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ORIGINAL INVESTIGATION

MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions

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Abstract
Rationale 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) increases sociability. The prosocial effects of MDMA may result from the release of the "social hormone" oxytocin and associated alterations in the processing of socioemotional stimuli.
Materials and methods We investigated the effects of MDMA (125 mg) on the ability to infer the mental states of others from social cues of the eye region in the Reading the Mind in the Eyes Test. The study included 48 healthy volunteers (24 men, 24 women) and used a double-blind, placebo-controlled, within-subjects design. A choice reaction time test was used to exclude impairments in psychomotor function. We also measured circulating oxytocin and cortisol levels and subjective drug effects.
Results MDMA differentially affected mind reading depending on the emotional valence of the stimuli. MDMA enhanced the accuracy of mental state decoding for positive stimuli (e.g., friendly), impaired mind reading for negative stimuli (e.g., hostile), and had no effect on mind reading for neutral stimuli (e.g., reflective). MDMA did not affect psychomotor performance, increased circulating oxytocin and cortisol levels, and produced subjective prosocial effects, including feelings of being more open, talkative, and closer to others.
Conclusions The shift in the ability to correctly read socioemotional information toward stimuli associated with positive emotional valence, together with the prosocial feelings elicited by MDMA, may enhance social approach behavior and sociability when MDMA is used recreationally and facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings.

Keywords Emotion · MDMA · Oxytocin · Cortisol · Social cognition · Face recognition

Introduction

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) increases empathic feelings and sociability (Bedi et al. 2009, 2010; Dumont et al. 2009). The prosocial effects of MDMA could result from the emotional interoceptive effects of the drug but also from the altered perception or processing of social signals. For example, acute administration of MDMA in ecstasy users decreased the accuracy of facial fear recognition (Bedi et al. 2010), attenuated responses to threatening faces in the amygdala (Bedi et al. 2009), and enhanced responses to happy expressions in the ventral striatum (Bedi et al. 2009). Thus, MDMA may increase sociability by reducing recognition and responses to threatening social stimuli and enhancing responses to rewarding stimuli. Here, we evaluated whether MDMA also alters the ability to identify more complex emotions assessed with the Reading the Mind in the Eyes Test (RMET).

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The neurochemical mechanisms that underlie the social effects of MDMA are largely unexplored. The social neuropeptide oxytocin is a key regulator of emotional and social behavior (Meyer-Lindenberg et al. 2011; Neumann 2008) and may mediate the social effects of MDMA. In fact, in rats, MDMA has been shown to activate oxytocin-containing neurons in the hypothalamus (Thompson et al. 2007), release oxytocin from the hypothalamus (Forsling et al. 2002), and increase plasma levels of oxytocin (Thompson et al. 2007). MDMA increased social interaction in male rats (Thompson et al. 2007, 2009), an effect blocked by intraventricular administration of an oxytocin receptor antagonist (Thompson et al. 2007). MDMA also elevated plasma concentrations of oxytocin in humans (Dumont et al. 2009; Wolff et al. 2006).

Oxytocin has been shown to improve mind reading in the RMET (Domes et al. 2007b; Guastella et al. 2010). MDMA releases oxytocin and may similarly improve performance in the RMET. However, in other tests, oxytocin selectively improved the recognition of happy facial expressions but impaired the decoding of negative facial expressions (Di Simplicio et al. 2009; Marsh et al. 2010). We therefore explored whether MDMA differentially interferes with the ability to decode complex emotions in the RMET depending on the emotional valence of the stimuli.

MDMA releases norepinephrine, serotonin, and dopamine from nerve terminals via their corresponding monoamine transporter (Rothman et al. 2001). To explore the mechanism of action of MDMA, we investigated the effects of three pretreatments on the response to MDMA. We used the norepinephrine transporter inhibitor reboxetine to block the MDMA-induced release of norepinephrine (Hysek et al. 2011). The dual serotonin and norepinephrine transporter inhibitor duloxetine was used to block the MDMA-induced release of both serotonin and norepinephrine (Simmler et al. 2011a). Clonidine was used to block any MDMA-induced transporter-independent vesicular release of norepinephrine (Hysek et al. 2012).

Materials and methods

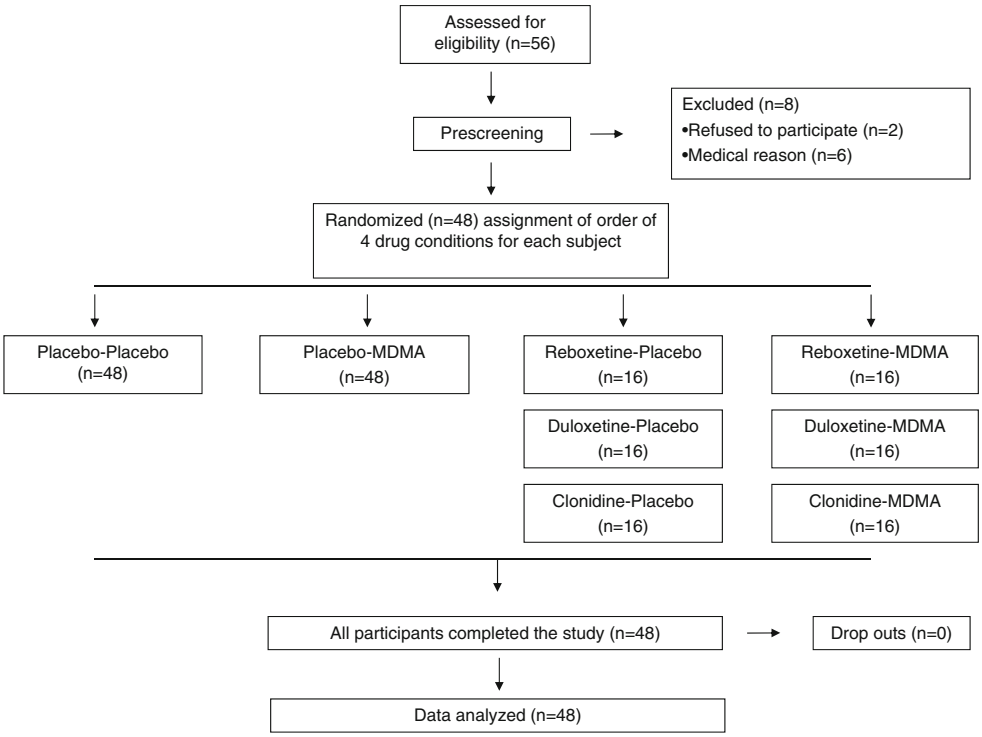
Study design

This was a prospectively designed pooled analysis of three double-blind, placebo-controlled, randomized, within-subjects studies (Hysek et al. 2011, 2012; Simmler et al. 2011a, b). The pre-specified primary endpoint of the pooled analysis was to demonstrate an effect of MDMA on RMET performance compared with placebo in 48 subjects. All subjects included in the three studies received MDMA, placebo, one of three different pretreatments prior to MDMA, or the pretreatment alone (Fig. 1). Thus, the four experiential conditions for all subjects were placebo-placebo, pretreatment-placebo, placebo-MDMA, and pretreatment-MDMA in balanced order. Of the 48 subjects, 16 (eight male, eight female) received the serotonin-norepinephrine transport inhibitor duloxetine as pretreatment, 16 (eight male, eight female) received the norepinephrine transport inhibitor reboxetine as pretreatment, and 16 (eight male, eight female) received the α_2 adrenergic receptor agonist clonidine as pretreatment. The random allocation sequence was developed by a clinical pharmacist and concealed from all individuals involved in study management. The washout periods between sessions were ≥10 days. The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines on Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland. The use of MDMA in healthy subjects was authorized by the Swiss Federal Office of Public Health, Bern, Switzerland. The studies were registered at ClinicalTrials.gov (NCT00886886, NCT00990067, and NCT01136278). Target sample size of the pooled study was based on the effects of oxytocin in the RMET in previous studies (Domes et al. 2007b; Guastella et al. 2010). The sample size of the individual studies was based on power analyses indicating that 13 subjects would be needed to detect a reduction of 20% in the subjective effects of MDMA (the primary outcome) by the pretreatments with more than 80% power using a within-subjects study design. Test sessions took place in a quiet hospital research ward with no more than two research subjects present per session.

Volunteers

Forty-eight healthy subjects (24 men, 24 women) aged 18 to 44 years (mean ± SD, 26 ± 5 years) and with a body weight of 68 ± 11 kg were recruited on the university campus. The exclusion criteria included the following: (1) age <18 or >45 years, pregnancy determined by a urine test before each test session; (2) body mass index <18.5 or >25 kg/m^2; (3) personal or family (first-degree relative) history of psychiatric disorder (determined by the structured clinical interview for axis I and axis II disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (Wittchen et al. 1997) supplemented by the SCL-90-R Symptom Checklist (Derogatis et al. 1976; Schmitz et al. 2000), Freiburg Personality Inventory (Fahrenberg et al. 1984), and Trait Scale of the State-Trait Anxiety Inventory (Spielberger et al. 1970); (4) the regular use of medications; (5) chronic or acute physical illness assessed by physical examination, electrocardiogram, standard hematology, and chemical blood analyses; (6) smoking more than 10 cigarettes per day; (7) a lifetime history of using illicit drugs more than five times, with the exception of cannabis; (8) illicit drug use within the last 2 months; and (9) illicit drug use during the study determined by urine tests conducted before the test sessions using TRIAGE 8 (Biosite, San Diego, CA, USA). The subjects were asked to abstain from

Fig. 1 Study diagram



excessive alcohol consumption between test sessions and limit alcohol use to one glass on the day before each test session. All of the subjects were nonsmokers. Thirty-six subjects had previously used cannabis. Fourteen subjects reported using illicit drugs (one to four times). Four subjects had tried ecstasy, two had tried lysergic acid diethylamide, seven had tried psilocybin, four had tried cocaine, and one had tried amphetamine. Importantly, 44 subjects were MDMA-naive. Female subjects were investigated during the follicular phase (days 2–14) of their menstrual cycle to account for the potential confounding effects of sex hormones and cyclic changes in the reactivity to amphetamines (White et al. 2002). All of the subjects provided their written informed consent before participating in the study, and they were paid for their participation.

Measures

Reading the Mind in the Eyes Test (RMET)

The RMET (Baron-Cohen et al. 2001) was used to assess the identification of complex emotions 90 min after the administration of 125 mg MDMA or identical placebo. The RMET was originally developed to assess the social cognitive abilities of high functioning individuals with autism spectrum disorder (Baron-Cohen et al. 2001). In the RMET, 36 pictures of the eye region of faces are presented on a computer screen, and participants are asked to decide which of four words best describes what the person in the picture is thinking or feeling (Baron-Cohen et al. 2001). RMET scores are calculated as the total number of correct discriminations of all 36 items. Additionally, subscores in the present study were computed for positive (eight items), negative (12 items), and neutral (16 items) emotional valence as previously described (Harkness et al. 2005) and used by others (Fertuck et al. 2009).

Choice reaction time task (CRTT)

We used an adaptive five CRTT to assess potential drug effects on sustained attention and executive motor function (Schachinger et al. 2003). In this test, the subjects had to respond to the presentation of five different colored lights by pressing the button with the corresponding color as quickly and accurately as possible (Schachinger et al. 2003). A training run was performed before the first baseline assessment and data were analyzed as drug-induced changes from baseline to correct for training effects (Haschke et al. 2010). The CRTT was performed before and 120 min after administration of MDMA or placebo in 32 subjects. The task is sensitive to benzodiazepine administration (Haschke et al. 2010).

Endocrine measures

Blood samples for the determination of plasma oxytocin and cortisol levels were collected in 32 and 48 subjects before and 120 min after drug administration, respectively. Plasma oxytocin concentrations were determined using a radioimmunoassay

in the Neurobiology Department (Inga D. Neumann), University of Regensburg, Germany, as previously described (Landgraf et al. 1995). Plasma cortisol concentrations were determined using an automated solid-phase chemiluminescence immunoassay (Immulite 2000 Cortisol, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).

Subjective effects

Subjective effects were assessed using the Addiction Research Center Inventory (ARCI) (Martin et al. 1971) and visual analog scales (VASs) (Hysek et al. 2011). The ARCI is a true–false questionnaire with five empirically derived scales (Martin et al. 1971). The Amphetamine scale is sensitive to the effects of d-amphetamine, the Benzedrine Group scale is a stimulant scale consisting mainly of items relating to intellectual efficiency and energy, the Morphine-Benzedrine Group scale is a measure of euphoria, the Pentobarbital-Chlorpromazine-Alcohol Group scale is a measure of sedation, and the Lysergic Acid Diethylamine Group scale is a measure of dysphoria and somatic symptoms. The ARCI has previously been shown to be sensitive to the effects of MDMA (Farre et al. 2007; Tancer and Johanson 2007). The ARCI was used in its validated German version (Bopp et al. 2005) before and 2.5 and 5 h after drug administration. Visual analog scores were used to assess "any drug effects" and prosocial effects, including "closeness to others," "open," and "talkative." VASs were presented as 100 mm horizontal lines marked from "not at all" on the left to "extremely" on the right. VASs assessing prosocial feelings were bidirectional (±50 mm). VAS scores were assessed before and 0, 0.33, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 h after drug administration. The study included additional pharmacodynamic and pharmacokinetic outcomes as reported elsewhere (Hysek et al. 2011, 2012; Simmler et al. 2011a, b). All outcome measures were assessed identically and at the same time points following MDMA or placebo administration across all three studies.

Drugs

(±) MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was obtained from the Swiss Federal Office of Public Health and prepared as gelatin capsules (100 and 25 mg). Identical placebo (lactose) capsules were prepared. MDMA was administered in a single absolute oral dose of 125 mg. This dose of MDMA corresponds to a typical recreational dose or the dose of MDMA used as an adjunct to psychotherapy (Mithoefer et al. 2010). In the reboxetine-MDMA study, reboxetine (8 mg, Edronax; Pfizer, Zurich, Switzerland) or identical placebo (lactose) was administered at 20:00 hours the day before the test session and again at 7:00 hours on the test day. MDMA or placebo was administered at 8:00 hours, 1 and 12 h after reboxetine. In the duloxetine-MDMA study, duloxetine (120 mg, Cymbalta, Eli Lilly, Vernier, Switzerland) or identical placebo (lactose) was administered at 20:00 hours the day before the test session and again at 8:00 hours on the test day. MDMA or placebo was administered at 12:00 hours, 4 and 16 h after duloxetine. Reboxetine and duloxetine were administered twice in high doses to obtain plasma concentrations similar to those reached with chronic daily administrations of the drugs and as previously used to manipulate the norepinephrine function in healthy subjects (Roelands et al. 2008). In the clonidine-MDMA study, clonidine (150 μg, Catapresan; Boeringer Ingelheim, Basel, Switzerland) or identical placebo (lactose) was administered at 8:00 hours, 1 h before MDMA or placebo (9:00 hours). Clonidine has previously been shown to produce sympatholytic effects in this dose in healthy subjects (Anavekar et al. 1982; Nieuwenhuis et al. 2007). The pretreatment times used for the three drugs resulted in maximal plasma concentrations of the pretreatments at the time of the maximal effect of MDMA (Hysek et al. 2011, 2012). On the test days, oral drug administration was supervised by study personnel. Compliance with the first administration of reboxetine and duloxetine in the evening prior to the test day was confirmed analytically in plasma (Hysek et al. 2011; Simmler et al. 2011a).

Statistical analyses

For the statistical analyses, data from the three studies were pooled, and endocrine measures and reaction times were transformed to differences from baseline. Peak effects (E_{max}) were determined for repeated measures. E_{max} values and RMET scores were compared using one-way General Linear Model repeated-measures analysis of variance (ANOVA) with drug (MDMA vs. placebo) as a factor using STATISTICA 6.0 (StatSoft, Tulsa, OK, USA). Data from the three substudies on all four treatment conditions were assessed using ANOVAs, with drug (placebo-placebo, placebo-MDMA, pretreatment-placebo, and pretreatment-MDMA) as a factor, followed by the Tukey post hoc test. Sequence effects were tested by including treatment order as a factor. Potential associations between MDMA-induced endocrine changes and subjective effects or RMET accuracy were assessed using Spearman's rank correlations. The criterion for significance was $p<0.05$.

Results

RMET

As shown in Fig. 2, MDMA improved mind reading performance in the RMET for stimuli with a positive emotional

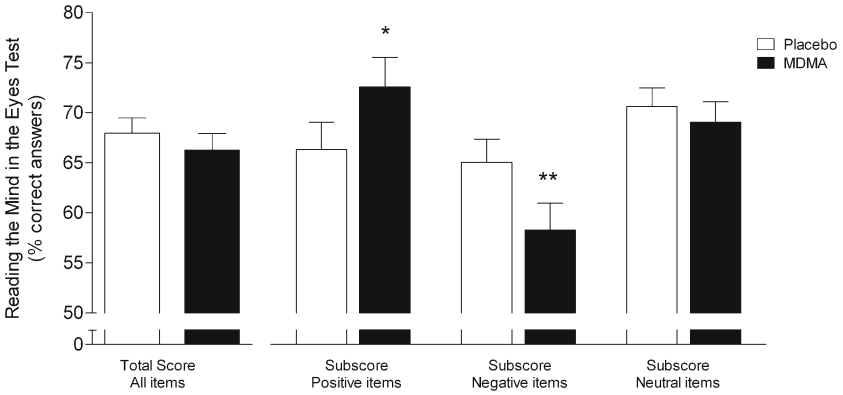


Fig. 2 MDMA had differential effects on performance in the Reading the Mind in the Eyes Test (RMET) depending on the emotional valence of the stimuli. MDMA increased the ability in affective mind reading for expressions with a positive emotional valence (positive items, *$p<0.05$) and impaired mind reading for negative items (**$p<0.01$) compared to placebo. MDMA did not alter performance for neutral items or the total score (all items). Values are mean ± SEM accuracy (percentage of correct items) in 48 subjects

valence ($F_{1, 47}=5.13$, $p<0.05$) and impaired performance for stimuli with a negative emotional valence ($F_{1, 47}=7.05$, $p<0.01$). Improvements in reading positive emotions were seen in 40 of the 48 participants, and impairments in reading negative emotions were seen in 38 of the 48 participants. MDMA had no effect on the accuracy of mind reading for emotionally neutral stimuli or the total performance score. There were no sex differences. No statistically significant main effects of sequence and no sequence×drug interaction were found, excluding sequence effects of treatment on test performance. Drug effects on the RMET in each of the three studies are shown in Tables 2, 3, and 4. MDMA consistently exerted similar effects on mind reading in each of the three studies as in the pooled analysis, but the effects did not reach statistical significance. Duloxetine nonsignificantly attenuated the effects of MDMA on RMET performance. Similar weak and nonsignificant reductions of the MDMA effect were also observed for reboxetine and clonidine.

CRTT

MDMA did not alter reaction time in the CRTT (Table 1) or the RMET ($F_{1, 47}=1.8$, p=NS). In the individual studies, none of the drugs altered reaction time in the CRTT (Tables 2, 3 and 4).

Endocrine effects

MDMA increased plasma levels of oxytocin ($F_{1, 31}=8.00$, $p<0.01$) and cortisol ($F_{1, 47}=110$, $p<0.001$) compared with placebo (Table 1). In the duloxetine-MDMA study sample, duloxetine reduced the MDMA-induced increase in plasma levels of oxytocin and cortisol (Table 3). Neither reboxetine nor clonidine significantly affected the endocrine effects of MDMA (Tables 2 and 4).

Subjective effects

MDMA increased scores on the Amphetamine Group, Benzedrine Group, Morphine-Benzedrine Group, Pentobarbital-Chlorpromazine-Alcohol Group, and LSD Group scales of the ARCI compared with placebo ($F_{1, 47}=36.4$, 5.1, 44.7, 36.4, and 15.2, respectively; all $p<0.001$, with the exception of the Benzedrine Group [$p<0.05$]; Table 1). MDMA also increased VAS scores for "any drug effect," "closeness," "open," and "talkative" ($F_{1, 47}=1183$, 98.0, 105, and 105, respectively; all $p<0.001$; Table 1). The endocrine effects of MDMA were not associated with the subjective effects of MDMA or performance on the RMET (all $r_s<0.28$, all $p>0.1$). Duloxetine reduced MDMA-induced increases in all VAS scores (Table 3). Duloxetine also reduced the effect of MDMA on the Amphetamine and Morphine-Benzedrine Group scales, which were the only scales that showed significant effects of MDMA in the ARCI in the duloxetine-MDMA study (Table 3). In the reboxetine-MDMA study, reboxetine lowered MDMA-induced increases in the VAS scores for "any drug effects" and "closeness" (Table 2). The effects of MDMA on all subscales of the ARCI were nonsignificantly lower after reboxetine administration. In contrast, clonidine had no effect on the subjective response to MDMA in the clonidine-MDMA study (Table 4). No severe adverse effects were reported.

Discussion

The main finding of the present study was that MDMA improved performance on the RMET for positive stimuli and impaired performance for negative stimuli, indicating that MDMA differentially affected the ability to correctly decode social facial stimuli depending on the emotional valence of the

Table 1 Mean ± SEM values for endocrine, psychomotor, and subjective effects of MDMA (n=48)

	Placebo	MDMA
Hormones		
Oxytocin (Δ pg/mL)	5.0±3.9	28.1±4.0**
Cortisol (Δ nmol/L)	−262.0±27.1	174.5±29.8***
Choice reaction time test (CRTT)		
Reaction time (Δ ms)	4.6±3.7	−1.7±6.1
Addiction Research Inventory (ARCI)		
Amphetamine	−0.1±0.1	2.4±0.4***
Benzedrine Group	0.6±0.18	1.3±0.3*
Morphine-Benzedrine Group	0.2±0.2	5.5±0.8***
Pentobarbital-Chlorpromazine-Alcohol Group	0.2±0.2	3.0±0.5***
LSD Group	0.5±0.2	2.1±0.4***
Visual analog scales		
Any drug effect	2.2±1.3	87.2±2.4***
Closeness	0.2±0.2	28.2±2.8***
Open	0.8±0.4	30.9±2.4***
Talkative	0.6±0.3	26.7±2.6***

*p<0.05, **p<0.01, ***p<0.001 compared to placebo

stimulus. In a party setting, the use of MDMA may therefore improve the correct reading of positive facial expressions and, combined with elevated mood and extroversion, may lead to higher approach behavior and sociability. In contrast, the misreading of negative social information as being more neutral or positive may result in higher social risk behavior. When

Table 2 Mean ± SEM values and statistics for the reboxetine-MDMA study (n=16)

	Placebo-Placebo	Reboxetine-Placebo	Placebo-MDMA	Reboxetine-MDMA	$F_{3,\ 45}$ =	p <
Hormones						
Oxytocin (Δ pg/mL)	NA	NA	NA	NA		
Cortisol (Δ nmol/L)	−203±46	−230±60$^{\#\#\#}$	245±47***	144±60***	21.86	0.001
Reading the Mind in the Eyes Test						
Total score	0.679±0.03	0.679±0.03	0.649±0.03	0.684±0.03	0.99	NS
Positive items	0.719±0.04	0.688±0.04	0.734±0.06	0.727±0.04	0.46	NS
Negative items	0.630±0.06	0.599±0.05	0.552±0.05	0.615±0.04	1.44	NS
Neutral items	0.695±0.04	0.734±0.04	0.680±0.04	0.715±0.04	1.19	NS
Choice reaction time task						
Mean reaction time (ms)	4.5±5.7	16.1±8.5	0.42±13.3	21.9±10.1	1.23	NS
Addiction Research Center Inventory						
Amphetamine	0.2±0.1	0.4±0.3$^{\#\#}$	4.1±0.9***	3.3±0.6**	12.04	0.001
Benzedrine Group	1.1±0.4	0.7±0.3$^{\#}$	2.5±0.4	1.7±0.5	5.74	0.05
Morphine-Benzedrine Group	0.4±0.2	0.7±0.5$^{\#\#\#}$	8.4±1.3***	5.4±1.1**	19.33	0.001
Pentobarbital-Chlorpromazine-Alcohol Group	0.6±0.2	1.4±0.6$^{\#\#}$	4.4±0.9***	3.1±0.7**	9.18	0.001
LSD Group	0.7±0.2	0.9±0.3$^{\#\#\#}$	4.3±0.8***	2.8±0.6*	10.4	0.001
Visual analog scales						
Any drug effect	1.9±1.3	8.0±3.4	85±4.8***	68±6.2***$^{,\#\#}$	120.40	0.001
Closeness	0.3±0.2	0.0±0.0$^{\#\#\#}$	34±5.9***	21±4.5***$^{,\#}$	22.66	0.001
Open	1.0±0.8	4.2±2.2$^{\#\#\#}$	30±3.1***	23±4.9	22.73	0.001
Talkative	0.5±0.4	2.2±1.3$^{\#\#\#}$	26±4.3***	20±5.1	18.56	0.001

NA not assessed, *NS* not significant

*p<0.05, **p<0.01, ***p<0.001, compared with Placebo-Placebo; $^{\#}$$p$<0.05, $^{\#\#}$$p$<0.01, $^{\#\#\#}$$p$<0.001, compared with Placebo-MDMA

Table 3 Mean ± SEM values and statistics for the duloxetine-MDMA study (n=16)

	Placebo-Placebo	Duloxetine-Placebo	Placebo-MDMA	Duloxetine-MDMA	$F_{3, 45}$ =	p <
Hormones						
Oxytocin (Δ pg/mL)	1.4±7.1	1.6±4.7	22.2±9.1*	1.8±5.9$^{\#}$	4.56	0.01
Cortisol (Δ nmol/L)	−354±46	−241±30$^{\#\#\#}$	157±62***	−181±29*,$^{\#\#\#}$	25.65	0.001
Reading the Mind in the Eyes Test						
Total score	0.665±0.02	0.661±0.02	0.656±0.02	0.689±0.02	1.28	NS
Positive items	0.656±0.05	0.680±0.04	0.750±0.05	0.711±0.04	1.71	NS
Negative items	0.630±0.02	0.661±0.03	0.578±0.04	0.667±0.03	2.26	NS
Neutral items	0.695±0.02	0.641±0.04	0.668±0.05	0.695±0.04	0.70	NS
Choice reaction time task						
Mean reaction time (ms)	4.7±7.1	3.4±32	−3.8±30	4.5±30	0.28	NS
Addiction Research Center Inventory						
Amphetamine	−0.1±0.2	−0.3±0.2	4.6±0.5***	0.9±0.5$^{\#\#\#}$	35.13	0.001
Benzedrine Group	0.6±0.2	−0.1±0.3	1.4±0.4	−0.2±0.5$^{\#}$	4.07	0.05
Morphine-Benzedrine Group	0.5±0.5	0.6±0.2	8.4±0.9***	2.3±0.8$^{\#\#\#}$	41.74	0.001
Pentobarbital-Chlorpromazine-Alcohol Group	0.1±0.4	1.9±0.5	3.1±0.8	2.3±0.9	3.92	0.05
LSD Group	0.8±0.2	0.1±0.3	0.6±0.5	0.9±0.5	0.84	NS
Visual analog scales						
Any drug effect	3.8±3.6	6.0±2.5	86.7±3.6***	33±8***,$^{\#\#\#}$	74.47	0.001
Closeness	0.0±0.0	0.0±0.0	27.3±3.9***	4.6±2.5$^{\#\#\#}$	37.32	0.001
Open	1.4±0.9	0.4±0.4	32.2±4.3***	6.0±3.3$^{\#\#\#}$	36.88	0.001
Talkative	1.2±0.8	0.3±0.3	28.8±5.1***	10.7±3.7$^{\#\#\#}$	21.13	0.001

NA not assessed, *NS* not significant

*p<0.05, **p<0.01, ***p<0.001, compared with Placebo-Placebo; $^{\#}$$p$<0.05, $^{\#\#}$$p$<0.01, $^{\#\#\#}$$p$<0.001, compared with Placebo-MDMA

MDMA is administered during psychotherapy to treat post-traumatic stress disorder (Mithoefer et al. 2010), the MDMA-induced shift in accuracy toward a better perception of positive emotional stimuli may facilitate the therapeutic alliance (Johansen and Krebs 2009).

MDMA did not affect total RMET score or the decoding of stimuli with neutral emotional valence. Thus, MDMA did not improve mind reading overall. Our finding in mostly non-ecstasy-experienced volunteers is consistent with a previous work, in which MDMA did not alter performance on the RMET in 21 ecstasy users (Bedi et al. 2010). The latter study did not evaluate whether emotional valence modulates the effect of MDMA on the RMET. However, in another test in the same study, MDMA differentially reduced the accurate identification of negative, threat-related facial signals but did not affect the identification of neutral or positive emotions (Bedi et al. 2010). The emotion-specific effect of MDMA on the decoding of facial expressions suggests that MDMA may differentially affect brain areas involved in the processing of emotional information. Indeed, functional magnetic resonance imaging showed that MDMA attenuated the response to angry faces in the amygdala, a structure activated by negative social signals and fear (Zald 2003), and enhanced the response to happy faces in the ventral striatum (Bedi et al. 2009), a structure activated by reward expectation (Knutson and Cooper 2005). Altogether, the data indicate that MDMA lowers reactivity to negative social stimuli, such as threat, and enhances responding to positive social stimuli, such as a smile.

We found that MDMA increased plasma levels of oxytocin, confirming a placebo-controlled MDMA study (Dumont et al. 2009) and observations in clubbers following the use of ecstasy pills (Wolff et al. 2006). Oxytocin is a candidate for the mediation of the empathic and social effects of MDMA (Thompson et al. 2007). For example, MDMA increased social interaction in rats that interacted for the first time, predominantly reflected by an increase in adjacent lying behavior. This effect of MDMA was reduced by pretreatment with an oxytocin antagonist (Thompson et al. 2007). Similar to MDMA, oxytocin also reduced activation of the amygdala in response to threatening social stimuli (Kirsch et al. 2005), although other work showed that oxytocin reduced amygdala responses regardless of the emotional valence of the facial stimuli (Domes et al. 2007a) in men and enhanced amygdala responses to fearful stimuli in women (Domes et al. 2010), suggesting both sex differences and more complex effects of oxytocin on emotion processing. Particularly relevant for the present study, intranasal oxytocin administration improved performance on the RMET in healthy male subjects (Domes

Table 4 Mean ± SEM values and statistics for the clonidine-MDMA study (n=16)

	Placebo-Placebo	Clonidine-Placebo	Placebo-MDMA	Clonidine-MDMA	$F_{3, 45}$ =	p <
Hormones						
Oxytocin (Δ pg/mL)	9.2±6.3	12.1±12.4	33.9±3.4*	20.2±5.5	3.32	0.05
Cortisol (Δ nmol/L)	−229±42	−241±43	122±42	190±36***	37.02	0.001
Reading the Mind in the Eyes Test						
Total score	0.69±0.03	0.698±0.02	0.684±0.03	0.698±0.03	0.16	NS
Positive items	0.62±0.05	0.641±0.04	0.695±0.05	0.656±0.05	0.88	NS
Negative items	0.69±0.04	0.641±0.04	0.620±0.05	0.661±0.04	1.12	NS
Neutral items	0.73±0.04	0.770±0.02	0.727±0.04	0.746±0.03	0.54	NS
Choice reaction time task						
Mean reaction time (ms)	NA	NA	NA	NA		
Addiction Research Center Inventory						
Amphetamine	−0.4±0.2	−0.5±0.3$^{###}$	3.3±0.4***	3.3±0.5***	37.11	0.001
Benzedrine Group	0.1±0.2	−1.5±0.5$^{##}$	0.7±0.6	0.5±0.4	5.36	0.01
Morphine-Benzedrine Group	−0.4±0.4	−0.9±0.5$^{###}$	7.7±1.0***	7.4±1.0***	46.12	0.001
Pentobarbital-Chlorpromazine-Alcohol Group	0.1±0.4	2.7±0.7	4.6±0.7***	4.0±0.8***	11.08	0.001
LSD Group	0.1±0.2	0.6±0.2	1.4±0.7	1.7±0.4*	3.84	0.05
Visual analog scales						
Any drug effect	0.9±0.9	16.8±6.2$^{###}$	89.6±4.0***	81.6±6.9***	87.55	0.001
Closeness	0.4±0.4	0.0±0.0$^{###}$	23.4±4.6***	24.1±4.7***	20.35	0.001
Open	0.0±0.0	0.0±0.0$^{###}$	30.3±4.4***	30.2±5.0***	33.71	0.001
Talkative	0.0±0.0	0.0±0.0$^{###}$	24.8±4.4***	24.7±4.5***	24.26	0.001

NA not assessed, *NS* not significant

*p<0.05, **p<0.01, ***p<0.001, compared with Placebo-Placebo; $^{#}p$<0.05, $^{##}p$<0.01, $^{###}p$<0.001, compared with Placebo-MDMA

et al. 2007b) or male subjects with autism spectrum disorders (Guastella et al. 2010). The effect of MDMA on the decoding of positive emotional information in the present study might therefore be explained by the oxytocinergic properties of MDMA. Notably, oxytocin selectively improved the recognition of specific emotions in previous studies, similar to MDMA in the present study. Specifically, oxytocin selectively enhanced the recognition of happy facial expressions (Marsh et al. 2010; Schulze et al. 2011), reduced misclassifications of positive or ambiguous emotions as negative emotions (Di Simplicio et al. 2009), increased the memory for positive faces (Guastella et al. 2008), and slowed reaction times during the recognition of negative fearful facial expressions (Di Simplicio et al. 2009). Altogether, these data support the hypothesis that the effects of MDMA on mind reading are very similar to those of oxytocin and are potentially mediated by this neuropeptide. MDMA-induced increases in the plasma concentration of oxytocin were not correlated with RMET performance in our study. However, plasma samples were not available for all subjects of the study and it is also unclear whether plasma concentrations of oxytocin reflect brain concentrations of this neuropeptide.

The administration of oxytocin in humans does not produce subjective mood effects. However, a drug discrimination study showed that rats trained to respond for MDMA also responded if MDMA was substituted by the oxytocin receptor agonist carbetocin, and responding for MDMA was reduced by administration of the oxytocin receptor antagonist atosiban (Broadbear et al. 2011). Oxytocin may therefore contribute to the interoceptive subjective effects of MDMA. Whether the subjective state of positive feelings and closeness to others elicited by MDMA in humans is also associated with increased emotional empathy (i.e., the sharing of experiences of emotional states perceived in others) remains to be tested. The finding that MDMA did not improve overall performance on the RMET in the present study and a previous study (Bedi et al. 2010) and the lack of improved face or vocal affect recognition (Bedi et al. 2010) suggest that MDMA does not improve cognitive empathy overall (i.e., the recognition of emotional states in others). Oxytocin has recently been shown to increase emotional but not cognitive empathy in healthy male volunteers (Hurlemann et al. 2010). We did not assess the effects of MDMA on emotional empathy. Studies on the effects of MDMA on different measures of emotional and cognitive empathy are needed.

In the present study, MDMA also increased plasma levels of cortisol, consistent with previous studies (Harris et al.

2002; Mas et al. 1999). We did not observe any association between cortisol levels and RMET performance, and high stress- compared with low stress-induced cortisol elevations in healthy subjects did not alter RMET scores in another study (Smeets et al. 2009).

In the ARCI, MDMA produced moderate amphetamine-type effects with only slight stimulation, pronounced euphoria, as well as moderate alcohol-like and moderate hallucinogen-like effects similar to earlier works (Farre et al. 2007; Tancer and Johanson 2007). In the VAS, MDMA produced its MDMA-typical "entactogenic" effects including closeness to others, openness, and talkativeness as described earlier (Hysek et al. 2011; Liechti et al. 2001). We also assessed the effects of different pretreatments on the response to MDMA. Duloxetine, which inhibits MDMA-induced monoamine transporter-dependent serotonin and norepinephrine release (Simmler et al. 2011a, b), reduced all the amphetamine-type and euphorigenic psychotropic effects of MDMA in the ARCI, the entactogen-like aspects of the MDMA response in all the VAS, and also endocrine effects of MDMA. Duloxetine also tended to attenuate the effects of MDMA on RMET, although these trends were not statistically significant. Reboxetine, which inhibits MDMA-induced norepinephrine release (Hysek et al. 2011), reduced some of the psychotropic effects in the VAS but not the endocrine effects of MDMA. Clonidine, which inhibits any MDMA-induced transporter-independent vesicular release of norepinephrine (Hysek et al. 2012), had no effect on either the subjective or endocrine response to MDMA. The finding that inhibition of the MDMA-induced serotonin and norepinephrine release by duloxetine was more effective in reducing the acute MDMA effects in humans than inhibition of the release of norepinephrine alone by reboxetine or clonidine suggests that serotonin may be primarily responsible for the acute effects of MDMA in humans. This view is also consistent with earlier mechanistic studies in humans (Farre et al. 2007; Liechti et al. 2000; Liechti and Vollenweider 2000; Tancer and Johanson 2007). The data also indicate a primary role for serotonin in the effects of MDMA on oxytocin release, emotion identification, and MDMA's potential prosocial effects.

In conclusion, the MDMA-induced shift in the ability to detect socioemotional information, together with the prosocial feelings elicited by MDMA, is likely to enhance social approach behavior and sociability when MDMA is used recreationally. The change in the processing of emotional information may also facilitate therapeutic relationships in MDMA-assisted psychotherapy.

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