

Is Ecstasy an “Empathogen”? Effects of \pm 3,4-Methylenedioxymethamphetamine on Prosocial Feelings and Identification of Emotional States in Others

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Background: Users of \pm 3,4-methylenedioxymethamphetamine (MDMA), “ecstasy,” report that the drug produces unusual psychological effects, including increased empathy and prosocial feelings. These “empathogenic” effects are cited as reasons for recreational ecstasy use and also form the basis for the proposed use of MDMA in psychotherapy. However, they have yet to be characterized in controlled studies. Here, we investigate effects of MDMA on an important social cognitive capacity, the identification of emotional expression in others, and on socially relevant mood states.

Methods: Over four sessions, healthy ecstasy-using volunteers ($n = 21$) received MDMA (.75, 1.5 mg/kg), methamphetamine (METH) (20 mg), and placebo under double-blind, randomized conditions. They completed self-report ratings of relevant affective states and undertook tasks in which they identified emotions from images of faces, pictures of eyes, and vocal cues.

Results: MDMA (1.5 mg/kg) significantly increased ratings of feeling “loving” and “friendly”, and MDMA (.75 mg/kg) increased “loneliness”. Both MDMA (1.5 mg/kg) and METH increased “playfulness”; only METH increased “sociability”. MDMA (1.5 mg/kg) robustly decreased accuracy of facial fear recognition relative to placebo.

Conclusions: The drug MDMA increased “empathogenic” feelings but reduced accurate identification of threat-related facial emotional signals in others, findings consistent with increased social approach behavior rather than empathy. This effect of MDMA on social cognition has implications for both recreational and therapeutic use. In recreational users, acute drug effects might alter social risk-taking while intoxicated. Socioemotional processing alterations such as those documented here might underlie possible psychotherapeutic benefits of this drug; further investigation of such mechanisms could inform treatment design to maximize active components of MDMA-assisted psychotherapy.

Key Words: Ecstasy, MDMA, methamphetamine, social cognition, emotion identification, empathy

The drug \pm 3,4-methylenedioxymethamphetamine (MDMA), “ecstasy,” is reported to have unusual, so-called “empathogenic” effects, such as increased empathy and prosocial feelings (1). Such effects are cited as a motivation to use ecstasy recreationally (2–3) and might contribute to its reinforcing capacity (4). The apparent empathogenic effects of MDMA are also central to the rationale for the use of the drug as a psychotherapeutic adjunct (1,5,6). Thus, the social behavioral profile of MDMA is relevant to understanding both recreational use and possible therapeutic effects of this drug.

To date, only a small number of controlled laboratory studies have assessed relevant subjective experiences after MDMA. These studies indicate that MDMA increases feelings related to empathy and sociability, including self-rated friendliness (7,8), extroversion (9,10), closeness to others (11), sociability (7,12), talkativeness (7,8), amicability, and gregariousness (13), although some of these effects are inconsistent (14–16). Despite these reports on subjective

effects of the drug, there have been no published reports in humans of the effect of controlled administration of MDMA on behaviors related to empathy and sociability. Using functional magnetic resonance imaging, we recently reported effects of MDMA on neural processing of social material (12), but in that study the drug did not alter the behavioral response to the stimuli (i.e., accuracy of identification of emotions from pictures of facial effect). Identification of the emotions of others on the basis of facial, vocal, or postural cues is a critical social cognitive capacity and an important “first step” in empathy (17) and thus might be an information processing domain that is useful for studying a purportedly empathogenic drug. The altered brain response in our imaging study suggested that emotion recognition might play a role in the effects of the drug, but the methods we used were not optimal to detect a behavioral effect. The emotional expressions shown were not subtle (18); they were presented for a long period (4 sec) (17), and we selected a relatively narrow range of basic emotions (e.g., fear, anger, and happiness) (19), excluding more complex, culturally determined affective states, such as shame and jealousy (20).

The present study was designed to further investigate the behavioral effects of MDMA on social cognition using emotional identification paradigms. We employed more sensitive methods than in our imaging study (12) to investigate the effect of MDMA on identification of basic emotions from facial cues. Other behavioral measures included a test of recognition of complex emotions on the basis of cues from the eye region (21) and a test of emotion identification from vocal cues (22). We also assessed a range of relevant subjective effects of MDMA and included a comparison drug, methamphetamine (METH), to determine the specificity of these effects to MDMA.

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We hypothesized that, in addition to increasing feelings related to sociability and empathy, MDMA would alter emotion recognition on the basis of pictures of faces, pictures of eyes, and voices. Notably, either increases or decreases in emotional identification could result in apparent empathogenic effects. Improved identification of emotions would be consistent with increased empathy (17), whereas decreased sensitivity to threat-related emotions such as fear and anger might reduce social avoidance (19) and hence increase social approach behavior (sociability). We further hypothesized that effects of MDMA on social cognition and relevant affective states would be specific to MDMA rather than generalizing to a prototypic psychostimulant, METH.

Methods and Materials

Participants

Healthy volunteers, aged 18–38, who reported using MDMA or ecstasy on at least two occasions were recruited with Internet advertisements and word-of-mouth. Candidates underwent extensive screening and were excluded on the basis of: psychiatric disorder (DSM-IV Axis I diagnosis including substance dependence) (23); signs of medical or neurological illness assessed with medical examination, electrocardiogram, and structured clinical interview; body mass index outside healthy range (18.5–30); cardiovascular illness in first-degree relative; prior adverse response to ecstasy; and pregnancy or lactation. All participants provided written informed consent after receiving protocol descriptions and were fully debriefed at study completion as approved by the University of Chicago Institutional Review Board.

Experimental Protocol

A four-session, within-participants, double-blind design was employed. At each session participants received a capsule containing: MDMA (.75 mg/kg [MDMA.75] or 1.5 mg/kg [MDMA1.5]), METH (20 mg), or placebo (PBO); capsules were administered in randomized order. Sessions were scheduled at least 5 days apart to allow for drug elimination. Participants were asked not to eat for 2 h before sessions. They were required to abstain from cannabis for 7 days, alcohol and medications for 24 h, and all other recreational drugs (e.g., ecstasy) for 48 h before sessions. Compliance was verified with urine (QuickTox Drug Screen Dipcard, Branan Medical Corporation, Irvine, California), saliva (Oratect III, Branan Medical Corporation), and Breathalyzer (Alco-sensor III, Intoximeters, St. Louis, Missouri) screens. Female participants were required to test negative for pregnancy at each session (Aimstrip, Craig Medical, Vista, California).

Drug doses were selected on the basis of previous research; MDMA doses in this low-to-moderate range have been safely administered to humans previously and produce modest to robust alterations in mood state (24). We have previously shown MDMA (1.5 mg/kg) to increase sociability (12); it is also within recreational dose ranges (25). Three prior studies have employed d-amphetamine as a reference compound for MDMA (7,15,26). Tancer and Johanson (7) used d-amphetamine (10 and 20 mg) and reported overlapping reinforcing and subjective effects of MDMA (2 mg/kg) and 20-mg amphetamine, although in many cases MDMA (2 mg) produced higher ratings. Johanson *et al.* (15) employed 20-mg d-amphetamine in a discriminative stimulus procedure and reported that 50% of participants discriminated MDMA (1, 1.5 mg/kg) as d-amphetamine (20 mg). Cami *et al.* (26) used a higher dose of amphetamine (40 mg) but only tested subjects with histories of amphetamine use. For the current study, we selected a METH dose

(20 mg) that is safe and induces robust stimulant and euphoric effects in amphetamine-naïve volunteers (27).

Drug sessions commenced at noon. After baseline measures (cardiovascular and subjective state; see following text), participants ingested an opaque gelatin capsule (size 00) containing MDMA or METH with lactose or dextrose or PBO (filler only). For at least 4.5 h after capsule ingestion, participants remained in a comfortable laboratory environment undergoing regular cardiovascular checks and subjective state questionnaires. Participants were alone in testing rooms; their only social contact was with a research assistant, who was instructed not to interact with participants outside of the requirements of the protocol. Participants did not have access to telephones or the Internet. They remained in the laboratory until they no longer showed noticeable drug effects. Participants started cognitive tasks (e.g., emotional recognition) 65 min after capsule administration, to coincide with peak drug effect onset (26).

Assessment Measures

Subjective measures included Visual Analogue Scales (VAS) (28) and the Profile of Mood States (POMS) (29). The VAS comprised the following adjectives: stimulated, bored, sedated, anxious, insightful, nauseated, loving, dizzy, sociable, confused, lonely, elated, playful, blank, and restless. The POMS is a 72-item adjective checklist rated on a 5-point Likert scale from 0 ("not at all") to 4 ("extremely"). The POMS yields eight subscores, including a friendliness scale. The VAS was administered at 0, 30, 60, 90, 120, 150, 210, and 240 min after capsule. The POMS was administered at 0, 90, and 240 min after capsule, with the middle time point designed to occur during peak drug effects (26). On the basis of the study hypotheses, subjective outcome measures were: 1) VAS Sociable, Playful, Loving, and Lonely; and 2) POMS Friendliness. The VAS outcome measures were single items. The POMS Friendliness subscale is the mean of scores for the following items: "friendly," "agreeable," "helpful," "forgiving," "good-natured," "warm-hearted," "good-tempered," and "kindly."

Cognitive measures included two facial affect identification tasks and a vocal affect task. Each cognitive task was completed once in each session, during the period of anticipated peak drug effects (26). The Facial Emotion Recognition task (FER) is sensitive to serotonin and norepinephrine reuptake inhibition (30). Stimuli consist of facial pictures from the Ekman and Friesen series (31). The version of the task employed includes four basic emotions (anger, fear, happiness, and sadness), with pictures morphed between neutral (0%) and prototype emotion (100%) in 10% increments (32). For each emotion, four different actors (two of each gender) were employed, resulting in 40 stimuli for each of four emotions (10 incrementally morphed pictures/actor/emotion). In addition, 10 neutral stimuli were added, for a total of 170 pictures. Faces were presented in randomized order for 500 msec and replaced by a rating screen. Participants rated each face by selecting the emotion depicted, from the four emotions and neutral. The main outcome measure was accuracy (proportion correct).

The Reading the Mind in the Eyes—Revised (Eyes) test was used to assess identification of complex emotions (21). This task consists of 36 images of the eye region of men and women presented in randomized order. Each pair of eyes is taken from a face expressing a complex emotional state, such as "reflective" or "ashamed." Participants choose between four options to describe the emotion depicted; after selection, the next image is presented. This task employs only the eye region, because this area carries subtle yet critical information about emotional state (21). The Eyes test is sensitive to oxytocin administration (33). The outcome measure was accuracy.

The vocal affect recognition task was the Diagnostic Analysis of Nonverbal Accuracy (DANVA-2) (22) Adult Paralanguage test. This task comprises 24 audio clips of professional actors saying a single neutral phrase ("I'm going out of the room now and I'll be back later") in a happy, sad, angry, or fearful tone. Within each emotion category, there are three high emotional intensity and three low emotional intensity items. After hearing each sentence, participants choose which emotion was expressed from the four previously described emotions. The outcome measure was accuracy.

Statistical Analyses

For subjective outcomes, repeated measures analyses of variance (ANOVAs) were used to assess the effects of drug on peak change from baseline scores. Significant omnibus *F* tests were followed with post hoc pairwise comparisons with full Bonferroni adjustment of the significance threshold. For the FER and DANVA-2 scores, two-way repeated measures ANOVAs assessed for main effects of drug and interactions between drug and emotion type. In the case that a significant interaction was identified, simple main effects analysis assessed for effects of drug on identification of each emotion. The significance threshold was set at .05 for the omnibus ANOVA, with Bonferroni-adjusted thresholds employed for each of the simple main effects analyses ($p = .05/\text{number of emotions}$). Significant simple main effects were followed with post hoc pairwise comparisons with full Bonferroni adjustment for the total number of analyses undertaken (i.e., .05 corrected for simple main effects analyses as well as pairwise comparisons). An ANOVA assessed the effect of drug on total Eyes score. The α was set at $p < .05$ (adjusted as described in the preceding text). In the case that Mauchley's test of sphericity indicated significant departure from sphericity ($p < .05$), Greenhouse-Geisser corrected degrees of freedom and significance levels were interpreted. Where the assumption of sphericity was met, we conservatively interpreted Huynh-Feldt corrected significance levels (34). Session order did not have a significant effect in any of the analyses and was therefore not retained in the models. We assessed for normality of the data and univariate outliers before analysis. Data for four outcome measures were non-normal (VAS Loving, VAS Lonely, POMS Friendly, and DANVA scores). In these cases, we conducted nonparametric analysis (Friedman's ANOVA followed by Wilcoxon signed rank tests). In all cases except VAS Lonely, the nonparametric approach yielded the same results; therefore parametric statistics are reported. For VAS Lonely, nonparametric statistics yielded slight alterations to the outcome; therefore nonparametric statistics are reported. Truncation of two outlying data points (both in DANVA scores) did not alter results, and original data were retained. Effect sizes are presented as η^2 for parametric analyses and r values for nonparametric analysis. All analyses were conducted with SPSS 17.0 (SPSS, Chicago, Illinois).

Results

Mean age of participants was 24.4 years ($SD = 4.9$ years), and 9 of the 21 were women. Seventeen participants identified as Caucasian, 2 were Asian, 1 was African-American, and 1 was of mixed race. Participants reported first use of ecstasy at a mean age of 19.8 ($SD = 2.7$) years and lifetime ecstasy use on a mean of 15.0 ($SD = 23.1$) occasions; 13 participants had used the drug < 10 times. In the month before participation, 12 reported smoking cigarettes at least weekly, all had consumed alcohol, and 16 had consumed cannabis. All participants had used cannabis at some time in their lives, all but two reported lifetime use of stimulants such as cocaine, and all but one had used hallucinogens.

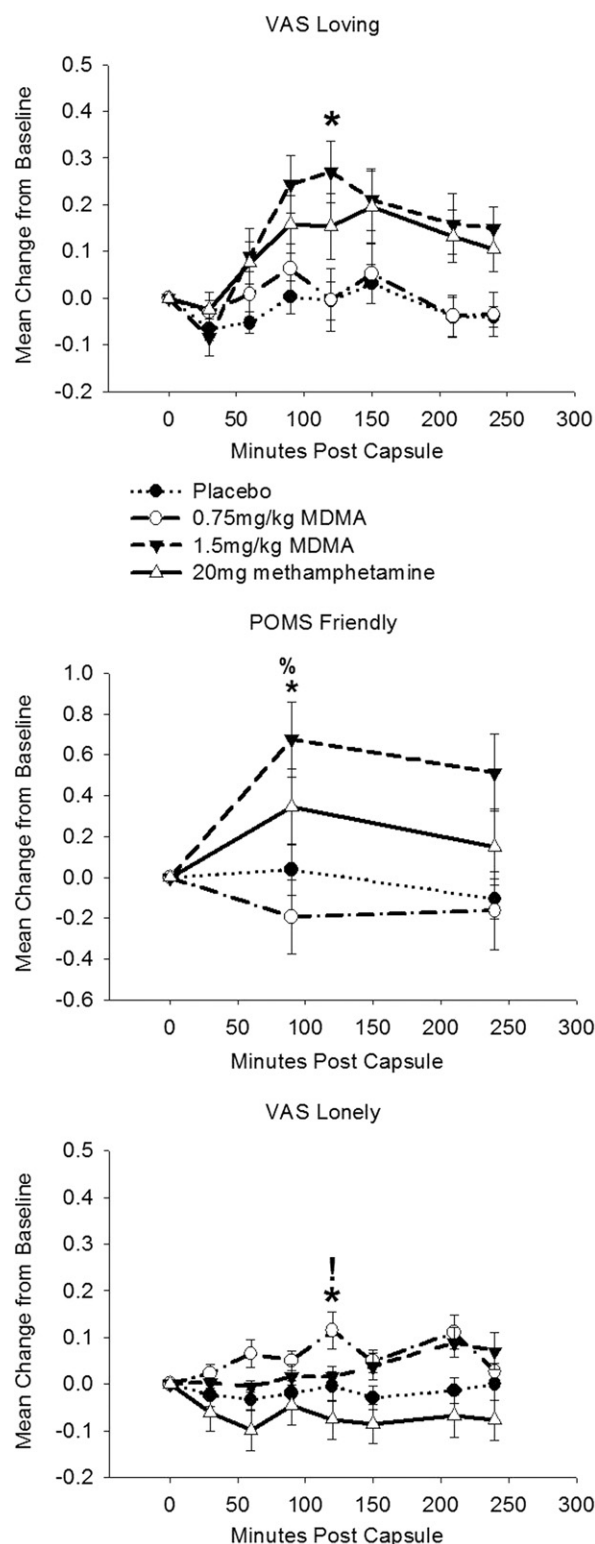


Figure 1. Drug effects on self-reported loving, friendly, and lonely feelings. Top: Visual Analogue Scale (VAS) Loving. Middle: Profile of Mood states (POMS) Friendly. Bottom: VAS Lonely. Data are mean change from predrug baseline (\pm SEM) as a function of minutes after capsule. $n = 20$ due to missing data. *Difference (peak change from baseline) from placebo ($p < .05$, with Bonferroni correction). %Difference from $\pm 3,4$ -methylenedioxymethamphetamine (MDMA) (.75 mg/kg; $p < .05$, with Bonferroni correction). !Difference from methamphetamine (20 mg; $p < .05$, with Bonferroni correction).

The drugs increased ratings on all five subjective state measures. The MDMA1.5 significantly increased loving and friendliness ratings, whereas MDMA.75 increased loneliness. Both MDMA1.5 and METH increased playfulness, whereas only METH significantly increased sociability.

Drug condition affected ratings on the VAS Loving scale [$F(3,57) = 5.04, p = .004; \eta^2 = .21$]. Follow-up analyses indicated that MDMA1.5 increased loving feelings relative to PBO. There was an effect of drug on POMS Friendliness [$F(2,7,51) = 6.81, p = .001; \eta^2 = .26$]. The MDMA1.5 increased friendliness ratings compared with both PBO and MDMA.75. Drug condition affected ratings on VAS Loneliness [$\chi^2(3) = 11.94, p = .008; r = .54$]. Post hoc analysis showed that MDMA.75 increased loneliness ratings relative to METH and PBO (Figure 1). Drug condition affected VAS Playfulness [$F(3,57) = 8.57, p < .001, \eta^2 = .31$], with MDMA1.5 increasing playfulness relative to PBO and MDMA.75 and METH increasing playfulness compared with PBO. There was a drug effect on VAS Sociability [$F(2,5,47.7) = 3.06, p < .05, \eta^2 = .14$]. Methamphetamine increased sociability relative to PBO (Figure 2).

There was a significant interaction between drug condition and emotion on the FER accuracy of emotion identification [$F(5,2,104.6) = 3.23, p = .008$]. After Bonferroni correction of the Type 1 error rate, simple main effects analysis did not yield significant effects of drug on identification of angry, happy, neutral, or sad faces. However, drug condition affected identification of fearful facial expressions [$F(2,8,56.0) = 4.45, p = .008, \eta^2 = .18$], indicating that MDMA1.5 decreased accuracy of fear recognition relative to PBO (Table 1).

MDMA did not affect accuracy on the Eyes or the DANVA-2 tests (Table 1). There was no interaction between drug condition and emotion type on DANVA-2 scores.

To explore possible mechanisms of the effect of MDMA1.5 on facial fear recognition, we conducted exploratory analysis on incorrectly identified emotional expressions. MDMA1.5 increased the tendency to misclassify emotional expressions as neutral, compared with PBO ($p < .05$, uncorrected; Table 1). We also attempted to determine whether subjects' apparent expectancies of receiving MDMA affected their responses during sessions. Data were reanalyzed according to the subjects' classification of what drug they thought they had received in each session. There was no significant relationship between drug identification and any of the measures that were sensitive to drug effects.

Discussion

We found that MDMA (1.5 mg/kg only) altered a behavioral indicator of social cognition. Specifically, it robustly reduced recognition of fearful faces, without changing recognition of other emotions from facial or vocal cues. Although previous studies have confirmed that the drug induces subjective feelings related to sociability and empathy, this is the first published demonstration of an overt behavioral effect of MDMA in humans.

The pattern of findings in our study might be more consistent with increased social approach behavior (i.e., sociability) than increased empathy. Anecdotal reports indicate that ecstasy increases interpersonal connection (3), which might suggest increased sensitivity to emotions in others. In the present study, MDMA produced self-reports of loving feelings and friendliness but decreased the accuracy of participants in identifying fear in others. A decreased ability to identify negative emotions, particularly threat-related signals such as fear, might facilitate social approach behavior (12,35). Thus, MDMA might facilitate social interactions because it reduces the impact of the negative emotions of others rather than enhancing recognition of and sensitivity to the emotions of others.

Unexpectedly, some subjective effects measured were increased by METH as well as MDMA. Indeed, only METH significantly increased self-rated sociability. Moreover, whereas MDMA (1.5 mg/kg) significantly increased loving feelings and friendliness compared with PBO, these ratings were not significantly different from ratings during METH sessions. These similarities were unexpected, because of the different pharmacological profile and anecdotal reports of the effects of amphetamine and MDMA (36,37). It is possible that the expectation of receiving MDMA influenced subjects' reports of empathogenic feelings. Although expectancies were minimized with double-blind conditions and a range of possible drugs to be administered, it was difficult to completely control expectancies. Indeed, 6 of 21 participants guessed that they had

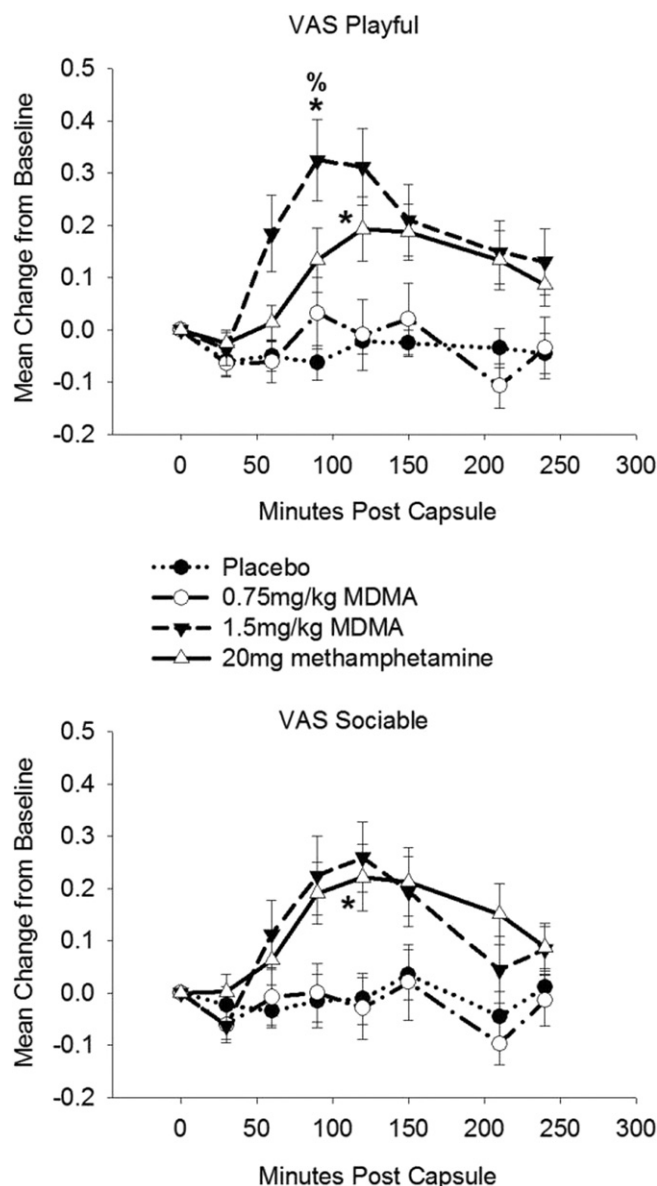


Figure 2. Drug effects on self-reported playfulness and sociability. Top: Visual Analogue Scale (VAS) Playful. Bottom: VAS Sociable. Data are mean change from predrug baseline (\pm SEM) as a function of minutes after capsule. $n = 20$ due to missing data. *Difference (peak change from baseline) from placebo ($p < .05$, with Bonferroni correction). %Difference from $\pm 3,4$ -methylenedioxymethamphetamine (MDMA) (.75 mg/kg; $p < .05$, with Bonferroni correction).

Table 1. Emotional Identification

	PBO Mean (SD)	MDMA.75 Mean (SD)	MDMA1.5 Mean (SD)	METH Mean (SD)	Overall F (df)	1 vs. 2 t (df)	1 vs. 3 t (df)	1 vs. 4 t (df)	2 vs. 3 t (df)	2 vs. 4 t (df)	3 vs. 4 t (df)
FER Happiness ^a	.74 (.07)	.71 (.09)	.71 (.11)	.73 (.10)	.96 (3,60)	—	—	—	—	—	—
FER Sadness ^a	.51 (.14)	.54 (.16)	.47 (.14)	.52 (.16)	3.60 (3,60)	—	—	—	—	—	—
FER Fear ^a	.63 (.07)	.59 (.12)	.55 (.10)	.59 (.10)	4.45 ^b (3,60)	2.27 (20)	3.94 ^b (20)	2.59 (20)	1.41 (20)	.12 (20)	1.31 (20)
FER Anger ^a	.64 (.07)	.63 (.09)	.59 (.11)	.63 (.06)	2.0 (3,60)	—	—	—	—	—	—
FER Neutral ^a	.69 (.17)	.68 (.15)	.77 (.12)	.67 (.20)	2.84 (3,60)	—	—	—	—	—	—
FER Neutral Errors ^d	44.90 (11.31)	46.52 (12.79)	51.71 (10.58)	46.48 (12.14)	3.25 ^c (3,60)	.79 (20)	2.52 ^c (20)	.84 (20)	2.02 (20)	.02 (20)	1.95 (20)
Eyes Total	26.81 (5.14)	26.67 (3.73)	26.10 (2.70)	27.24 (3.08)	.58 (3, 60)	—	—	—	—	—	—
DANVA2 Total ^e	18.05 (1.70)	18.00 (1.97)	17.20 (2.19)	18.70 (2.11)	3.01 (3, 57)	—	—	—	—	—	—

PBO, placebo; MDMA.75, .75-mg/kg \pm 3.4-methylendioxyamphetamine (MDMA); MDMA1.5, 1.5-mg/kg MDMA; METH, 20-mg methamphetamine; FER, Facial Emotion Recognition task; Eyes, Reading the Mind in the Eyes-Revised; DANVA2, Diagnostic Assessment of Nonverbal Accuracy 2 Adult Paralanguage test. 1 vs. 2, PBO vs. MDMA1.5; 1 vs. 3, PBO vs. MDMA.75; 1 vs. 4, PBO vs. METH; 2 vs. 3, MDMA.75 vs. MDMA1.5; 2 vs. 4, MDMA.75 vs. METH; 3 vs. 4, MDMA1.5 vs. METH.

^aProportion correct.

^b $p < .05$, with Bonferroni adjustment for multiple comparisons.

^c $p < .05$, uncorrected.

^dFER number of misclassifications of emotions as neutral.

^e $N = 20$, missing data due to equipment malfunction.

consumed ecstasy when they had received METH. However, follow-up analyses revealed that the guesses of participants about the drug received were not significantly related to outcome measures, suggesting that expectancies play a minor role in these results. A more likely alternative is that METH might have a more prosocial profile than previously thought. Psychostimulants have been shown to enhance the rewarding value of social interactions in rodents (38) and humans (39), and METH is associated with social and particularly sexual enhancement in some subcultures (40). Thus, the prosocial effects of MDMA might be less selective than believed.

The effect of MDMA on social cognition was limited to identification of emotions from facial expressions, with no apparent effect on recognition of affective cues from the eye region or from voices. Thus, it seems that performance alterations arising from MDMA are specific to processing of whole-face visual affective cues. However, whereas the facial task required participants to identify emotions on the basis of subtle, briefly presented pictures, there were no time limits on responding to items in the Eyes task. Moreover, whereas the vocal stimuli presented contained two levels of emotion intensity (high vs. low), the facial task included 10 levels (from neutral to 100% intensity, in 10% increments). Thus, it might be that MDMA affects identification of subtle emotional cues rather than having modality-specific effects. Future research requiring affect recognition from subtle, briefly presented vocal and eye-region stimuli could clarify this issue.

Some limitations should be noted. First, as noted previously, the behavioral tasks we used might not have been sensitive to all the unusual social effects attributed to MDMA. For example, the static photos of facial affect we employed might be less ecologically valid than dynamic stimuli (41). At the time of study initiation, no suitable dynamic stimuli were available. Second, we are not aware of tasks that include both social and nonsocial stimuli, making it difficult to determine the specificity of these findings to social stimuli. A third possible limitation was that we adjusted the dose to the body weight for MDMA but not for METH. This is unlikely to be a major factor, because participants were within a narrow weight range (body mass index 18.5–30), and post hoc analysis indicated that only one measure of the effects of METH (playfulness) correlated with body weight ($r = -.45$, $p = .04$). A final limitation is that, for ethical reasons, all participants had prior experience with ecstasy or MDMA, so the findings might not generalize to MDMA-naïve individuals (42). However, we intentionally recruited candidates with limited previous exposure, to minimize possible effects of prior use.

There are a number of directions for future inquiry. In rodents, MDMA increases prosocial behavior (36,43), and this effect is attenuated by an oxytocin receptor antagonist (2). Oxytocin is a neuropeptide known to be a critical modulator of social behavior in mammals (44,45). In humans, MDMA increases plasma oxytocin levels (13,46), and plasma oxytocin levels also vary positively with enhanced subjective sociability after MDMA (13). This suggests that a fruitful area of future research will be to examine the role of oxytocin in the social cognitive, affective, and behavioral effects of MDMA in humans. Second, there is a need for studies of the cognitive mechanisms underlying alterations to social cognition. For example, we found that MDMA (1.5 mg/kg) increased the number of non-neutral faces erroneously identified as neutral, apparently reducing the capacity to detect subtle emotional signals. This phenomenon, which might underlie the reduced fear identification demonstrated in this study, requires further investigation. Finally, it is possible that certain social predispositions, such as high or low levels of trait sociability, affect the degree to which MDMA alters

social processing in humans, potentially contributing to individual preferences for MDMA.

The present findings have implications for both recreational and therapeutic MDMA use. Recreational ecstasy users might benefit from knowledge that, although it might increase feelings of interpersonal connection, ecstasy can subtly impair interpersonal competence. For instance, compromised social cognition might increase social risk-taking while under the influence of the drug. In addition, considering that social expectancies predict use of other drugs, such as alcohol (47), modifying the expectations of users about positive social effects of MDMA might alter ecstasy-use behavior (48). With regard to therapeutic use of MDMA, ongoing research on MDMA-assisted therapy should investigate possible mechanisms of any therapeutic effects (1,6). A recent placebo-controlled pilot study has indicated that MDMA-assisted psychotherapy might be useful in reducing symptoms in patients with treatment-resistant posttraumatic stress disorder. Although mechanisms of this apparent effect remain unclear, reductions in the intensity of fear perception, including but not limited to those reported here, might facilitate engagement with traumatic material during therapy (49). Moreover, reduced sensitivity to subtle signs of negative emotions in others (e.g., the therapist) might enable a patient to express thoughts or feelings that were previously inhibited because of perceived negative responses in the listener. In addition to further controlled research to investigate the effectiveness of MDMA in psychotherapy, an understanding of the socio-emotional cognitive mechanisms underlying such effects will help clinical researchers design treatments that optimize the therapeutic potential of this drug.

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- Parrott A (2007): The psychotherapeutic potential of MDMA (3,4-methylenedioxymethamphetamine): An evidence-based review. *Psychopharmacology* 191:181–193.
- Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGreor IS (2007): A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4-methylenedioxymethamphetamine ("ecstasy"). *Neuroscience* 146:509–514.
- Sumnall HR, Cole JC, Jerome L (2006): The varieties of ecstasy experience: An exploration of the subjective experiences of ecstasy. *J Psychopharmacol* 20:670–682.
- McGregor IS, Callaghan PD, Hunt GE (2008): From ultrasocial to antisocial: A role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use? *Br J Pharmacol* 154:358–368.
- Holland J (2001): *Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Rochester, Vermont: Park Street Press.
- Johansen PO, Krebs TS (2009): How could ecstasy help anxiety disorders? A neurobiological rationale. *J Psychopharmacol* 23:389–391.
- Tancer ME, Johanson CE (2003): Reinforcing, subjective, and physiological effects of MDMA in humans: A comparison with d-amphetamine and mCPP. *Drug Alcohol Depend* 72:33–44.
- Tancer ME, Johanson CE (2007): The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* 189:565–573.
- Vollenweider FX, Remensberger S, Hell D, Geyer MA (1999): Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. *Psychopharmacology* 143:365–372.
- Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX (2000): Psychological and physiological effects of MDMA ("ecstasy") after pretreatment with the 5-HT-sub-2 antagonist ketanserin in healthy humans. *Neuropsychopharmacology* 23:396–404.
- Kolbrich EA, Goodwin RS, Gorelick DA, Hayes RJ, Stein EA, Huestis MA (2008): Physiological and subjective responses to controlled oral, 3,4-methylenedioxymethamphetamine administration. *J Clin Psychopharmacol* 28:432–440.
- Bedi G, Phan KL, Angstadt M, de Wit H (2009): Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology* 207:73–83.
- Dumont GJH, Sweep FCJG, van der Steen R, Hermens R, Donders ART, Touw DJ, *et al.* (2009): Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci* 4:359–66.
- Liechti ME, Baumann C, Gamma A, Vollenweider FX (2000): Acute psychobiological effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology* 22:513–521.
- Johanson CE, Kilbey M, Gatchalian K, Tancer M (2006): Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans trained to discriminate among d-amphetamine, meta-chlorophenylpiperazine and placebo. *Drug Alcohol Depend* 81:27–36.
- Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT (2002): Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* 162:396–405.
- Clark TF, Winkelman P, McIntosh DN (2008): Autism and the extraction of emotion from briefly presented facial expressions: Stumbling at the first step of empathy. *Emotion* 8:803–809.
- Philippot P, Kornreich C, Blairy S (2003): Nonverbal deficits and interpersonal regulation in alcoholics. In: Coates EK, Feldman RS, Philippot P, editors. *Nonverbal Behavior in Clinical Setting*. New York: Oxford University Press.
- Ekman P (2003): *Emotions Revealed: Recognizing Faces and Feelings to Improve Communication and Emotional Life*. New York: Times Books/Henry Holt, and Company.
- Golan O, Baron-Cohen A, Hill J (2006): The Cambridge Mindreading (CAM) face-voice battery: Testing complex emotion recognition in adults with and without Asperger syndrome. *J Autism Dev Disord* 36:169–183.
- Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I (2001): The "Reading the Mind in the Eyes" Test Revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry* 42:241–251.
- Baum KM, Nowicki S Jr (1998): Perception of emotion: Measuring decoding accuracy of adult prosodic cues of varying intensity. *J Nonverbal Behav* 22:89–107.
- APA (1994): *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. MD, USA: American Psychiatric Association.
- Dumont GJH, Verkes RJ (2006): A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. *J Psychopharmacol* 20:176–187.
- Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA (2002): The content of ecstasy tablets: Implications for the study of their long-term effects. *Addiction* 97:1531–1536.
- Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, *et al.* (2000): Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): Psychomotor performance and subjective effects. *J Clin Psychopharmacol* 20:455–466.
- Wachtel SR, Ortengren A, de Wit H (2002): The effects of acute haloperidol or risperidone on subjective responses to methamphetamine in healthy volunteers. *Drug Alcohol Depend* 68:23–33.
- Folstein MF, Luria R (1973): Reliability, validity, and clinical application of the Visual Analogue Mood Scale. *Psychol Med* 3:479–486.
- McNair DLM, Droppleman L (1971): *Profile of Mood States*. San Diego: Educational and Industrial Testing Service.
- Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004): Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry* 161:1256–1263.
- Ekman P, Friesen WV (1976): *Pictures of Facial Affect*. Palo Alto, California: Consulting Psychologists Press.
- Young AW, Rowland D, Calder AJ, Etcoff NL, Seth A, Perrett DI (1997): Facial expression megamix: Tests of dimensional and category accounts of emotional recognition. *Cognition* 63:271–313.

33. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC (2007): Oxytocin improves "mind-reading" in humans. *Biol Psychiatry* 61:731–733.
34. Field A (2009): *Discovering Statistics Using SPSS, 3rd ed.* London: Sage Publications.
35. Porter MA, Coltheart M, Langdon R (2007): The neuropsychological basis of hypersociability in Williams and Down syndrome. *Neuropsychologia* 45:2839–2849.
36. Morley KC, McGregor IS (2000): (\pm)-3,4, -methylenedioxymethamphetamine (MDMA, "Ecstasy") increases social interaction in rats. *Eur J Pharmacol* 408: 41–49.
37. Clemens KJ, McGregor IS, Hunt GE, Cornish JL (2007): MDMA, methamphetamine and their combination: Possible lessons for party drug users. *Drug Alcohol Rev* 26:9–15.
38. Thiele KJ, Okun AC, Neisewander JL (2008): Social reward-conditioned place preference: A model revealing an interaction between cocaine and social context rewards in rats. *Drug Alcohol Depend* 96:202–212.
39. Heishman SJ, Stitzer ML (1989): Effect of d-amphetamine, secobarbital and marijuana on choice behavior: Social versus non-social options. *Psychopharmacology* 99:156–162.
40. Meyer JS, Grande M, Johnson K, Ali SF (2004): Neurotoxic effects of MDMA ("ecstasy") administration to neonatal rats. *Int J Dev Neurosci* 22:261–271.
41. Zaki J, Bolger N, Ochsner K (2008): It takes two: The interpersonal nature of empathic accuracy. *Psychol Sci* 19:399–404.
42. Thompson MR, Callaghan PD, Hunt GE, McGregor IS (2008): Reduced sensitivity to MDMA-induced facilitation of social behavior in MDMA pre-exposed rats. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1013–1021.
43. Morley KC, Arnold JC, McGregor IS (2005): Serotonin (1A) receptor involvement in acute, 3,4-methylenedioxymethamphetamine (MDMA) facilitation of social interaction in the rat. *Prog Neuropsychopharmacol Biol Psychiatry* 29:648–657.
44. Heinrichs M, Domes G (2008): Neuropeptides and social behavior: Effects of oxytocin and vasopressin in humans. *Prog Brain Res* 170:337–350.
45. Skuse DH, Gallagher L (2009): Dopaminergic-neuropeptide interactions in the social brain. *Trends Cogn Sci* 13:27–35.
46. Wolff K, Tsapakis EM, Winstock AR, Hartley D, Holt D, Forsling ML, Aitchison KJ (2006): Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. *J Psychopharmacol* 20:400–410.
47. Darkes J, Greenbaum P, Goldman M (2004): Alcohol expectancy mediation of biopsychosocial risk: Complex patterns of mediation. *Exp Clin Psychopharmacol* 12:27–38.
48. Lau-Barraco C, Dunn D (2008): Evaluation of a single-session expectancy challenge intervention to reduce alcohol use among college students. *Psychol Addict Behav* 22:168–175.
49. Mithoefer M, Wagner MT, Mithoefer AT, Jerome L, Doblin R (2010): The safety and efficacy of \pm 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized, controlled pilot study [published online ahead of print July 19]. *J Psychopharmacol*.