

MDMA does not alter responses to the Trier Social Stress Test in humans

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Abstract

Rationale $\pm$ 3,4-Methylenedioxymethamphetamine (MDMA, “ecstasy”) is a stimulant-psychedelic drug with unique social effects. It may dampen reactivity to negative social stimuli such as social threat and rejection. Perhaps because of these effects, MDMA has shown promise as a treatment for post-traumatic stress disorder (PTSD). However, the effect of single doses of MDMA on responses to an acute psychosocial stressor has not been tested.

Objectives In this study, we sought to test the effects of MDMA on responses to stress in healthy adults using a public speaking task. We hypothesized that the drug would reduce responses to the stressful task.

Methods Volunteers ($N = 39$) were randomly assigned to receive placebo ($N = 13$), 0.5 mg/kg MDMA ($N = 13$), or 1.0 mg/kg MDMA ($N = 13$) during a stress and a no-stress session. Dependent measures included subjective reports of drug effects and emotional responses to the task, as well as salivary cortisol, heart rate, and blood pressure.

Results The stress task produced its expected increase in physiological responses (cortisol, heart rate) and subjective ratings of stress in all three groups, and MDMA produced its expected subjective and physiological effects. MDMA alone increased ratings of subjective stress, heart rate, and saliva cortisol concentrations, but contrary to our hypothesis, it did not moderate responses to the Trier Social Stress Test.

Conclusions Despite its efficacy in PTSD and anxiety, MDMA did not reduce either the subjective or objective responses to stress in this controlled study. The conditions under which MDMA relieves responses to negative events or memories remain to be determined.

Keywords MDMA · Stress · Trier Social Stress Test · Anxiety · Cortisol

Introduction

$\pm$ 3,4-Methylenedioxymethamphetamine (MDMA, “ecstasy”) is a widely used stimulant-psychedelic drug that produces unique prosocial effects. Users report that it enhances feelings of empathy and social closeness, and controlled studies indicate that it dampens both behavioral and neural reactivity to negative social stimuli such as social threat and rejection (Bedi et al. 2009; Bershad et al. 2016; Frye et al. 2014; Hysek et al. 2012; Kirkpatrick et al. 2012; Wardle and de Wit 2014). Interestingly, the drug is used recreationally in high-intensity social settings that may be physiologically stressful (Curran 2000; Parrott 2001, 2004). Although the drug may be used to cope with the psychological stress of these settings, it has been suggested that MDMA may actually increase the physiological stress response in these contexts (Parrott 2009). Several studies have investigated the effects of MDMA on responses to threatening social stimuli under controlled laboratory conditions (for reviews, see Kamilar-Britt and Bedi 2015; Bershad et al. 2016). These studies show that MDMA reduces reactivity to faces expressing negative emotions. Even though there is a large body of literature suggesting a relationship between MDMA use and aspects of stress, including both physiological stress and psychological reactivity to threatening social stimuli, the effects of MDMA on an acute

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psychosocial stressor have never been tested. Here, we examined the effects of low doses of MDMA on subjective and physiological responses to a stressful public speaking task in healthy adult volunteers.

Several lines of evidence suggest that MDMA may itself elicit a physiological stress response, or worsen responses to environmental stress (Parrott et al. 2014). MDMA produces physiological changes consistent with a stress response, including increased cortisol, heart rate, and blood pressure (Hysek et al. 2011, 2012, 2013; Mas et al. 1999; Schmid et al. 2014; Seibert et al. 2014). Furthermore, the drug is typically used in settings that induce stress including loud music, high temperatures, and sustained physical activity. The combined effects of MDMA and these settings may increase cortisol up to 800% from baseline levels (Parrott et al. 2013), compared to 100–200% for MDMA alone (Harris et al. 2002). These combined effects may pose a safety risk, or, it has been suggested that the combined effects enhance the stimulant-like subjective effects of MDMA, making them more attractive to recreational users (Parrott 2009). In addition to eliciting a physiological stress response, there are also reports that single doses of MDMA can increase anxiety (Baggott et al. 2015; Kirkpatrick et al. 2012), and chronic MDMA users report high levels of stress and anxiety (Parrott 2001; Rodgers et al. 2006). Chronic MDMA users also exhibit heightened basal cortisol levels and perhaps relatedly, reduced cortisol responses to acute stress (Gerra et al. 2003).

On the other hand, there is also evidence that MDMA has stress-dampening effects. Laboratory studies indicate that MDMA reduces neural, psychophysiological, and subjective responses to negative and threatening social stimuli. It decreases the ability to identify angry facial expressions, reduces amygdala reactivity to threatening faces, and reduces feelings of rejection during simulated social rejection (Bedi et al. 2010, 2009; Frye et al. 2014; Hysek et al. 2012; Kirkpatrick et al. 2014b; Schmid et al. 2014; Wardle and de Wit 2014; Kuypers et al. 2014). In one recent study, Baggott et al. (2015) reported that MDMA reduced fear of negative evaluation by others. Why MDMA sometimes appears to increase and other times reduce sensitivity to stress or social threat is not understood. Here, we examined the effects of MDMA on a stressful evaluative public speaking task.

We examined the effects of 0, 0.5, or 1.0 mg/kg MDMA on the hormonal, subjective, and cardiovascular responses to a standardized social stress procedure in healthy men and women. The Trier Social Stress Test (TSST; Kirschbaum et al. 1993) is a widely implemented procedure for inducing psychosocial stress in a laboratory setting (Kudielka et al. 2007). Based on evidence that MDMA reduces responses to threatening social stimuli, we hypothesized MDMA would dampen negative subjective responses to a stressful public speaking task that involves social evaluation by mock examiners. We

hypothesized that MDMA might reduce the perceived stressfulness of the task while at the same time increasing physiological responses.

Materials and methods

Study design

This study used a mixed within-subject (stress vs. no-stress) and between-subjects (placebo, 0.5 mg/kg MDMA, 1.0 mg/kg MDMA) design. Participants were randomly assigned to receive placebo, 0.5 or 1.0 mg/kg MDMA under double-blind conditions, on each of two sessions: a stress session and a non-stressful control session. They participated in two 4-h laboratory sessions, conducted 7 days apart. On each session, subjects ingested a capsule containing drug or placebo, and 90 min later completed either a stressful public speaking task (TSST) or a non-stressful control task, in counterbalanced order. Responses to the drug and the stress were assessed at regular intervals, including mood, subjective drug effects, salivary cortisol, heart rate, and blood pressure.

Participants

Healthy adult participants with light to moderate past “ecstasy” experience (i.e., used 4–40 times in their lifetime) were recruited via newspaper, community bulletin board, and online advertisements. Potential participants were screened with an in-person psychiatric evaluation and medical examination, including an electrocardiogram and physical examination. Inclusion criteria were age 18–35 years, at least high school education, fluency in English, body mass index (BMI) between 19 and 26, no regular medications, and no past year history of a DSM IV Axis I disorder. Women were tested during the follicular stage of their menstrual cycle (days 2–14) to control for the effects of hormonal fluctuations on stress responses and stimulant drugs (Kirschbaum et al. 1999; White et al. 2002). Participants who had previously participated in a study involving the TSST were excluded.

Drugs

MDMA and placebo capsules were prepared by the University of Chicago Hospitals investigational pharmacy. MDMA hydrochloride powder was encapsulated in size 00 opaque capsules with lactose filler. Placebo capsules contained only lactose. The doses were given as milligrams per kilogram body weight to minimize variation related to body weight. These doses have been used in previous studies without adverse reactions (e.g., Bedi et al. 2009; Kirkpatrick et al. 2014a; Wardle and de Wit 2014; Wardle et al. 2014).

Procedure

Volunteers first attended a 1-h orientation session during which they provided informed consent and were familiarized with the study procedure. They were told that they might receive placebo, a sedative (e.g., Valium), a stimulant (e.g., MDMA), or a marijuana-like substance during the two study sessions. Participants were instructed to refrain from using alcohol and recreational drugs for 48 h before each session, and compliance was verified using breath alcohol (Alcosensor III, Intoximeters, St. Louis, MO) and urine drug tests (ToxCup, Branan Medical, Irvine, CA) before each session. All procedures were approved by the University of Chicago Institutional Review Board and were carried out in accordance with the Declaration of Helsinki.

Participants were randomly assigned to one of the three drug conditions (0 mg/kg ($N = 13$), 0.5 mg/kg MDMA ($N = 13$), or 1.0 mg/kg MDMA ($N = 13$)). They attended two study sessions (stress and no-stress) conducted between 12:00 and 16:00, scheduled 7 days apart. They were tested individually, in a comfortable room with couches and a television. Upon arrival to the laboratory, they provided breath and urine samples to detect recent drug use or pregnancy and then completed baseline mood and drug effect questionnaires. Portable electrocardiogram (ECG) electrodes were placed for continuous heart rate monitoring. At 12:40, participants consumed a capsule containing placebo or MDMA (0.5 or 1.0 mg/kg). Subjects received the same drug and dose on both sessions. During the next 60 min, they were allowed to relax, read, or watch a movie. Ninety minutes after drug administration, they were given instructions for the TSST or control task and completed pre-task questionnaires. During the TSST, participants were given 10 min to prepare for a 5-min speech for a mock job interview. Then, they performed the speech followed by 5 min of mental arithmetic (about which they were not informed ahead of time) in front of two interviewers and a video camera. During the non-stressful control session, participants were given 10 min to think about their favorite book or movie, then spoke about it with a research assistant for 5 min, and then played a 5-min game of solitaire. The order of the TSST and control tasks was counterbalanced among participants in each drug condition. Immediately after the tasks, participants completed questionnaires assessing how threatening and challenging they found the task, how satisfied they were with their performance, and rated their feelings of stress and insecurity. At baseline (15 min before drug administration), 60, 85, 115, 145, and 175 min after drug administration, participants answered drug effect and mood questionnaires and had their blood pressure measured. Salivary cortisol samples were collected at baseline, 60 min after drug administration and 10, 20, and 60 min after the stress or control task.

Measures

Mood and subjective effects of drug and stress

Participants completed the drug effects questionnaire (DEQ; Fischman and Foltin 1991; Morean et al. 2013), which consisted of five visual analog scales (VAS) from 0 to 100 on which participants indicated how much they feel, like, dislike, and want more of the drug as well as how “high” they feel. Participants also completed VAS measures of stress, tension, and insecurity. These questionnaires were completed at baseline (15 min before drug administration) and at 60, 85, 115, 145, and 175 min after capsule administration. Before the tasks, they completed the primary appraisal secondary appraisal rating scale (Gaab et al. 2005), and afterward, they completed VAS ratings of how stressful and challenging they found the tasks, in addition to how satisfied they were with their performance (e.g., “How stressful did you find the task?”).

Physiological measures

Heart rate was recorded continuously using an ambulatory monitor (Mobile Impedance Cardiograph, Mindware Technologies, Gahanna, OH). Blood pressure measures were taken with portable monitors (Omron 790IT 10+ Series Upper Arm Blood Pressure Monitor, Omron, Lake Forest, IL). Saliva samples were collected using Salivette® cotton wads (Sarstedt Inc., Newton, NC). Samples were analyzed by the Core Laboratory at the University of Chicago Hospitals General Clinical Research Center for levels of cortisol (Salimetrics LLC, State College PA, sensitivity = 0.003 µg/dL).

Statistical analyses

Analyses were conducted using SPSS version 16.0 for Windows. Missing cases (due to equipment malfunction or other data collection problems) were deleted listwise, which led to smaller sample sizes for some analyses. To verify that the two dose groups were matched on demographic information, we compared the groups using a one-way analysis of variance (ANOVA). Drug effects during the no-stress control session provided a measure of the direct effects of the drug and were analyzed using a mixed ANOVA, with time as the within-subjects factor and treatment group (0.5 mg/kg MDMA vs. 1.0 mg/kg MDMA vs. placebo) as the between-subjects factor. Responses to stress were analyzed using mixed ANOVAs, with task (TSST vs. control) and time as within-subjects factors, and treatment group as the between-subjects factor. Significant effects were further investigated post hoc Dunnett’s tests. The cortisol values were transformed with the natural logarithm function, and two outliers with

baseline cortisol levels greater than two standard deviations from the mean were excluded (as described in Adam and Kumari 2009). Repeated-measures ANOVAs were performed with Greenhouse-Geisser correction where violations of sphericity were observed. Differences were considered to be significant if $p < 0.05$. Effect sizes are reported using partial eta squared (η^2) for analyses of variance: 0.01, 0.06, and 0.14 are considered small, medium, and large effect sizes, respectively.

Results

Demographics and baseline differences

Of the participants, 44% were Caucasian, and most were in their 20s (24.1 ± 3.4 years of age, range 18–32). The three groups did not differ on demographic characteristics or drug use history (Table 1).

Subjective drug effects

There were no differences between the groups in physiological and subjective measures before capsule administration. The higher dose of MDMA significantly increased ratings of “feel high” (drug $\times$ time, $F(2,150) = 3.8$, $p < 0.001$, $\eta^2 = 0.2$; 1.0 mg/kg vs. placebo, $p < 0.001$, peak at 85 min post administration; 1.0 mg/kg vs. placebo $p < 0.05$ at 60 min through 175 min), “like drug” (drug $\times$ time, $F(2,150) = 2.5$, $p < 0.01$, $\eta^2 = 0.14$, 1.0 mg/kg vs. placebo $p < 0.05$ at 60 min through 145 min), and “feel drug” (drug $\times$ time, $F(2,150) = 3.0$, $p < 0.01$, $\eta^2 = 0.17$; 1.0 mg/kg vs. placebo $p < 0.05$ at 60 min through 175 min). The lower dose did not produce these significant effects.

Table 1 Demographic and baseline characteristics of participants in each group

	Placebo	0.5 mg/kg MDMA	1.0 mg/kg MDMA
<i>N</i> (male/female)	13 (10/3)	13 (9/4)	13(11/2)
Race <i>N</i>			
Caucasian	7	5	5
African American	1	1	1
Asian	2	2	3
Other	3	5	4
Age (years)	22.7 ± 2.9	24.8 ± 3.9	24.5 ± 3.0
BMI	23.9 ± 2.3	22.5 ± 2.1	22.8 ± 2.1
Education (years)	14 ± 1.6	14.8 ± 1.7	15.1 ± 1.6
Drug use			
Caffeine (servings/day)	1.3 ± 1.2	1.5 ± 1.1	0.98 ± 0.89
Alcohol (drinks/week)	2.8 ± 1.72	3.8 ± 2.1	3.8 ± 2.2
Lifetime MDMA use (mean number of times used)	10.3 ± 14.3	11.3 ± 8.8	11.2 ± 7.2

Subjective effects of the TSST

Effects of stress

For all groups, the TSST increased VAS ratings of feelings of stress (task, $F(1,35) = 30.5$, $p < 0.001$, $\eta^2 = 0.47$; during task and 0 min post-task vs. baseline, $p < 0.001$), tension (task, $F(1,35) = 17.4$, $p < 0.001$, $\eta^2 = 0.33$; during task and 0 min post-task vs. baseline, $p < 0.001$), and insecurity (task, $F(1,35) = 18.0$, $p < 0.001$, $\eta^2 = 0.34$; during task and 0 min post-task vs. baseline, $p < 0.001$). On the pre-task appraisal questionnaire, participants rated the TSST as significantly more threatening (task, $F(1,35) = 5.4$, $p < 0.05$, $\eta^2 = 0.13$) and challenging (task, $F(1,35) = 33.1$, $p < 0.001$, $\eta^2 = 0.49$) than the control task and were less confident in their ability to perform the task (self-efficacy) (task, $F(1,35) = 8.2$, $p < 0.01$, $\eta^2 = 0.19$). On the post-task questionnaire, participants were less satisfied with their performance on the TSST versus the control task (task, $F(1,35) = 35.0$, $p < 0.001$, $\eta^2 = 0.51$).

Effects of MDMA on subjective responses to the TSST

The higher dose of MDMA increased VAS ratings of stress relative to placebo (drug, $F(2,35) = 3.6$, $p < 0.05$, $\eta^2 = 0.17$; 1.0 mg/kg vs. placebo, $p < 0.05$), tension (drug, $F(2,35) = 6.0$, $p < 0.01$, $\eta^2 = 0.25$; 1.0 mg/kg vs. placebo, $p < 0.05$), and insecurity (Fig. 1) (drug, $F(2,35) = 3.4$, $p < 0.05$, $\eta^2 = 0.16$; $p < 0.05$ for both doses vs. placebo) during both the stress and non-stress sessions. Both doses of MDMA also increased how challenging participants found both tasks (drug, $F(2,35) = 4.4$, $p < 0.05$, $\eta^2 = 0.20$; both doses vs. placebo $p < 0.05$), and tended to increase how threatening they rated them (drug, $F(2,35) = 4.5$, $p = 0.1$, $\eta^2 = 0.12$). There was no

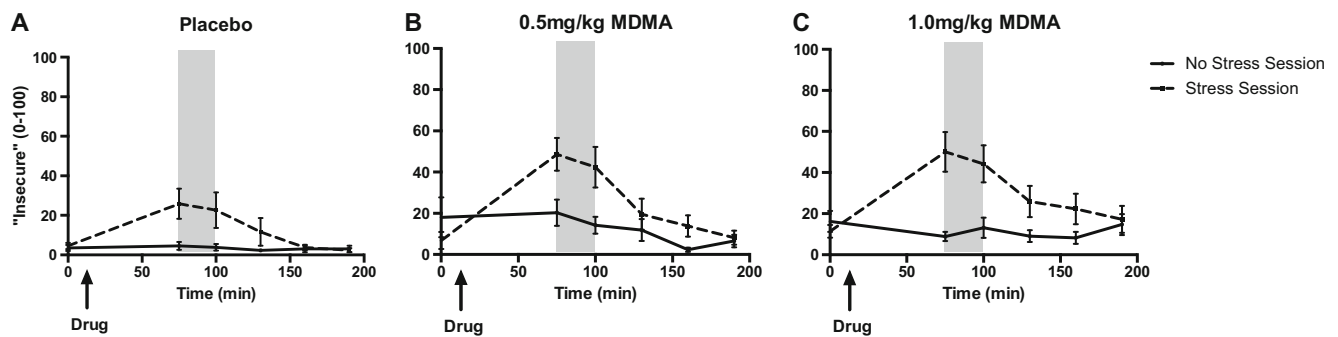


Fig. 1 Effects of MDMA on subjective ratings of insecurity. Effects of MDMA on ratings of insecurity **a** in the group receiving placebo, **b** in the group receiving 0.5 mg/kg MDMA, and **c** in the group receiving

1.0 mg/kg MDMA. Shaded area indicates the time during which the task took place. Bars depict mean $\pm$ SEM

significant task $\times$ drug interaction for any subjective effects (Table 2). The drug did not affect post-task ratings of performance satisfaction.

Physiological effects of the tasks

Effects of the TSST

As expected, the TSST significantly increased heart rate (task, $F(1,34) = 20.4$, $p < 0.001$, $\eta^2 = 0.38$; during task and 0 min post-task vs. baseline, $p < 0.001$), systolic blood pressure (task, $F(1,35) = 6.5$, $p < 0.05$, $\eta^2 = 0.16$; during task and 0 min post-task vs. baseline, $p < 0.05$), and cortisol (task, $F(1,33) = 5.0$, $p < 0.01$, $\eta^2 = 0.13$; 10 min post-task and 20 min post-task vs. baseline, $p < 0.01$) overall as compared to the non-stressful control task (please see Figs. 2 and 3).

Effects of MDMA

The higher dose of MDMA increased blood pressure overall (drug, $F(2,35) = 7.4$, $p < 0.01$, $\eta^2 = 0.30$; 1.0 mg/kg vs. placebo, $p < 0.05$ at 60 through 135 min). Both doses of MDMA also increased cortisol responses compared to placebo (drug, $F(2,33) = 33.2$, $p < 0.001$, $\eta^2 = 0.67$; $p < 0.001$ for 1.0 mg/kg and $p < 0.05$ for 0.5 mg/kg at 60 through 135 min, and task $\times$ drug $\times$ time $F(8,136) = 3.0$, $p < 0.01$). There were no significant task $\times$ drug interactions for cardiovascular measures.

Discussion

In this study, we assessed the effects of MDMA (0.5 and 1.0 mg/kg) or placebo on physiological and subjective

Table 2 F values for drug and stress main effects and interactions

Measure	Drug		Task		Drug $\times$ task	
	Drug	Drug $\times$ time	Task	Task $\times$ time	Drug $\times$ task	Drug $\times$ task $\times$ time
VAS ratings						
Stress	3.6*	1.2	30.5***	24.8***	0.8	1.2
Tension	6.0**	2.1*	17.4***	19.8***	0.8	1.0
Insecurity	3.4*	1.5	18.0***	16.0***	0.9	1.1
PASA						
Threat	2.4	—	5.4*	—	2.0	—
Challenge	4.4*	—	33.1***	—	2.3	—
Self-efficacy	2.0	—	8.2**	—	0.26	—
Performance satisfaction	0.08	—	35.0***	—	0.01	—
Heart rate	4.3*	2.8**	20.4***	18.4***	0.6	1.7
Systolic blood pressure	7.4**	4.2***	6.5*	5.5***	1.7	0.8
Cortisol	33.2***	9.2***	5.0*	6.3***	1.7	3.0**

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Dashes indicate the measure was only collected once

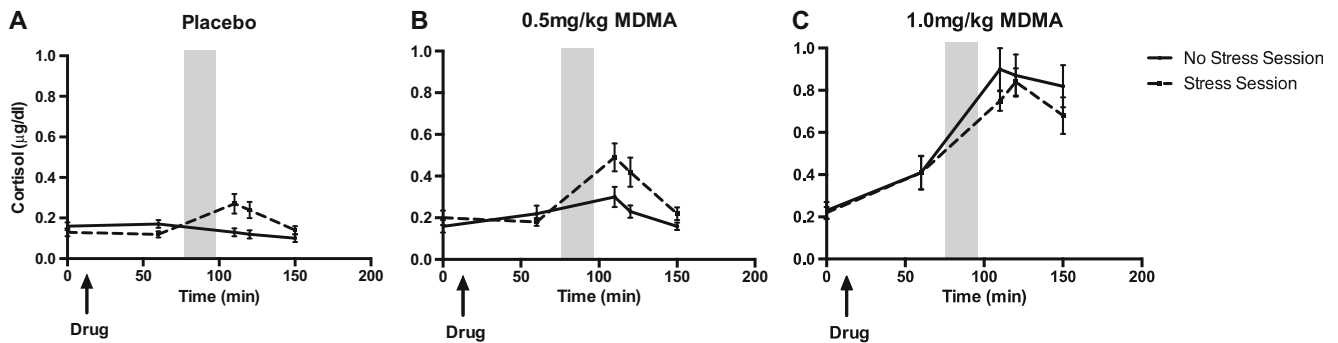


Fig. 2 Effects of MDMA on salivary cortisol. Effects of MDMA on cortisol levels **a** in the group receiving placebo, **b** in the group receiving 0.5 mg/kg MDMA, and **c** in the group receiving 1.0 mg/kg MDMA. *Shaded area* indicates the time during which the task took place. *Bars* depict mean $\pm$ SEM

responses to a stressful public speaking task. Based on evidence that MDMA reduces responses to threatening social stimuli in humans, we hypothesized that these relatively low doses of the drug would decrease reactivity to psychosocial stress. Contrary to our hypothesis, MDMA did not reduce subjective responses to stress and instead produced stress-like effects on both physiological (heart rate, blood pressure, cortisol) and subjective (ratings of stress, tension, and insecurity) ratings on both the stress and no-stress sessions. This is the first laboratory based study to test the acute effect of MDMA on responses to a psychosocial stressor in healthy volunteers.

Even though MDMA is known to produce stress-like physiological responses, we hypothesized that MDMA might reduce subjective responses to psychosocial stress. First, many studies have demonstrated that MDMA produces positive, “prosocial” effects, such as the facilitation of social interaction in humans and other species (Bedi et al. 2010; Hysek et al. 2013; Kamilar-Britt and Bedi 2015; Kirkpatrick et al. 2015; Thompson et al. 2007). We reasoned that these prosocial effects might reduce the negative emotional impact of the public speaking task. Second, MDMA reduces responses to negative social contexts specifically, including subjective, behavioral, psychophysiological, and neural responses to images of threatening faces (Bedi et al. 2009; Hysek et al. 2011; Wardle and de Wit 2014) and emotional responses to social rejection using the Cyberball task (Frye et al. 2014). If

MDMA dampens the ability to recognize threatening faces, it may reduce how negatively subjects perceive the evaluators during the TSST. Even if the drug makes it more difficult to perform the task, this reduction in response to threat of social evaluation may serve to reduce the perceived stressfulness of the task. Similarly, our previous Cyberball results suggest that MDMA reduces the negative mood experienced in response to acute social rejection. Finally, MDMA has shown promise in the treatment of post-traumatic stress disorder (PTSD; Bouso et al. 2008; Mithoefer et al. 2011; Oehen et al. 2013), suggesting that it may reduce anxiety while processing memories of stressful events. Despite these prior findings, MDMA failed to dampen negative mood responses to the TSST.

On the other hand, there is a large body of research showing that MDMA exerts physiological effects that resemble the effects of an acute psychosocial stressor, including increasing cortisol (Harris et al. 2002; Hysek et al. 2011; Parrott et al. 2013; Schmid et al. 2014; Seibert et al. 2014). As a stimulant drug, MDMA is known to increase blood pressure and heart rate even in the absence of stress (Torre et al. 2000; Vollenweider et al. 1998). Consistent with this, MDMA in the present study increased heart rate and blood pressure even during the control session without stress. It has been argued that the effects of MDMA on cortisol levels may contribute to its stimulating effects, particularly in stimulating social settings (Parrott 2009; Parrott et al. 2014). We saw no evidence of this in the present study. Subjects did not indicate that they

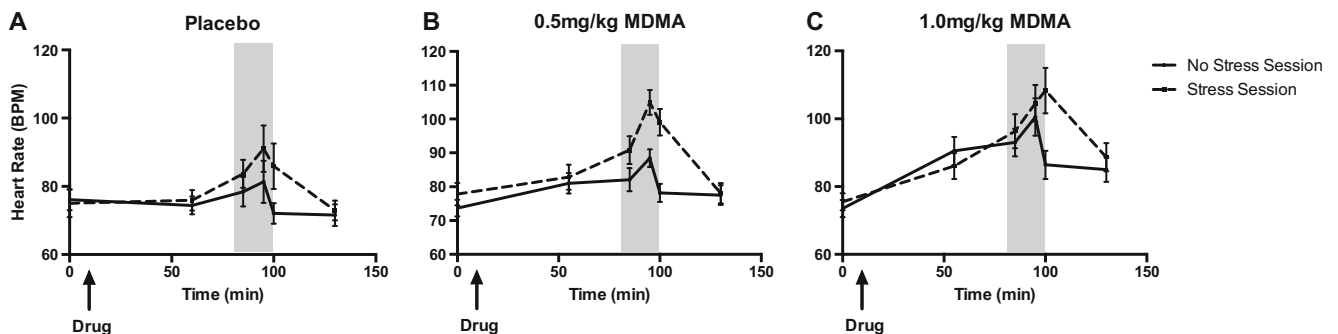


Fig. 3 Effects of MDMA on heart rate **a** in the group receiving placebo, **b** in the group receiving 0.5 mg/kg MDMA, and **c** in the group receiving 1.0 mg/kg MDMA. *Shaded area* indicates the time during which the task took place. *Bars* depict mean $\pm$ SEM

liked the drug more after acute stress, when their cortisol levels were elevated. MDMA can also, like acute social stress, increase ratings of anxiety (Baggott et al. 2015; Kirkpatrick et al. 2012). Interestingly, in one study, the drug increased ratings of anxiety even while dampening fear of negative social evaluation (Baggott et al. 2015). Thus, MDMA has some stress-like effects on both physiological and subjective ratings, but these are nuanced and may depend on both the setting and the population.

The apparently mixed anxiolytic and anxiogenic effects of MDMA raise many questions. When does the drug alleviate stress responses and when does it worsen them? How does MDMA differ from other stimulant drugs in this respect? Are the effects dependent on dose, or subject sample, or context? Or, does MDMA reduce memories of adverse events without affecting acute responses to adverse events? Previous studies addressing the behavioral and subjective mechanisms of MDMA-related effects have provided some insights into these questions. MDMA may specifically dampen negative memories, as described in a recent report by Baggott et al. (2015). This study found that acute doses of MDMA increased self-reported anxiety, but it also paradoxically increased how comfortable participants felt describing emotional memories. This suggests that anxiety and social discomfort are dissociable processes, with distinct underlying mechanisms. Although previous evidence suggests that the drug alters perception of positive or negative social stimuli, it may also independently changes behavioral responses, biasing these responses in a prosocial manner. In this way, it might increase anxiety, while simultaneously altering behavioral responses to the experience of such anxiety.

Some of the differences across studies may be related to the doses of MDMA used. MDMA increases plasma levels of oxytocin, and oxytocin itself reduces responses to acute stress (Heinrichs et al. 2003). There is some evidence that the prosocial effects of MDMA are mediated by oxytocin (Dumont et al. 2009; Hysek et al. 2013, 2012; Schmid et al. 2014). However, MDMA only increases plasma oxytocin levels at higher doses (i.e., 1.5 mg/kg (Kirkpatrick et al. 2014a) and 1.1 mg/kg in a single study (Schmid et al. 2014)), raising the possibility that a stress-dampening effect only occurs at higher doses. Interestingly, the doses used for PTSD therapy are higher than the doses we used in this study (Mithoefer et al. 2013). Our doses were selected because of safety concerns about the possible combined effects of MDMA and stress, but higher doses might yield different results.

This study has several limitations. First, as just noted, the doses of MDMA were low, and it may be that higher doses of MDMA are needed to dampen the stress response. Furthermore, our sample size was small and not large enough to examine sex differences or other sources of individual differences that might affect responses to MDMA. It is also possible that the TSST was not the optimal task to detect the unique social effects of MDMA, and that the drug's effects

might interact with characteristics of the participants in the social interaction (e.g., familiarity, degree of threat, gender). Finally, while we tested participants in a comfortable laboratory setting, the drug may produce different effects in a non-laboratory setting or in a psychotherapeutic setting. Future studies might address these questions of dosing, oxytocin release, individual differences, and contexts.

In conclusion, we found no evidence for a stress-dampening effect of MDMA in healthy young adults. Our results were surprising in light of previous evidence of MDMA's ability to dampen responses to threatening social input, and the recent evidence in support of its potential as a treatment, in combination with psychotherapy, for PTSD. It remains to be determined what the conditions are under which the drug dampens responses to negative social stimuli, including contextual conditions (laboratory, natural, or psychotherapeutic), doses, participants, or outcome measures.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflicts of interest.

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