3.3. Visual Analogue Scales

There were significant drug × hour interactions on 8 of the 19 VAS scales (Table 1). All three drugs produced increases in Friendly, Good Drug Effect (Fig. 2C), Liking, Stimulated, and Talkativeness and decreased Hungry with MDMA and d-amphetamine also increasing Social. For each of these scales, the effects of MDMA were greater in magnitude and with the
Table 1  
Physiological measures and subjective effects scales showing significant drug × hour interactions and significant planned simple effects tests

<table>
<thead>
<tr>
<th>Vitals</th>
<th>Simple effects tests</th>
<th>Amphetamine 20 mg</th>
<th>mCPP 0.75 mg/kg</th>
<th>MDMA 2 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug × hour interaction, $F_-, P$-value (df 30, 330)</td>
<td>$F_-, P$-value (df 1, 11)</td>
<td>$F_-, P$-value (df 1, 11)</td>
<td>$F_-, P$-value (df 1, 11)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>6.3, 0.0001</td>
<td>33.4, 0.0001</td>
<td>11.3, 0.006</td>
<td>120.8, 0.0001</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 3</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>2.8, 0.0001</td>
<td>10.6, 0.003</td>
<td>8.5, 0.007</td>
<td>58.2, 0.0001</td>
</tr>
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<td></td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>5.9, 0.0001</td>
<td>26.0, 0.0001</td>
<td>NS</td>
<td>88.1, 0.0001</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 3</td>
<td>NS</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Oral temperature</td>
<td>1.9, 0.02</td>
<td>13.9, 0.002</td>
<td>9.6, 0.006</td>
<td>9.2, 0.007</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 4</td>
<td>↑ Hr 4</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>ARCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3.8, 0.0001</td>
<td>15.3, 0.005</td>
<td>7.1, 0.04</td>
<td>82.0, 0.0001</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>BG</td>
<td>1.9, 0.03</td>
<td>9.6, 0.01</td>
<td>11.3, 0.005</td>
<td>12.4, 0.004</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 3</td>
<td>↓ Hr 1</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>LSD</td>
<td>6.8, 0.0001</td>
<td>NS</td>
<td>72.6, 0.0001</td>
<td>44.7, 0.0001</td>
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<tr>
<td></td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>MBG</td>
<td>5.5, 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>70.3, 0.0001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Hr 2</td>
<td></td>
</tr>
<tr>
<td>PCAG</td>
<td>1.9, 0.02</td>
<td>9.0, 0.01</td>
<td>25.8, 0.0001</td>
<td>4.9, 0.05</td>
</tr>
<tr>
<td></td>
<td>↓ Hr 3</td>
<td>↑ Hr 1</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.0, 0.002</td>
<td>NS</td>
<td>84.9, 0.0001</td>
<td>19.8, 0.007</td>
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<td></td>
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<td></td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
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<tr>
<td>Confusion</td>
<td>3.5, 0.003</td>
<td>NS</td>
<td>67.3, 0.0001</td>
<td>16.8, 0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Elation</td>
<td>3.0, 0.0002</td>
<td>4.8, 0.05</td>
<td>6.7, 0.03</td>
<td>39.7, 0.0001</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 3</td>
<td>↓ Hr 1</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>Positive Mood</td>
<td>3.2, 0.0001</td>
<td>NS</td>
<td>13.6, 0.004</td>
<td>36.6, 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Hr 1</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friendly</td>
<td>2.1, 0.01</td>
<td>7.7, 0.02</td>
<td>8.5, 0.02</td>
<td>47.7, 0.0001</td>
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<td></td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
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<tr>
<td>Good Drug Effect</td>
<td>6.6, 0.0001</td>
<td>11.2, 0.003</td>
<td>30.5, 0.0001</td>
<td>174.0, 0.001</td>
</tr>
<tr>
<td></td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>High</td>
<td>4.7, 0.0003</td>
<td>NS</td>
<td>45.0, 0.0003</td>
<td>65.6, 0.0001</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Hungry</td>
<td>3.4, 0.0006</td>
<td>26.8, 0.0006</td>
<td>5.7, 0.05</td>
<td>54.6, 0.0001</td>
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<tr>
<td></td>
<td>↑ Hr 4</td>
<td>↓ Hr 4</td>
<td>↓ Hr 4</td>
<td></td>
</tr>
<tr>
<td>Liking</td>
<td>5.8, 0.0001</td>
<td>14.9, 0.003</td>
<td>20.6, 0.0006</td>
<td>159.4, 0.0001</td>
</tr>
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<td></td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
<td>↑ Hr 3</td>
<td>↑ Hr 2</td>
</tr>
<tr>
<td>Social</td>
<td>2.0, 0.02</td>
<td>8.8, 0.02</td>
<td>NS</td>
<td>50.1, 0.0001</td>
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<td>↑ Hr 3</td>
<td>↑ Hr 2</td>
<td>↑ Hr 2</td>
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<tr>
<td>Stimulated</td>
<td>5.5, 0.0001</td>
<td>7.2, 0.03</td>
<td>20.8, 0.0004</td>
<td>109.6, 0.0001</td>
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<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
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<tr>
<td>Talkativeness</td>
<td>2.3, 0.0003</td>
<td>9.8, 0.007</td>
<td>6.0, 0.03</td>
<td>53.1, 0.0001</td>
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<td>↑ Hr 2</td>
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<tr>
<td>Affect</td>
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<td>14.2, 0.003</td>
<td>21.4, 0.0003</td>
<td>190.6, 0.0001</td>
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<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
</tr>
<tr>
<td>Cognition</td>
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<td>47.0, 0.0001</td>
<td>35.5, 0.0001</td>
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<td>↑ Hr 1</td>
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<tr>
<td>Intensity</td>
<td>5.7, 0.0001</td>
<td>20.4, 0.0009</td>
<td>81.5, 0.0001</td>
<td>139.7, 0.0001</td>
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<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
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<tr>
<td>Perception</td>
<td>4.4, 0.002</td>
<td>NS</td>
<td>29.4, 0.002</td>
<td>120.2, 0.0001</td>
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<tr>
<td>Soma</td>
<td>8.8, 0.0001</td>
<td>11.0, 0.02</td>
<td>85.9, 0.0001</td>
<td>203.5, 0.0001</td>
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<td>↑ Hr 2</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
<td>↑ Hr 1</td>
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</table>

NS, simple effects test not significant ($P > 0.05$). Arrows indicate direction of difference compared to placebo at time of peak effect which is indicated (e.g. Hr 1 means that drug and placebo were compared at the hour 1 time period because that was the greatest difference in average scores). See Fig. 3 for examples.
exception of Hungry, Friendly and Good Drug Effect, the effects of MDMA and mCPP peaked 1–2 h earlier than d-amphetamine. MDMA and mCPP increased high and although the effects peaked at the same time point, the effects of MDMA were greater in magnitude.

3.3.4. Hallucinogen rating scale
There were significant drug × hour interactions on all the HRS scales except volition. Except for d-amphetamine on perception, all three drugs increased scale scores on these five scales but the effects of MDMA and mCPP peaked at least 1 h earlier compared to d-amphetamine (Fig. 2D). On all scales but cognition, MDMA produced the greatest changes whereas the effects of d-amphetamine were the smallest in magnitude. On cognition, the effects of MDMA and mCPP were similar in magnitude and again greater in magnitude than d-amphetamine.

3.4. End-of-session questionnaire
Participants rated their liking of the drug at the end of each session and there was a significant main effect of drug (Fig. 1 (bottom panel); \( F(6, 66) = 12.3; P < 0.0001 \)). On the simple effects tests, the scores for both doses of MDMA were significantly higher than placebo (\( F(1, 11) = 26.8 \) and \( 53.3 \), respectively, both \( P < 0.0001 \)), as were the scores for 20 mg d-amphetamine (\( F(1, 11) = 10.3; P < 0.003 \) and 0.5 mg/kg mCPP (\( F(1, 11) = 6.1; P < 0.02 \)). The 10 mg d-amphetamine and
0.75 mg/kg mCPP were not significantly different compared to placebo. In addition, 2 mg/kg MDMA produced a significantly higher score than 20 mg d-amphetamine ($F(1, 11) = 16.7; P < 0.002$). The binomial correlation between MCP and liking scores was significant for 0.5 mg/kg mCPP ($r = 0.71; P < 0.009$), 0.75 mg/kg mCPP ($r = 0.67; P < 0.02$), and placebo ($r = -0.65; P < 0.03$) but not for the remaining drug conditions.

Participants were also asked to identify the substance ingested that day. Placebo was labeled as placebo by 9 of the 12 participants whereas d-amphetamine was labeled a stimulant by only 5 of the 12 people with 3–5 of the remainder labeling this drug as a placebo and 1–2 as an empathogen. On the other hand, both doses of mCPP and MDMA were labeled a hallucinogen or empathogen by 8–10 of the participants and labeled as a placebo by at most one of the participants.

### 3.5. Physiological effects

There was a significant drug by time interaction for systolic blood pressure (Fig. 3), diastolic blood pressure, heart rate, and oral temperature (Table 1). Simple effects tests showed that the highest dose of each drug produced significantly higher values than placebo for blood pressure and oral temperature. The magnitude of blood pressure changes were greatest for MDMA, followed by d-amphetamine with only minimal changes after mCPP. In contrast, d-amphetamine produced the greatest change in temperature with MDMA and mCPP producing similar changes. None exceeded 1° at any time period. Only d-amphetamine and MDMA significantly increased heart rate compared to placebo. For MDMA the maximum effect at the highest dose was about 20 bpm and for d-amphetamine about 10 bpm.

### 3.6. Cortisol

There was a significant drug by hour interaction for cortisol levels ($F(30, 330) = 5.1; P < 0.002$ Fig. 4). Simple effects tests demonstrated that both 2 mg/kg MDMA ($F(1, 11) = 100; P < 0.0001$) and 0.75 mg/kg mCPP ($F(1, 11) = 10; P < 0.03$) values were significantly higher than placebo values at 3 and 2 h after drug administration, respectively. MDMA levels were significantly higher than those following mCPP ($F(1, 11) = 28.4; P < 0.003$). D-Amphetamine had no effect on cortisol levels at any time point.

### 4. Discussion

Despite evidence of increased illicit use of MDMA, few laboratory studies have evaluated the reinforcing effects of MDMA in humans or nonhuman primates. Instead, many studies have focused on the neurotoxic effects of MDMA, which appear to be primarily disruptions in serotonin function. While this research is extremely important, it is also important to evaluate the pharmacological properties of MDMA that are related to drug-taking behavior. Obviously, unless MDMA is highly reinforcing and these effects contribute to continued drug-taking behavior, the neurotoxic effects may never become manifest unless a therapeutic indication can be demonstrated (Pentney, 2001). The medical use of MDMA in psychotherapy has remained controversial and at the present time it appears that therapeutic benefits can not been clearly demonstrated (Pham and Puzantian, 2001; Turner and Parrott, 2000).

The reinforcing effects of MDMA have been evaluated in nonhuman primates with results indicating moderate reinforcing effects (Beardsley et al., 1986; Fantegrossi et al., 2002; Lamb and Griffiths, 1987). However, similar studies in humans using methods that are considered direct measures of drug-taking have not been done. In humans, choice procedures are most frequently used to measure drug-taking behavior (de Wit and Johanson, 1987). Participants are given a drug at a certain dose during one session (sample) and an alternative reinforcer (e.g. placebo or a fixed amount of money) during another session. Following these experiences, the participants are given a choice of which reinforcer they wish to receive on subsequent sessions. The drawback of these procedures is that several sessions are needed, often as many as nine (Johanson and Uhlenhuth, 1980), to evaluate a single choice option. In an attempt to develop a more efficient choice method, Griffiths et al. (1993) designed the MCP. A modification of this procedure was utilized in the present study. At the end of every drug session, participants made 20 discrete choices between the drug they had received that day and different amounts of money arranged in increasing amounts. The measure of reinforcing efficacy was the average money amount across participants when they switched from the drug option to the money option (termed the cross-over value). After all seven drug sessions were completed, a lottery session was held and one of the 140 options was picked randomly and delivered. While this procedure is very similar to simply asking participants how much a drug is worth to them, the choice behavior is actually consequtated during the lottery session, providing a direct measure of reinforcement (Griffiths et al., 1993).

In the present study, the high dose of MDMA and d-amphetamine had crossover values that were significantly higher than placebo but this was not true for the other drug treatments. The value for MDMA was $4.00, close to the maximum possible. This could be interpreted to indicate that MDMA is highly reinforcing and thus has high relative abuse liability. However, it is difficult to compare MDMAs magnitude of crossover
value to other studies. While the MCP procedure has been used extensively with several classes of drugs, including benzodiazepines (Mumford et al., 1995), amphetamine (Schuh et al., 2000), and cocaine (Jones et al., 1999), the parameters of the procedure (number of options, amounts of money, the use of negative amounts of money, etc.) vary considerably and reliability across studies has not always been demonstrated. For instance, in the one study that used a procedure almost identical to the present one (i.e. same number of choice, amounts of money, and use of negative amounts of money), the cross-over value for 20 mg d-amphetamine was $0.42 (Schuh et al., 2000), considerably lower than $2.30 in the present study. At best, only within-study comparisons seem valid. In the present study, while the magnitude of the cross-over value was highest for MDMA, this value was not significantly different than the value for 20 mg d-amphetamine. However, in contrast, mCPP was not a reinforcer compared to placebo and the crossover value of the higher dose actually decreased relative to the lower dose.

Corresponding to the finding that MDMA and d-amphetamine functioned as positive reinforcers using the MCP, MDMA also had a profile of physiological and subjective effects that overlapped with those of d-amphetamine. Both MDMA and d-amphetamine increased amphetamine-related scale scores (A and BG) on the ARCI, Elation on the POMS, Friendly, Good Drug Effect, Liking, Social, Stimulated and Talkativeness on the VAS, and end-of-session liking. On the other hand, MDMA but not d-amphetamine increased the MBG scale score on the ARCI, Positive Mood on the POMS, and High on VAS, suggesting the possibility of greater reinforcing effects. Further, in most cases, the effects of MDMA were greater than d-amphetamine and also peaked earlier. Even though Cami et al. (2000)
compared a higher (40 mg) dose of d-amphetamine to an 
approximate dose of 1.8 mg/kg of MDMA, MDMA still 
tended to produce greater subjective effects.

Despite its lack of reinforcing effects on the MCP, 
mCPP also shared a wide range of positive subjective 
effects with both MDMA and d-amphetamine, replicat-
ing previous studies (Benkelfat et al., 1991; Buydens-
Branchey et al., 1997; McCann et al., 1999; Tancer and 
Johanson, 2001). All three drugs increased scale scores 
on the A of the ARCI, Friendly, Good Drug Effect, 
Liking, Stimulated, and Talkativeness on the VAS, and 
eand-of-session liking. mCPP and MDMA also had 
similar effects on several scales that could be considered 
negative and were not found with d-amphetamine. 
Similar observations have been reported by Vollenweider 
et al. (1998) and Cami et al. (2000). Both drugs 
increased the LSD scale scores on the ARCI, and Anxiety 
and Confusion on the POMS. These effects may be less 
related to reinforcement and indicate the need for 
care in interpreting studies based solely on a 
profile of subjective effects. In addition, there were 
scalars on which mCPP produced an effect opposite to 
that of MDMA and d-amphetamine. mCPP decreased 
scalars scores on BG of the ARCI and decreased Elation 
and Positive Mood on the POMS, further corroborating 
its lack of effects indicative of reinforcement. Interest-
ingly, there were significant positive correlations be-
tween MCP values and end-of-session liking scores for 
both doses of mCPP but none of the doses of d-
amphetamine or MDMA.

Although stimulant-like effects have been reported for 
MDMA in several studies including the present one, 
MDMA is also touted as having hallucinogenic-like properties. Unfortunately, validated questionnaires 
for characterizing hallucinogens are generally lacking 
although the Hallucinogenic Rating Scale (Gouzoulis-
Mayfrank et al., 1999; Strassman et al., 1994) appears to 
to measure effects that might be relevant. The HRS 
taps into several dimensions of perceptual disturbance from 
frank hallucinations to more subtle drug effects such as 
distortions in time and changes in intensity of emotions, 
looks, or colors. Interestingly, all three drugs had 
similar effects on the HRS, increasing scores on most of 
the scales. However, MDMA produced the largest 
increases while d-amphetamine had effects small in 
magnitude on all the scales. On some of these scales 
(Cognition, Intensity, and Soma), the effects of mCPP 
were comparable to MDMA. Like Cami et al. (2000) 
and unlike the reports of Harris et al. (2002) and 
Vollenweider et al. (1998), none of our participants 
reported any hallucinations or delusions. Although the 
HRS showed significant elevations following MDMA 
and mCPP compared to placebo, the magnitude of the 
elevation was considerably lower than scores reported 
by Strassman et al. (1994) following dimethyltryptamine 
and Gouzoulis-Mayfrank et al. (1999) following psilo-
trybin and 3,4-methylenedioxymethylamphetamine (MDE) 
administration. The failure of d-amphetamine to have 
robust effects on the HRS, as well as a similar failure 
with methamphetamine in the study by Gouzoulis-
Mayfrank et al. (1999), may indicate that the subjective 
effects characterized by the HRS do not contribute 
substantially to the reinforcing effects and might be 
considered side-effects.

MDMA produced increases in blood pressure and 
heart rate that were substantially higher than the effects 
of mCPP and d-amphetamine with the former produ-
cing only mild effects. The physiological effects of 
MDMA peaked rapidly and started dissipating within 
2 h and appeared dose-dependent. These results are 
similar to the findings in previous studies and once again 
indicate that the cardiovascular effects of MDMA are 
substantial and in vulnerable individuals might produce 
utward consequences (Lester et al., 2000; Mas et al., 
1999; Vollenweider et al., 1998). The effects of these 
three drugs on temperature, although significant, were 
small, in the range of 0.5°C, and are somewhat difficult to 
interpret because of hourly fluctuations even under 
placebo conditions. These studies were not conducted 
in an environment where room temperature could be 
controlled and thus it is likely that fluctuations in room 
temperature influenced oral temperature unrelated to 
drug effect. However, for each of the three drugs, 
temperatures exceeded the highest temperature mea-
sured under placebo conditions, if only minimally, 
similar in magnitude to the temperature increases 
reported by Liechti et al. (2001) in males. Given the 
potential relationship hypothesized between tempera-
ture changes and neurotoxicity (Hansen et al., 2002), 
further studies under better controlled conditions are 
warranted.

MDMA and mCPP to a lesser degree increased cortisol levels whereas d-amphetamine had no effect. 
The robust cortisol-response to MDMA administration 
coupled with the absence of cortisol-response following 
amphetamine administration was reported by Mas et al. 
(1999). The increase in cortisol levels following MDMA 
and mCPP but not d-amphetamine administration is 
consistent with a serotonergic mechanism (Kahn and 
Wetzler, 1992). On the other hand, Harris et al. (2002) 
argued that the elevation in cortisol following MDMA 
may mediate some of the positive effects of the drug. 
Our findings with mCPP suggest that mere elevation 
of cortisol following drug administration is not sufficient 
to mediate a reinforcing effect and the d-amphetamine 
results suggest that a euphoria-like response can occur 
in the absence of cortisol increases.

In summary, the present study makes a case that the 
reinforcing effects of MDMA resemble those of 
d-amphetamine, not mCPP, indicating a dopaminergic 
mechanism. At the same time, however, many of the 
subjective effects of MDMA may be mediated by
serotonergic systems, given the similarity of MDMA profiles to that of mCPP. However, these subjective effects may not play a role in controlling drug-taking. This contrasts with the findings of Fantegrossi et al. (2002) that serotonin antagonists attenuated MDMA-maintained responding. Furthermore, although reinforcing effects were not directly measured, Liechti et al. (2000) reported that in humans positive subjective effects of MDMA were attenuated by citalopram, a serotonin reuptake inhibitor. Clearly, these discrepant results have significant treatment implications in terms of the types of medications that might specifically block the effects of MDMA that contribute to its abuse and indicate the need for further research.

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