

MDMA enhances emotional empathy and prosocial behavior

Running title: MDMA enhances empathy and prosociality

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA, “ecstasy”) releases serotonin and norepinephrine. MDMA is reported to produce empathogenic and prosocial feelings. It is unknown whether MDMA in fact alters empathic concern and prosocial behavior. We investigated the acute effects of MDMA using the Multifaceted Empathy Test (MET), dynamic Face Emotion Recognition Task (FERT), and Social Value Orientation (SVO) test. We also assessed effects of MDMA on plasma levels of hormones involved in social behavior using a placebo-controlled, double-blind, random-order, cross-over design in 32 healthy volunteers (16 women). MDMA enhanced explicit and implicit emotional empathy in the MET and increased prosocial behavior in the SVO test in men. MDMA did not alter cognitive empathy in the MET but impaired the identification of negative emotions, including fearful, angry, and sad faces, in the FERT, particularly in women. MDMA increased plasma levels of cortisol and prolactin, which are markers of serotonergic and noradrenergic activity, and of oxytocin, which has been associated with prosocial behavior. In summary, MDMA sex-specifically altered the recognition of emotions, emotional empathy, and prosociality. These effects likely enhance sociability when MDMA is used recreationally and may be useful when MDMA is administered in conjunction with psychotherapy in patients with social dysfunction or posttraumatic stress disorder.

Keywords: MDMA, ecstasy, empathy, emotion recognition, social cognition, social behavior

Introduction

3,4-Methylenedioxymethamphetamine (MDMA, “ecstasy”) and similar phenethylamines release brain serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine and are classified as “entactogens” or “empathogens”. MDMA produces subjective prosocial feelings (Dumont *et al.*, 2009) and the enhancement of empathy and sociability is also considered a major reason for the recreational use of MDMA and its therapeutic effects in psychotherapy (Bedi *et al.*, 2010; Hysek *et al.*, 2012b; Mithoefer *et al.*, 2013). However, it is unknown whether MDMA indeed increases empathic concern for others or prosocial behavior when measured objectively.

The empathy construct includes cognitive and emotional aspects (Blair, 2005; Dziobek *et al.*, 2008). Cognitive empathy is defined as the ability to recognize emotional states in others, and emotional empathy refers to the emotional response to another person’s emotional state (Blair, 2005). Two previous studies assessed the effects of MDMA on emotion recognition which relates to the cognitive aspects of empathy using a static Face Emotion Recognition Task (FERT) (Bedi *et al.*, 2010) and the Reading the Mind in the Eyes Test (RMET) (Bedi *et al.*, 2010; Hysek *et al.*, 2012b). MDMA did not improve emotion recognition overall in any of these tests (Bedi *et al.*, 2010; Hysek *et al.*, 2012b). However, MDMA impaired the recognition of fearful faces (Bedi *et al.*, 2010) and mind-reading of negative emotions and enhanced the identification of positive emotions in the RMET (Hysek *et al.*, 2012b). Thus, MDMA may differentially alter emotion recognition, depending on the emotional valence of the stimuli. Whether MDMA modulates the emotional aspects of empathy such as empathic concern and whether it changes social behavior has not yet been tested.

The present study investigated the effects of MDMA using the Multifaceted Empathy Test (MET) (Dziobek *et al.*, 2008), a test specifically designed to assess different aspects of empathy. As an additional assessment of the cognitive component of empathy, and to confirm previously documented effects of MDMA on emotion recognition, we used a novel FERT, which uses more naturalistic dynamic presentations of facial affect (Domes *et al.*, 2008). Furthermore, we assessed the effects of MDMA on prosocial behavior using the Social Value Orientation (SVO) test (Murphy *et al.*, 2011). Because several neuropeptides and steroid hormones are involved in the regulation of social cognition and behaviors (Kosfeld *et al.*, 2005; Thompson *et al.*, 2006; Domes *et al.*, 2007; Guastella *et al.*, 2010), we determined the plasma concentrations of oxytocin (Dumont *et al.*, 2009; Hysek *et al.*, 2012b), C-terminal provasopressin (copeptin) (Simmler *et al.*, 2011), cortisol, prolactin (Harris *et al.*, 2002), and testosterone in all of the subjects before and after MDMA or placebo administration.

We hypothesized that MDMA enhances both emotional empathy and prosocial behavior consistent with the self-rated social effects of the drug. The study included equal numbers of both sexes to test the modulatory effects of the MDMA response by sex, which has been observed for oxytocin (Hurlemann *et al.*, 2010).

Materials and Methods

Participants

Thirty-two healthy subjects (16men, 16women) with a mean age of 25 ± 3 years (mean \pm SD; range 20-31 years) were recruited from the University of Basel campus. Subjects with a personal or first-degree relative history of psychiatric disorders or chronic or acute physical illness were excluded as previously described (Hysek *et al.*, 2012c). Additional exclusion criteria were smoking, a lifetime history of using illicit drugs more than five times, with the exception of past cannabis use, and any illicit drug use including cannabis within the last 2 months or during the study period, determined by repeated urine tests conducted during screening and before each test session using TRIAGE 8 (Biosite, San Diego, California). Nineteen subjects had used cannabis more than 5 times in the past. Fifteen participants reported using other illicit drugs one to four times. Most of the subjects ($n=22$) were completely MDMA-naïve while 10 subjects had less than five previous experiences with

MDMA. The use of a within-subjects study design avoided confounding of the acute MDMA effect by drug-history in this study. Female subjects were investigated during the follicular phase (day 2-14) of their menstrual cycle to account for cyclic changes in the reactivity to amphetamines.

Experimental protocol

We used a double-blind, placebo-controlled cross-over design where all 32 subjects were treated with both MDMA (125 mg) and placebo (64 assessments). The use of a within-subject design eliminated inter-individual differences and increased the power of the study considerably above that of a parallel design ($n > 64$). The washout period was at least 10 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonization Guidelines in Good Clinical Practice (GCP) and approved by the local Ethics Committee. The study was registered at ClinicalTrials.gov (NCT01386177 and NCT01465685). All of the subjects provided written informed consent before participating in the study and were paid for their participation.

Study drug

MDMA (Lipomed AG, Arlesheim, Switzerland) was prepared as gelatin capsules with mannitol as filler. Identical placebo capsules contained only mannitol. MDMA was administered orally at a dose of 125 mg, corresponding to a mean dose of 1.89 ± 0.30 mg/kg body weight (mean \pm SD).

Measures

Subjective effects. Visual analog scales (VASs) (Hysek *et al.*, 2012b) were repeatedly used to assess subjective effects related to prosociality, including feeling “happy,” “open,” and “close to others.” Additionally, the 60-item Adjective Mood Rating Scale (AMRS) was used to assess subjective mood effects (Janke and Debus, 1978; Hysek *et al.*, 2011).

Multifaceted Empathy Test. The MET was used to assess the cognitive and emotional aspects of empathy (Dziobek *et al.*, 2008; Hurlermann *et al.*, 2010). The test consisted of 40 photographs that showed people in emotionally charged situations (Hurlermann *et al.*, 2010). To assess cognitive empathy, the participants were required to infer the mental state of the subject in each scene and indicate the correct one from a list of four responses. Cognitive empathy was defined as the percentage of correct responses in the total responses. To measure emotional empathy, the subjects were asked to rate how much they were feeling for the individual in each scene (i.e., explicit emotional empathy) and how much they were aroused by each scene (i.e., implicit emotional empathy) on a 1-9 point scale. The latter rating provides an inherent assessment of emotional empathy, which is considered to reduce the likelihood of socially desirable answers (Dziobek *et al.*, 2008). The three aspects of empathy were each tested with 20 stimuli with positive valence and 20 stimuli with negative valence, resulting in a total of 120 trials. The MET was performed 3 h after drug administration and after the initial intense subjective peak drug effects had reached a stable level.

Interpersonal reactivity. A validated German version (Paulus, 2009) of the interpersonal reactivity index (IRI) (Davis, 1983) was used once to assess trait empathy.

Social Value Orientation test. The paper-based SVO measure was used to assess social behavior (Murphy *et al.*, 2011). In such a resource allocation task, prosociality is defined as a behavior that maximizes the sum of resources for the self and others and minimizes the difference between the two (Haruno and Frith, 2010; Murphy *et al.*, 2011). The test consists of six primary and nine secondary SVO slider items with a resource allocation choice over a defined continuum of joint payoffs (Murphy *et al.*, 2011). The participants were instructed to choose their allocation that defines their most preferred joint distribution between themselves and another person. Allocated funds had real value, and two randomly selected subjects received the funds they earned.

For the primary items, mean allocations for self and the other were calculated. The inverse tangent of the ratio of these two means then produced an angle that indicated the participants' SVO index. A greater SVO angle indicates that the participant more often chose the option that maximized the allocation for the other person, consistent with prosocial or altruistic behavior. The nine secondary items were used to differentiate between two prosocial motivations, inequality aversion and joint gain maximization. The inequality-aversion index was calculated as previously described (Murphy *et al.*, 2011). An index of 0 indicates perfect inequality aversion, and 1 indicates maximal preference for joint gain maximization. The test was administered after the MET at 4 h after drug administration.

Facial affect recognition. Facial affect recognition was tested using a dynamic FERT (Domes *et al.*, 2008) (see Supplementary data). As dependent variables, the emotional intensity at which the trial was stopped for correct answers was recorded. The emotion recognition accuracy was then assessed, defined as the percentage of correctly identified emotions (Domes *et al.*, 2008). The FERT was performed 2 h after MDMA or placebo administration during the peak effect of MDMA.

Endocrine measures and pharmacokinetics of MDMA. Plasma levels of oxytocin and copeptin were determined before and 1 and 2 h and levels of cortisol, prolactin, and testosterone before and 2 h after drug administration using different immunoassays (Morgenthaler *et al.*, 2006; Simmler *et al.*, 2011; Neumann *et al.*, 2013) and Supplementary material. The concentrations of MDMA were determined repeatedly (Figure 4E) using HPLC-tandem mass spectrometry according to (Hysek *et al.*, 2012a; Hysek *et al.*, 2012d).

Statistical analysis

Repeated measures were expressed as peak changes from baseline (ΔE_{\max}). Drug effects were first analyzed by an overall analysis of variance (ANOVA), with drug as a within-subject factor. The modulatory effects of sex were then analyzed by ANOVAs, with drug as within- and sex as between-subjects factors. The effects of trait empathy in the IRI on MDMA-induced changes in state empathy in the MET were analyzed using the IRI scale scores (low vs. high median split) as between subject factor. Tukey *post hoc* comparisons were based on significant main effects or interactions in the ANOVAs. Order effects were excluded by ANOVAs, with session order as a factor. Confounding effects of previous cannabis use on the sex-drug interaction were excluded by ANOVAs, with drug experience as additional factor. Pearson's correlation coefficients were used to determine associations between measures.

Results

Mean \pm SEM values and detailed statistics for all outcomes are shown in Supplementary Table S1.

Subjective effects

Significant MDMA treatment effects were found on VAS scores for "happy" ($F_{1,31}=120.59$, $p<0.001$), "open" ($F_{1,31}=80.77$, $p<0.001$), and "close to others" ($F_{1,31}=67.52$, $p<0.001$; Figure 1). MDMA also increased AMRS scores for activity ($F_{1,31}=24.48$, $p<0.001$), inactivity ($F_{1,31}=7.72$, $p=0.009$), extroversion ($F_{1,31}=40.58$, $p<0.001$), introversion ($F_{1,31}=10.05$, $p=0.003$), well-being ($F_{1,31}=37.00$, $p<0.001$), emotional excitation ($F_{1,31}=28.46$, $p<0.001$), and dreaminess ($F_{1,31}=25.48$, $p<0.001$) but not for anxiety (Supplementary Figure S1). A significant sex \times treatment interaction was found for "happy" ratings ($F_{1,31}=10.49$, $p=0.003$), but the *post hoc* tests showed no significant differences between men and women in "happy" ratings after MDMA administration. No other sex \times treatment interactions were found.

Empathy

MDMA significantly increased explicit and implicit emotional empathy ratings for all stimuli ($F_{1,31}=6.05$, $p=0.019$ and $F_{1,31}=4.29$, $p=0.047$, respectively) (Figure 2A and B). For both explicit and implicit empathy, the MDMA-induced increase was significant for positive

valence stimuli ($F_{1,31}=8.60$, $p=0.006$ and $F_{1,31}=5.02$, $p=0.032$, respectively) but not negative valence stimuli (Supplementary Figure S2A-D). MDMA influenced emotional empathy differently in male and female subjects as evidenced by a significant treatment \times sex interaction for implicit emotional empathy ($F_{1,31}=4.68$, $p=0.039$) and a similar trend effect for explicit emotional empathy ($F_{1,31}=3.03$, $p=0.092$). The *post hoc* tests showed that MDMA increased explicit and implicit emotional empathy ratings only in men ($p=0.025$ and $p=0.022$, respectively) and not in women (Figure 2A-B). Men tended to score non-significantly lower on both measures of emotional empathy compared with women after placebo administration. MDMA increased empathy ratings in men to the levels of empathy in women after placebo administration. No effect of treatment was found on cognitive empathy scores (Figure 2C). Trait empathy in the IRI did not moderate the state empathy response to MDMA in the MET. As expected and validating the tasks, IRI trait empathy ratings of fantasy and empathic concern were associated with explicit empathy scores in the MET ($R_p=0.60$, $p<0.05$, and $R_p=0.47$, $p<0.05$, respectively; $n=32$), and IRI trait empathy ratings of personal distress were associated with implicit emotional empathy ratings in the MET ($R_p=0.63$, $p<0.01$; $n=32$) after placebo administration.

Social value orientation

MDMA increased prosociality. A significant MDMA treatment effect was found on the SVO angle ($F_{1,31}=4.42$, $p=0.044$; Figure 3A), with a significant treatment \times sex interaction ($F_{1,31}=5.52$, $p=0.026$). The *post hoc* tests showed that MDMA significantly increased prosocial behavior in men ($p=0.008$) but not women. In men, prosocial behavior increased after MDMA administration to the levels of placebo-treated women (Figure 3A). Moreover, MDMA tended to reduce the inequality-aversion index ($F_{1,20}=3.39$, $p=0.079$) in subjects with a prosocial orientation, indicating that MDMA promoted the shift from joint gain maximization to inequality aversion (Figure 3B).

Facial emotion recognition

MDMA impaired the accuracy of emotion recognition compared with placebo ($F_{1,31}=28.63$, $p<0.001$) when all of the stimuli were analyzed together, regardless of valence (Supplementary Figure S3A). MDMA differently affected emotion recognition in male and female subjects ($F_{1,31}=6.04$, $p=0.020$). Women performed significantly worse after MDMA treatment compared with placebo treatment ($p<0.001$), whereas no significant effect of MDMA was found in men (Supplementary Figure S3A). Valence-specific analyses of recognition accuracy showed that MDMA significantly impaired the correct recognition of fearful ($F_{1,31}=14.90$, $p<0.001$), angry ($F_{1,31}=18.60$, $p<0.001$), disgusted ($F_{1,31}=5.81$, $p=0.022$), and surprised ($F_{1,31}=9.79$, $p=0.004$) faces compared with placebo (Supplementary Figure S3D-E,G-H). In contrast, MDMA did not alter the correct identification of happy ($F_{1,31}=0.27$, $p=0.607$) faces compared with placebo (Supplementary Figure 3C). MDMA affected recognition accuracy for fearful and sad faces differently in male and female subjects ($F_{1,31}=6.61$, $p=0.015$, and $F_{1,31}=9.42$, $p=0.005$, respectively). Significant impairments in the recognition accuracy for fearful ($p<0.001$), angry ($p=0.007$), and sad ($p=0.010$) faces after MDMA treatment compared with placebo were found only in women (Supplementary Figure S3E-F). Fear recognition accuracy inversely correlated with the C_{max} and AUC_{0-6h} of MDMA in women ($R_p=-0.62$, $p=0.014$, and $R_p=-0.66$, $p=0.006$, respectively; $n=16$).

Consistent with labeling errors for fearful faces, MDMA increased the detection threshold for fearful faces compared with placebo ($F_{1,31}=4.92$, $p<0.032$). MDMA did not alter the detection threshold for any other valence or all of the emotions together (Supplementary Figure S3B). Accuracy in the MET significantly correlated with overall emotion recognition accuracy in the FERT ($R_p=0.42$, $p=0.018$; $n=32$) after placebo treatment, thus cross-validating both tasks. No correlations were found between the effects of MDMA on emotion recognition and the endocrine effects of MDMA.

Endocrine effects and pharmacokinetics of MDMA

MDMA significantly increased the plasma levels of oxytocin ($F_{1,31}=19.84$, $p<0.001$), cortisol ($F_{1,31}=98.70$, $p<0.001$), and prolactin ($F_{1,31}=127.81$, $p<0.001$) compared with placebo (Figure 4A, C-D). In contrast, MDMA did not alter the plasma concentrations of copeptin (Figure 4B) or testosterone (Supplementary Table S1). No correlations were found between the neuroendocrine and empathogenic or prosocial effects of MDMA.

Both the maximum concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{0-6h}) were higher in women compared with men ($F_{1,15}=35.73$, $p<0.001$, and $F_{1,15}=20.77$, $p<0.001$, respectively) (Figure 4E). The mean C_{max} values of MDMA were 209 ± 6.4 ng/ml (mean \pm SEM) in men and 269.9 ± 9.3 ng/ml (mean \pm SEM) in women. Mean AUC_{0-6h} values were 926.8 ± 29.3 ng/ml·h (mean \pm SEM) in men and 1146.5 ± 37.9 ng/ml·h (mean \pm SEM) in women. The relative doses of MDMA were 1.68 ± 0.14 mg/kg body weight (mean \pm SD) in men and 2.09 ± 0.29 mg/kg body weight (mean \pm SD) in women. Higher plasma exposure to MDMA was significantly associated with deficits in the recognition of fearful faces in women as described above. No other correlations were found between plasma exposure to MDMA and the pharmacodynamic effects of MDMA. The time to maximum concentration (T_{max}) was reached after a mean time of 2.44 ± 0.14 h (mean \pm SEM) after MDMA administration. Mean T_{max} values were 2.10 ± 0.20 h (mean \pm SEM) and 2.75 ± 0.17 h (mean \pm SEM) in men and women, respectively. The pharmacokinetic data were consistent with previous studies (Hysek *et al.*, 2011; Hysek and Liechti, 2012).

Discussion

The novel findings of this study are that MDMA increased emotional empathy and prosocial behavior. This effect was observed primarily in men. Consequently, male subjects showed more empathic concern and less competitive behavior and exhibited a more prosocial orientation after MDMA treatment, equal to that observed in women with placebo. Additionally, MDMA tended to increase the preference for fairness, reflected by a trend reduction in inequality-aversion compared with placebo. Although MDMA is reported to be an “empathogen” and has been shown to produce increased self-ratings of prosocial feelings (Dumont *et al.*, 2009) and sociability (Bedi *et al.*, 2009; Bedi *et al.*, 2010), this is the first study that actually observed enhanced emotional empathy in men using an empathy test. In addition, the study also documented increased MDMA-induced prosociality in men in a behavioral task.

MDMA did not alter cognitive empathy in the MET and impaired emotion recognition of basic emotions in the FERT especially in women, consistent with impaired cognitive empathy with regard to decoding of basic emotions. Specifically, MDMA reduced the recognition of negative facial emotions, including fear, anger, and disgust, consistent with the reduced recognition of fearful faces in a static FERT (Bedi *et al.*, 2010) and the impaired mind-reading accuracy of negative emotions in the RMET (Hysek *et al.*, 2012b). MDMA did not affect the recognition of happy faces as previously shown (Bedi *et al.*, 2010), while improved recognition of happy expressions in the RMET was found in another study (Hysek *et al.*, 2012b). MDMA reduced affect recognition accuracy particularly in women. The largest MDMA-induced deficit in women was found in fear recognition and involved both accuracy and intensity detection thresholds. A functional imaging study showed that MDMA enhanced the response to happy faces in the ventral striatum (Bedi *et al.*, 2009), a structure activated by expected rewards (Knutson and Cooper, 2005), and attenuated the response to angry faces in the amygdala, which is a core region for fear processing (Zald, 2003). Because women generally exhibit greater left amygdala activation to negative emotional stimuli than men (Stevens and Hamann, 2012), MDMA may alter emotional processing in a valence- and sex-specific manner by modulating the brain circuits involved in the processing of reward and anxiety.

The findings from the MET and FERT indicate that MDMA overall enhances the emotional but not cognitive components of empathy. More specifically, MDMA appears to reduce the recognition of negative but not positive emotions in others across different tests and studies. Altogether, these effects of MDMA likely result in a shift in the processing of

social-emotional information toward enhanced perception and possibly responses to positive emotional stimuli. Both the positive and prosocial mood effects and valence-specific social cognitive effects of MDMA likely enhance sociability when MDMA is used as a club drug. The effects of MDMA on social cognition may also facilitate the processing of emotionally distressing material when MDMA is used in combination with psychotherapy for patients with social dysfunction and social threat, such as posttraumatic stress disorder and social anxiety disorder (Mithoefer *et al.*, 2013).

Sex-differences in various effects of MDMA have previously been described. MDMA produced more intense acute subjective effects (Liechti *et al.*, 2001) and greater negative long-term effects (Reneman *et al.*, 2001; Ogeil *et al.*, 2013) in women compared with men. Women also more frequently developed hyponatremia in association with ecstasy use compared with men (Rosenson *et al.*, 2007; van Dijken *et al.*, 2013). These findings indicate that women may be generally more susceptible to the effects MDMA compared with men. Consistently, we observed MDMA-induced deficits in the recognition of sad faces only in women but not in men and significantly greater deficits in the recognition of fearful faces in women compared with men. A reduced ability to detect and process negative emotional information is likely therapeutically relevant when MDMA is used in the treatment of post-traumatic stress disorder. It will be of interest to see whether there are sex-differences in the treatment response to MDMA in clinical studies, which have so far included 85% women (Mithoefer *et al.*, 2010; Mithoefer *et al.*, 2013; Oehen *et al.*, 2013).

In the present study, we documented increased levels of oxytocin, cortisol, and prolactin along with alterations in emotional cognition. However, we found no correlations between MDMA-induced endocrine and emotional changes. The lack of associations does not exclude a role for oxytocin in the empathogenic and prosocial effects of MDMA as discussed below. There are several possible reasons for the lack of significant correlations. First, circulating levels of neurohormones may not reflect their brain levels (Neumann, 2007). Second, blood drawings to determine the endocrine markers had to be done before or after the computer tasks for practical reasons. Third, the use of only one relatively high dose of MDMA likely resulted in maximal threshold effects precluding the detection of correlations between the endocrine biomarkers and emotional measures across subjects. We have previously documented an identical lack of correlations between the subjective and autonomic effects of MDMA across a large number of subjects once peak drug effects are reached while there are strong associations over time within subjects (Hysek and Liechti, 2012).

Which neurotransmitters or hormones may contribute to the effects of MDMA on social cognition? The primary mechanism of action of MDMA is to release serotonin and norepinephrine in the brain and both neurotransmitters have been shown to mediate most of the acute psychotropic effects of MDMA (Hysek *et al.*, 2011; Hysek *et al.*, 2012d). Serotonin and norepinephrine release also likely mediates the effects of MDMA on emotional processing. In fact, we previously demonstrated that the inhibition of MDMA-induced serotonin and norepinephrine release with duloxetine not only prevented the subjective effects of MDMA (Hysek *et al.*, 2012d) but also tended to reduce the effects of MDMA on emotion identification in the RMET (Hysek *et al.*, 2012b). Similar to MDMA, the 5-HT_{1A/2A} receptor agonist psilocybin impaired the recognition of negative facial expressions in healthy subjects, and this effect was prevented by a 5-HT_{2A} antagonist (Kometer *et al.*, 2012). Additionally, serotonin transporter inhibitors, such as citalopram, also alter emotional processing, depending on emotional valence (Anderson *et al.*, 2011), and generally increase the recognition of positive facial emotions (Harmer *et al.*, 2003a) and diminish the perception of negative emotions (Pringle *et al.*, 2013), including fear (Harmer *et al.*, 2004) and sadness (Hinkemann *et al.*, 2010). Furthermore, polymorphisms in the serotonin transporter gene were also associated with altered emotion recognition, particularly of fearful faces (Hinkemann *et al.*, 2010). Serotonin is also a supposed regulator of social behavior. Enhancing serotonin via transporter inhibition increases aspects of prosocial behavior (Knutson *et al.*, 1998; Crockett *et al.*, 2010), whereas tryptophan depletion decreases

cooperative behavior (Wood *et al.*, 2006). Finally, the norepinephrine transporter inhibitor reboxetine increased the recognition of happy faces and impaired the recognition of fearful faces (Harmer *et al.*, 2003b; Harmer *et al.*, 2004), similar to MDMA. Altogether, the effects of the serotonin and norepinephrine releaser MDMA on emotional processing and social behavior are consistent with the effects reported for other pharmacological manipulations of these neurotransmitters. However, the extent to which downstream stimulating effects on social neuropeptides and hormones are involved is unclear. Oxytocin is a key candidate for the mediation of the empathic and prosocial effects of MDMA (Thompson *et al.*, 2007; Hysek *et al.*, 2012b). MDMA activates oxytocin neurons, increases plasma oxytocin levels through 5-HT_{1A} receptors, and increases social interaction in rats (Thompson *et al.*, 2007). Blocking oxytocin receptors in the brain reduced the prosocial effects of MDMA in rats (Thompson *et al.*, 2007). In the present study, MDMA increased the plasma levels of oxytocin in parallel with its empathogenic and prosocial effects. Increases in plasma oxytocin have previously been shown after MDMA administration (Dumont *et al.*, 2009; Hysek *et al.*, 2012b). The empathogenic effects of MDMA in the MET are also strikingly similar to those of oxytocin in the same test (Hurlemann *et al.*, 2010). Analogous to MDMA, oxytocin enhanced emotional but not cognitive empathy in the MET in men (Hurlemann *et al.*, 2010). In the RMET, oxytocin improved emotion recognition in healthy subjects (Domes *et al.*, 2007) and patients with autism (Guastella *et al.*, 2010). MDMA similarly improved emotion recognition in the RMET, although only for positive stimuli (Hysek *et al.*, 2012b). A comparable selective increase in the sensitivity in detecting positive vs. negative facial expressions was also reported for oxytocin (Marsh *et al.*, 2010). Similar to the effects of MDMA in the FERT in the present study, oxytocin slowed reaction times for identifying fearful faces (Di Simplicio *et al.*, 2009). Both MDMA and oxytocin reduced the response of the amygdala to negative emotional stimuli (Kirsch *et al.*, 2005; Bedi *et al.*, 2009). Comparable to the prosocial effects of MDMA, oxytocin has been shown to increase generosity (Zak *et al.*, 2007) and trust (Kosfeld *et al.*, 2005). The MDMA-induced release of oxytocin and overall very similar emotional-cognitive effects of oxytocin and MDMA might implicate oxytocin as a crucial mediator of the effects of MDMA on empathy and social behavior. Directly testing the role of oxytocin in the effects of MDMA in humans will be difficult because clinically used oxytocin receptor antagonists or PET ligands do not cross well the blood-brain barrier (Smith *et al.*, 2012). MDMA response modulation by genetic polymorphisms in the oxytocin receptor gene (e.g., rs53576 and rs1042778) (Kumsta and Heinrichs, 2013) could be tested. In addition, effects of MDMA or of pharmacologically similar but less toxic drugs could be evaluated in patients with social dysfunction where oxytocin is implicated such as autism (Guastella *et al.*, 2010). As expected (Harris *et al.*, 2002), MDMA also increased the plasma levels of cortisol and prolactin. Cortisol and prolactin are primarily markers of hypothalamic-pituitary-adrenal, serotonergic, and noradrenergic activity but there are limited data on the role of cortisol in social cognition. In men, high stress-induced cortisol levels were associated with better social cognition (Smeets *et al.*, 2009).

This study has limitations. First, we used only one dose of MDMA. We did not perform a dose-response study because we did not want to expose the mostly drug-naïve subjects to more than two doses of MDMA. Second, we used a relatively high dose of MDMA with obvious subjective effects. Although we used a double-blind design and identical placebo most participants realized which treatment they had been administered over the course of the experimental session. Thus, unblinding the subjective effects of MDMA may have biased task performance. We felt that it is important to use relevant doses of MDMA, which correspond to those typically used in recreational settings (Brunt *et al.*, 2012) or in clinical trials (125 mg plus 62.5 mg after 2h) (Mithoefer *et al.*, 2010; Mithoefer *et al.*, 2013; Oehen *et al.*, 2013). Lower doses of MDMA and active placebo could be used in future studies. Third, the evaluation of many aspects of social cognition in this study required a relatively large number of statistical comparisons.

In summary, the novel findings are that MDMA increases emotional empathy and prosocial behavior in healthy subjects. The social cognitive effects of MDMA may explain its

popularity as a recreational drug and potential beneficial effects of MDMA in the treatment of “social disorders” and posttraumatic stress disorder.

Supplementary data

Supplementary data are available at SCAN online.

Conflict of Interest

None declared.

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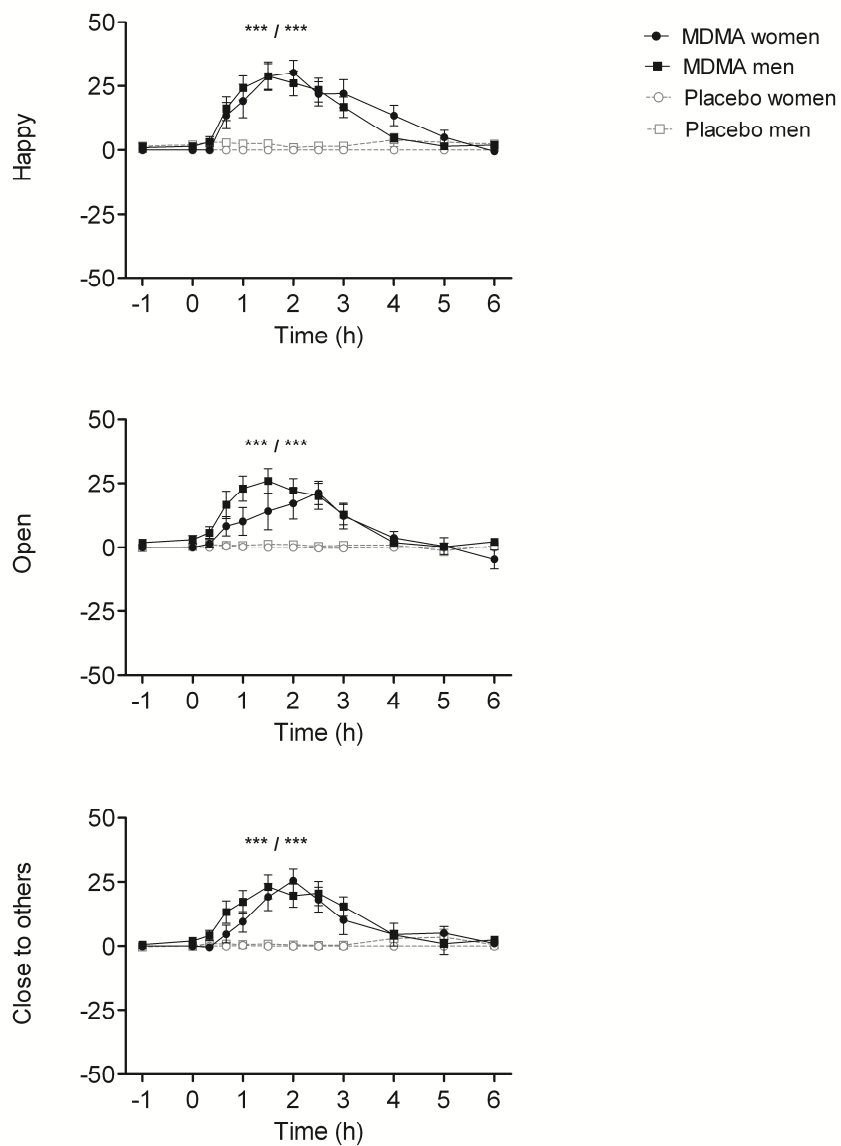


Figure 1. Subjective effects of MDMA measured using visual analog scales (VASs). The data are expressed as mean \pm SEM score changes from predrug baseline in 32 subjects. *** $p < 0.001$, significant differences (E_{max}) from placebo in women/men.

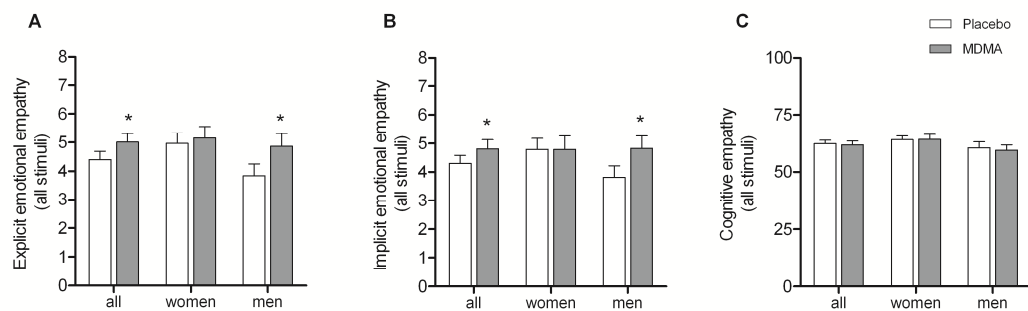


Figure 2. Effect of MDMA on (A) explicit and (B) implicit emotional empathy and (C) cognitive empathy in the Multifaceted Empathy Test (MET). MDMA significantly increased emotional empathy in all subjects due to increases in men but not in women. The data are expressed as mean \pm SEM in 32 subjects. * $p < 0.05$, significant difference from placebo.

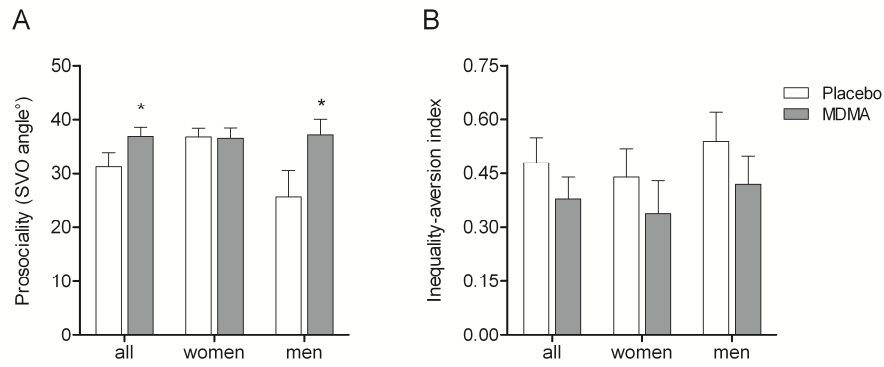


Figure 3. Effect of MDMA on prosociality and inequality-aversion in the Social Value Orientation (SVO) test. (A) MDMA had prosocial effects in men, resulting in levels of prosociality equal to those of placebo-treated women. (B) MDMA tended to reduce the inequality-aversion index ($p = 0.079$), consistent with an increased preference for fairness. The data are expressed as mean \pm SEM. * $p < 0.05$, significant difference from placebo.

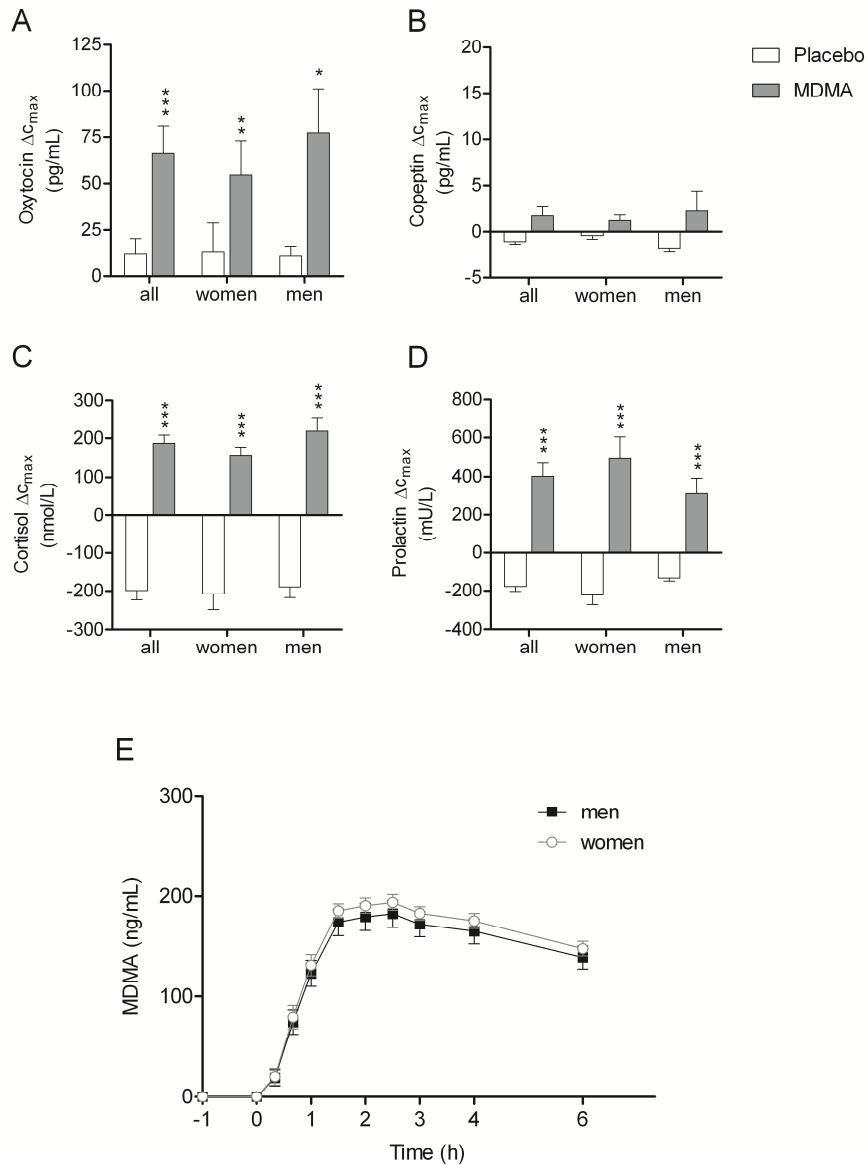


Figure 4. (A-D) Endocrine effects of MDMA and (E) plasma concentration-time curve of MDMA. MDMA increased the plasma concentrations of (A) oxytocin, (C) cortisol, and (D) prolactin but not (B) copeptin. The data are expressed as mean \pm SEM of differences from baseline in 32 subjects. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, significant difference (change in C_{max}) from placebo.