Original Paper

Differential effects of MDMA and methylphenidate on social cognition

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Abstract

Social cognition is important in everyday-life social interactions. The social cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) and methylphenidate (both used for neuroenhancement and as party drugs) are largely unknown. We investigated the acute effects of MDMA (75 mg), methylphenidate (40 mg), and placebo using the Facial Emotion Recognition Task (FERT), Multifaceted Empathy Test (MET), Movie for the Assessment of Social Cognition (MASC), Social Value Orientation Test (SVO), and Moral Judgment Task (MJT) in a cross-over study in 30 healthy subjects. Additionally, subjective, autonomic, pharmacokinetic, endocrine, and adverse drug effects were measured. MDMA enhanced emotional empathy for positive emotionally charged situations in the MET and tended to reduce the recognition of sad faces in the FERT. MDMA had no effects on cognitive empathy in the MET or social cognitive inferences in the MASC. MDMA produced subjective “empathogenic” effects, such as drug liking, closeness to others, openness, and trust. In contrast, methylphenidate lacked such subjective effects and did not alter emotional processing, empathy, or mental perspective-taking. MDMA but not methylphenidate increased the plasma levels of oxytocin and prolactin. None of the drugs influenced moral judgment. Effects on emotion recognition and emotional empathy were evident at a low dose of MDMA and likely contribute to the popularity of the drug.

Trial registration: Registration identification number: NCT01616407

ClinicalTrials.gov: http://www.clinicaltrials.gov/ct2/show/NCT01616407

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

Introduction

Social cognition including emotion recognition, empathy, and mental perspective-taking ("Theory of Mind" [ToM]) describes the ability to infer another's thoughts, feelings, and intentions relevant for human social every-day interactions. Few studies have evaluated the acute effects of recreationally used stimulant drugs on aspects of social cognition. The acute social cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") are particularly interesting because ecstasy users explicitly use MDMA to elicit empathic feelings and enhance sociability (Morgan et al., 2013). When tested under laboratory conditions, MDMA indeed increased emotional empathy and prosociality and impaired the identification of negative emotions (Bedi et al., 2010; Hysek et al., 2012a; Hysek et al., 2013). These social cognitive effects of MDMA likely contribute to the high popularity of ecstasy, which is the third most prevalent recreational drug among young adults, with an average lifetime prevalence of 5.7% in the European Union (EMCDDA, 2013). Enhanced empathy and reduced perception of negative emotions could also be relevant when MDMA is used in psychotherapy for example in the treatment of posttraumatic stress disorder (PTSD) (Mithoefer et al., 2010; Oehen et al., 2013).

Our previous investigations of the social cognitive effects of psychostimulants used a relatively high dose of MDMA (125 mg) and methylphenidate (60 mg) with marked psychoactive effects, which may have affected performance in the social-cognitive tasks (Hysek et al., 2012a; Hysek et al., 2013; Hysek et al., 2014). Additionally, we used a relatively small set of social cognitive tests. It is unclear whether a lower dose MDMA with lower subjective effects also alters emotion recognition, empathy, or prosocial behavior. In the present study, we therefore reevaluated the social cognitive and subjective effects of lower doses of both MDMA (75 mg) and methylphenidate (40 mg) using a more comprehensive social cognitive test battery. MDMA predominantly enhances serotonergic and noradrenergic neurotransmission (Hysek et al., 2012b) and releases oxytocin (Dumont et al., 2009; Hysek et al., 2012a; Hysek et al., 2013), whereas methylphenidate enhances dopaminergic and

noradrenergic neurotransmission (Schmeichel and Berridge, 2013). Thus, the present study allowed us to investigate the contribution of serotonin (5-hydroxytryptamine [5-HT]) and oxytocin *vs*. dopamine to aspects of social cognition using these pharmacological tools. Methylphenidate was also selected because it is a widely used stimulant for the treatment of attention-deficit/hyperactivity disorder, but it is also misused as a cognitive enhancer and recreationally (McCabe et al., 2005). However, currently unknown is whether methylphenidate alters social cognition. For example, acute amphetamine or methylphenidate administration facilitated the identification of facial expression of emotions in healthy subjects (Wardle et al., 2012; Hysek et al., 2014). Methylphenidate also improved ToM and empathy in children with attention-deficit/hyperactivity disorder (ADHD; Maoz et al., 2014), but similar effects on social cognition have not yet been studied in healthy subjects.

MDMA (125 mg) reduced the recognition of sad, angry, or fearful faces (Hysek et al., 2014). The 5-$HT_{1A/2A}$ receptor agonist psilocybin impaired the recognition of negative facial expressions in healthy subjects (Kometer et al., 2012) and oxytocin also biased emotion recognition (Di Simplicio et al., 2009). Accordingly, we hypothesized that the 5-HT and oxytocin releaser MDMA (75 mg) would similarly impair the decoding of negative facial emotions. In contrast, we hypothesized that methylphenidate (40 mg) would enhance face emotion recognition in particular of negative emotions as observed with the higher dose (Hysek et al., 2014) and more similar to amphetamine (Wardle et al., 2012).

MDMA increased social interaction in rats that interacted for the first time and these effects were mediated by MDMA-induced release of oxytocin (Thompson et al., 2007; Ramos et al., 2013). In humans, oxytocin enhanced emotional empathy (Hurlemann et al., 2010). Oxytocin may therefore contribute to the empathogenic and prosocial effects of MDMA (Thompson et al., 2007; Hysek et al., 2013; Ramos et al., 2013). Accordingly, we hypothesized that MDMA, but not methylphenidate, would increase emotional empathy and prosociality in the present study similar to oxytocin and as previously observed with 125 mg MDMA (Hysek et al., 2013). These evaluations of the effects of MDMA on emotion recognition, empathy, and

prosociality aimed at confirming previous findings with a higher dose of MDMA (Bedi et al., 2010; Hysek et al., 2013).

Additionally, we also wanted to explore effects of MDMA on additional aspects of ToM using a more ecologically valid test including everyday-life social situations presented in a movie (Dziobek et al., 2006). Because 125 mg MDMA did not alter overall mind reading accuracy (Hysek et al., 2012a) or cognitive empathy (Hysek et al., 2013) we did not expect that 75 mg MDMA would produce general impairments in cognitive empathy or ToM (Hysek et al., 2012a; Hysek et al., 2013).

We also explored effects of MDMA on moral judgment, which has been shown to be altered after enhancing 5-HT transmission using the 5-HT transport inhibitor citalopram (Crockett et al., 2010). We expected that MDMA would make subjects more likely to judge harmful actions as unacceptable compared with placebo as previously shown for citalopram (Crockett et al., 2010).

In the presents study, we also measured circulating levels of cortisol and prolactin, which are endocrine markers of 5-HT activity, as well as of oxytocin because of its suggested role in social cognition. We expected all these hormones to be increased after MDMA but not after methylphenidate administration.

Method

We studied the effects of MDMA, methylphenidate, and placebo on several aspects of social cognition using the Facial Emotion Recognition Task (FERT; Bedi et al., 2010; Hysek et al., 2014), Multifaceted Empathy Test (MET; Dziobek et al., 2008), Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006), Social Value Orientation Test (SVO; Murphy et al., 2011), and Moral Judgment Task (MJT; Crockett et al., 2010). Negative mood recognition in the FERT and emotional empathy in the MET were considered the primary endpoint measures based on the previously documented effects of MDMA on these tasks (Bedi et al., 2010; Hysek et al., 2013; Hysek et al., 2014).

Additionally, we measured subjective, autonomic, pharmacokinetic, endocrine, and adverse drug effects. Importantly, we also combined the present and previously published data (Hysek et al., 2013; Hysek et al., 2014) into a pooled analysis of the effects of MDMA and methylphenidate in a larger sample including the dose-response for both MDMA and methylphenidate.

Study design

We used a double-blind, placebo-controlled, randomized, cross-over design with three experimental sessions (75 mg MDMA, 40 mg methylphenidate, and placebo) in 30 subjects. The order of the three experimental sessions was counterbalanced, and the washout periods between sessions were 7-28 days (mean 16 days). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Basel and Swiss Agency for Therapeutic Products (Swissmedic). All of the subjects provided written consent before participating in the study, and they were paid for their participation. The study was registered at ClinicalTrials.gov (NCT01616407). The effects of the drugs on emotion recognition and empathy were the predefined primary endpoints of the study.

Participants

Thirty healthy subjects (15 men, 15 women) with a mean ± s.d. age of 24 ± 4.2 years (range, 18-32 years) were recruited from the University of Basel. Inclusion criteria were age 18-45 years and body mass index 18-27 kg/m^2. The exclusion criteria were a personal or first-degree relative history of psychiatric disorders (determined by the Structured Clinical Interview for Axis I and II Disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) or chronic or acute physical illness (assessed by physical examination, electrocardiogram, standard hematology, and chemical blood analysis). Additional exclusion criteria were tobacco smoking, a lifetime history of using illicit drugs more than five times, with the exception of occasional cannabis use in the past, and any illicit drug use, including cannabis, within the last 2 months or during the study period, determined by urine tests

conducted during screening and before the test sessions using TRIAGE 8 (Biosite, San Diego, CA, USA). Thus, we included only subjects with no recreational drug experience or only very limited recreational drug experience to study acute drug effects that are not biased by intensive previous drug experiences. Twenty-two subjects were MDMA-naive. Eight subjects had used MDMA less than five times. Twelve subjects had occasionally used cannabis more than five times in the past. Fifteen subjects had used cannabis less than five times, and three subjects had no cannabis experience. Seven participants reported having used other illicit drugs one to four times in the past. One subject had used lysergic acid diethylamide. Two subjects had used amphetamines. Three subjects had used cocaine. Three subjects had used psilocybin. One subject reported using methylphenidate once previously as a cognitive enhancer. Female subjects were investigated during the follicular phase of their menstrual cycle (day 2-14) when the reactivity to amphetamines is expected to be similar to men (White et al., 2002).

Study procedures

The study included a prescreening telephone interview, a screening visit, three experimental sessions, and an end-of-study visit. The experimental sessions were conducted in a quiet hospital research ward. Experimental sessions began at 9:00 AM. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling, and baseline measurements were performed. MDMA, methylphenidate, and placebo were administered at 10:00 AM. The FERT was performed at 11:15 AM and the MET at 11:30 AM during the peak drug effects. The MJT was performed at 12:00 AM, the MASC was shown at 1:00 PM and the SVO was administered at 2:00 PM. A standardized small lunch was served at 1:30 PM, and the subjects were sent home at 4:30 PM. On the day after each test session at 10:00 AM, the participants completed subjective effects measurements and rated subacute adverse effects. During the end-of-study visit, the subjects were asked to retrospectively indicate the treatment order prior to opening the randomization code.

Drugs

± MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was prepared as gelatin capsules with mannitol as filler. Identical placebo (only mannitol) capsules were prepared. MDMA was administered in a single absolute dose of 75 mg that corresponded to 1.1 ± 0.13 mg/kg body weight. This dose of MDMA is similar to the one typically found in one ecstasy pill (Brunt et al., 2012) but is lower than the doses used in clinical studies of patients with PTSD (125 mg followed by 62.5 mg after 2 h; Mithoefer et al., 2010; Oehen et al., 2013). Immediate-release methylphenidate tablets (4 × 10 mg, Ritalin, Novartis AG, Bern, Switzerland) were encapsulated within opaque gelatin capsules (with mannitol as filler), and identical placebo capsules (mannitol pill plus mannitol filler) were prepared. Methylphenidate was administered in a single dose of 40 mg.

Measures

Social cognition

Facial Emotion Recognition Task

We used the FERT that was previously used with high doses of MDMA (Bedi et al., 2010; Hysek et al., 2014) and methylphenidate (Hysek et al., 2014) and was sensitive to the effects of both drugs or to 5-HT or norepinephrine uptake inhibition (Harmer et al., 2004).The task included 10 neutral faces and 160 faces that expressed one of four basic emotions (i.e., happiness, sadness, anger, and fear), with pictures morphed between 0% (neutral) and 100% in 10% steps. Two female and two male pictures were used for each of the four emotions. Stimuli were shown in random order for 500 ms and were then replaced by the rating screen where participants had to indicate the correct emotion. The main outcome measure was accuracy (proportion correct). Additionally, we analyzed whether incorrectly identified emotional expressions were misclassified as neutral or other emotions (Bedi et al., 2010).

Multifaceted Empathy Test

The MET is a reliable and valid task to assess the cognitive and emotional aspects of empathy (Dziobek et al., 2008). The MET has been shown to be sensitive to high doses of MDMA (Hysek et al., 2013). The computer-assisted test consisted of 40 photographs that showed people in emotionally charged situations. To assess cognitive empathy, the participants were required to infer the mental state of the subject in each scene and indicate the correct mental state 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 an 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 additional 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.

Movie for the Assessment of Social Cognition

The ecologically valid MASC was used to further evaluate aspects of cognitive empathy and assess the subject's ability to infer mental states in complex, everyday-life, social situations (Dziobek et al., 2006). The MASC has been shown to reliably detect even subtle mind-reading difficulties in psychiatric patients (Dziobek et al., 2006) or cocaine users (Preller et al., 2013). The MASC displays a broad range of mental states and includes classic social cognition concepts, such as false belief, persuasion, faux pas, metaphor, and sarcasm (Dziobek et al., 2006). The test consists of a 15 min movie about four characters (two men, two women) who spend an evening together. The video was stopped repeatedly, and the subjects answered 45 questions that referred to the feelings, intentions, emotions, and thoughts of the characters. The participants had to choose one of four possible answers with no time limit. The subjects' answers were grouped into correct mental state inferences, correct ToM, and incorrect ToM that included three subcategories: no ToM (non-mental state

inferences; i.e., physical causation), insufficient ToM (i.e., mental state inferences are insufficient), and excessive ToM (i.e., mental state inferences are excessive). Six control questions for non-social inferences were included (e.g., “What is the weather outside”).

Social Value Orientation Task

We used the paper version of the validated SVO to assess social behavior (Murphy et al., 2011). The SVO measure was sensitive to a high dose of MDMA (Hysek et al., 2013). In this economic resource allocation task, prosociality is defined as behavior that maximizes the sum of resources for the self and others and minimizes the difference between the two (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 a resource 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. Mean allocations for self and the other were calculated (Murphy et al., 2011; Hysek et al., 2012a), and the inverse tangent of the ratio of these two means produced an angle that indicated the participants’ SVO index. A smaller SVO angle indicates more individualistic or competitive behavior, and a larger SVO angle indicates more prosocial or even altruistic behavior. The nine secondary items were used to differentiate between two prosocial motivations, inequality aversion and joint gain maximization. An index of 0 indicates perfect inequality aversion, and 1 indicates maximal preference for joint gain maximization. The inequality-aversion index was calculated as previously described (Murphy et al., 2011; Hysek et al., 2012a).

Moral Judgment Task

Using the MJT (Moore et al., 2008), the participants were asked to make decisions in a series of hypothetical scenarios from opposing utilitarian outcomes (e.g., saving five lives) to highly aversive harmful actions (e.g., harming one innocent person). Twenty scenarios were presented as text. For each scenario, a question was posed that was related to the personal

judgment of the scenario (e.g., Is it acceptable for you to...?). Responding “Yes” indicated endorsement of the proposed action. The MJT included eight more emotionally salient scenarios (e.g., “personal” harms), eight less emotionally salient harms (e.g., “impersonal” harms), and four non-moral (neutral) scenarios, resulting in a total of 20 scenarios. Both personal and impersonal scenarios included avoidable and inevitable harms that were equally distributed. In each test session, the subjects completed another set of scenarios, and the order was balanced across sessions and drug order.

Subjective effects

Subjective effects were assessed using psychometric scales that have been previously used with MDMA (Hysek et al., 2011; Hysek et al., 2012b; Hysek et al., 2013) and methylphenidate (Hysek et al., 2014). Visual analog scales (VASs; (Hysek et al., 2012a) were used 1 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 24 h after drug administration. The 60-item Adjective Mood Rating Scale (AMRS; (Janke and Debus, 1978; Hysek et al., 2011) was administered 1 h before and 1.25, 4, and 24 h after drug administration. The 5-Dimensions of Altered States of Consciousness Rating Scale (5D-ASC; (Studerus et al., 2010) was used 5 h after drug administration to retrospectively rate the effects of the drugs.

Vital signs

Blood pressure, heart rate, and tympanic body temperature were repeatedly measured 1 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after drug administration as previously described in detail (Hysek and Liechti, 2012). The rate pressure product was calculated as systolic blood pressure $\times$ heart rate.

Endocrine and pharmacokinetic measures

The plasma levels of prolactin, cortisol, oxytocin, and copeptin were measured at baseline and 2 h after drug administration and analyzed as described previously (Simmler et al., 2011; Hysek et al., 2012a; Neumann et al., 2013). The plasma levels of catecholamines

(i.e., norepinephrine and epinephrine) were measured at baseline and 1 and 2 h after drug administration (Dunand et al., 2013). The plasma levels of MDMA, 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxymethamphetamine (HMMA), and methylphenidate were determined 1 h before and 0.5, 1, 1.5, 2, 3, 4, and 6 h after drug administration (Hysek et al., 2014).

Adverse effects

Adverse effects were assessed 1 h before and 5 and 24 h after drug administration using the 66-item List of Complaints (Zerssen, 1976). The scale yields a total adverse effects score and reliably measures physical and general discomfort.

Statistical and pharmacokinetic analyses

The sample size calculation was based on previous studies that similarly assessed effects of pharmacological interventions on the FERT or MET (Bedi et al., 2010; Hurlemann et al., 2010; Hysek et al., 2013; Hysek et al., 2014). Specifically, we previously showed that MDMA (125 mg) impaired recognition of sad faces in particular compared to methylphenidate (60 mg) by 16% (SD of the difference = 16%) in the FERT (Hysek et al., 2014). A sample size of 7 would achieve 80% power to detect an increase by 16% with a known standard deviation of 16% and with a significance level (alpha) of 0.05 using a one-sided one-sample t-test. We also previously showed that MDMA increased explicit emotional empathy in particular for positive stimuli compared to placebo by 19% (SD of the difference = 36%) (Hysek et al., 2013). A sample size of 23 would achieve 80% power to detect an increase by 19% with a known standard deviation of 36% and with a significance level (alpha) of 0.05 using a one-sided one-sample t-test. We decided to include 30 subjects to account for possible drop outs and inaccuracies in the sample estimation.

The data were analyzed using repeated-measures analysis of variance (ANOVA) with drug as within-subjects factor. Repeated measures are expressed as peak effects (E_{max}) prior

to analysis of variance (ANOVA). The FERT data were similarly analyzed, with emotion type as an additional within-subjects factor. Tukey *post hoc* comparisons were performed based on significant main effects or drug × emotion interactions. Order effects were excluded by ANOVAs with session order as a factor. The criterion for significance was $p < 0.05$. Pearson correlation coefficients were used to determine associations between measures. The pharmacokinetic data were analyzed using non-compartmental models. Maximal plasma concentration (C_{max}) and the time to maximal plasma concentration (T_{max}) were obtained directly from the observed concentration-time curves. For methylphenidate, the terminal elimination rate constant (λ_z) was estimated by log-linear regression after semilogarithmic transformation of the data using three data points of the terminal linear phase of the concentration-time curve, and the terminal elimination half-life ($t_{1/2}$) was calculated using λ_z and the equation $t_{1/2} = ln2 / \lambda_z$.

Dose-Response evaluation (pooled data)

To assess the dose-response effects of MDMA and methylphenidate, we directly compared the social cognitive effects and subjective and autonomic (vital signs) effects of MDMA and methylphenidate using the low dose data from the present study in 30 subjects and the high dose data from our previous studies (Hysek et al., 2013; Hysek et al., 2014). Our previous studies used a dose of MDMA of 125 mg (Hysek et al., 2013) and a dose of methylphenidate of 60 mg (Hysek et al., 2013; Hysek et al., 2014) and identical outcome measures as the present study that allow direct comparisons of the effects of the low and high drug doses. The dose-response was evaluated for each drug and outcome separately using ANOVA, with dose (low dose *vs*. high dose) as the between-subjects factor and drug (MDMA/methylphenidate *vs*. placebo/placebo) as the within-subjects factor. A significant main effect of drug indicates a significant difference between drug and placebo in the pooled study sample. A significant dose × drug interaction indicates a significant difference between the low and high doses (significant dose-response). Tukey *post hoc* tests were based on significant main effects of drug or dose × drug interactions.

Results

All 30 participants completed the study. Peak drug effects and statistics are shown in detail in Supplementary Table S1. The dose-response findings are shown in Supplementary Tables S2 and S3 and Supplementary Fig. S4-S7.

Social cognition

Facial Emotion Recognition Task

The effects of MDMA and methylphenidate on the FERT are shown in Fig. 1. The ANOVA revealed a significant main effect of emotion ($F_{14,116}$ = 28,94, p < 0.001), indicating that emotion types were differently well identified. Performance accuracy was highest for happy faces, followed by angry, fearful, and sad faces. No main effect of drug on FERT accuracy was found, with no emotion × drug interaction, indicating that neither MDMA nor methylphenidate altered the correct identification of facial emotions overall. Consistently, no significant drug effects on emotion identification accuracy for happy, anger, and fearful faces were found. However, a trend toward an effect of drug on the identification of sad faces was observed ($F_{2,58}$ = 2.98, p = 0.059), with nearly significant impaired recognition of sad faces in the MDMA condition compared with methylphenidate (p = 0.056). In the pooled data, methylphenidate significantly and dose-dependently increased the identification of happy, sad, and fearful faces (Table S3) and MDMA significantly impaired the identification of sad, angry, and fearful faces, with no significant dose-response effect (Table S2). No main effect of drug on the misclassification of emotions as happy, sad, angry, or fearful faces was observed, indicating that there was no bias toward one of these emotions. Emotions that were not correctly identified were in most cases misclassified as neutral (Table S1). A significant effect of drug on the misclassification of emotions as neutral was found ($F_{2,58}$ = 5.12, p < 0.01), and the *post hoc* test indicated that MDMA significantly increased the misclassification of emotions as neutral compared with placebo (p < 0.05) and methylphenidate (p < 0.05).

Multifaceted Empathy Test

The drug effects on the MET are shown in Fig. 2. Significant effects of drug on both explicit and implicit emotional empathy scores for positive emotional stimuli were found ($F_{2,58}$ = 3.84, p = 0.027, and $F_{2,58}$ = 3.23, p = 0.047, respectively). MDMA significantly increased both explicit and implicit emotional empathy scores for positive emotional stimuli compared with placebo (both $p < 0.05$). Consistently, MDMA increased both explicit and implicit emotional empathy in the pooled sample, with no significant dose-response effect (Table S2). In contrast, no effects of drug on emotional empathy associated with negative emotional situations or explicit or implicit emotional empathy scores were found when positive and negative emotions were analyzed together. Methylphenidate had no effect on emotional empathy ratings in the present and in the pooled study. Neither drug altered cognitive empathy scores.

Movie for the Assessment of Social Cognition

No significant main effects of drug were observed on any of the MASC subscales, indicating that neither MDMA nor methylphenidate affected ToM (Table S1). Methylphenidate increased correct accuracy for the non-mental control questions compared with MDMA (drug main effect: $F_{2,58}$ = 3.78, p = 0.029; *post hoc* test: $p < 0.05$), indicating enhanced performance.

Social Value Orientation Test

No significant main effects of drug on the SVO angle or inequality-aversion index were found (Table S1), indicating that neither low-dose MDMA nor methylphenidate altered prosocial behavior.

Moral Judgment Task

No significant main effects of drug were found on the proportion of personal or impersonal scenarios judged as acceptable, indicating that neither MDMA nor methylphenidate acutely altered moral judgment (Table S1).

Subjective effects

Subjective drug effects are shown in Fig. 3 and S1. MDMA produced more pronounced subjective drug effects compared with methylphenidate (Fig.3, Table S1). Only MDMA but not methylphenidate produced significant “empathogenic” effects, including increases in happiness, openness, trust, and closeness compared with placebo (all $p < 0.001$; Fig. 3). In the pooled study (Fig. S4, Table S2), the high dose of MDMA increased the MDMA-typical “empathogenic” effects “happiness,” “open,” “trust,” and “closeness” significantly more than the low dose of MDMA. Only the high dose of methylphenidate increased “concentration” ratings (Fig. S6). On the AMRS (Fig. S1), MDMA but not methylphenidate increased well-being ($p < 0.01$) compared with placebo, whereas methylphenidate but not MDMA increased efficacy-activity compared with placebo ($p < 0.05$).. On the 5D-ASC (Table S1), MDMA increased Oceanic Boundlessness, Anxious Ego-Dissolution, and Visionary Restructuralization scores compared with placebo (all $p < 0.001$). In the pooled study (Table S2), the extents of alterations of consciousness were dose-dependent. The high dose of MDMA increased the total ASC score and ratings in the dimension Oceanic Boundlessness significantly more than the low dose. Methylphenidate did not alter any of the 5D-ASC scores.

Vital signs

Drug effects on vital signs are shown in Fig. S2 and Table S1. Both MDMA and methylphenidate significantly increased the rate pressure product compared with placebo ($p < 0.001$). No difference was found in the response between MDMA and methylphenidate, indicating an overall similar hemodynamic response to the doses used. A nearly significant drug effect on body temperature was observed ($F_{2,58} = 2.93$, $p = 0.061$), with a difference in the thermogenic response to methylphenidate compared with placebo ($p < 0.05$). In the pooled study, only the high doses of MDMA (Fig. S5) and methylphenidate (Fig. S7) significantly increased body temperature compared with placebo.

Endocrine effects

The effects of MDMA and methylphenidate on plasma hormone levels are shown in Table S1. MDMA significantly increased the plasma levels of cortisol ($p < 0.001$), prolactin ($p < 0.001$), oxytocin ($p < 0.001$), and epinephrine ($p < 0.01$) compared with placebo. Methylphenidate significantly increased the plasma levels of cortisol ($p < 0.01$) and epinephrine ($p < 0.05$) compared with placebo. No correlations were found between drug-induced endocrine and emotional or social cognitive drug effects.

Pharmacokinetics

The C_{max} values for MDMA, MDA, HMMA, and methylphenidate were 125 ± 5.2, 6.1 ± 0.3, 64 ± 5.8, and 16.7 ± 0.9 ng/ml, and the T_{max} values were 2.6 ± 0.2, 5.7 ± 0.1, 3.4 ± 0.2, and 2.2 ± 0.2 h, respectively. The $T_{1/2}$ of methylphenidate was 3.2 ± 0.27 h (Fig. S3).

Adverse effects

Both MDMA and methylphenidate produced significant acute adverse effects compared with placebo (both $p < 0.05$; Table S1). MDMA also tended to increase subacute adverse effects compared with placebo ($p = 0.059$). No severe adverse effects were reported.

Discussion

The main findings of the present study were that a low dose of MDMA enhanced emotional empathy for positive emotional stimuli on the MET and tended to reduce the recognition of sad faces on the FERT. The positive bias in emotion recognition and increase in emotional empathy induced by a low dose of MDMA were accompanied by only moderate subjective effects. MDMA had no acute effects on cognitive empathy on the MET or mental perspective-taking on the MASC, indicating that MDMA did not acutely alter complex social-cognitive inferences. Methylphenidate did not affect emotion processing, emotional or cognitive empathy, or correct mental perspective-taking at the dose used in the present study.

On the MET, MDMA increased emotional empathy for positive but not negative stimuli. This finding is consistent with our previous study, in which a higher dose of MDMA also increased emotional empathy for positive but not negative emotionally charged situations (Hysek et al., 2013). However, MDMA at a dose of 75 mg did not increase emotional empathy ratings overall, whereas the higher dose of 125 mg did (Hysek et al., 2013). Additionally, the MDMA-induced increase in emotional empathy in our previous high-dose study was observed mainly in men, whereas we found no such sex difference in the present low-dose study (Hysek et al., 2013). The sex difference may be partially attributable to a ceiling effect in women.

The effects of a low dose of MDMA on emotion recognition on the FERT were small. MDMA produced only a nearly significant trend toward a reduction of accuracy of decoding sad emotions on the FERT. However, the trend was consistent with the significant effects seen with higher doses of MDMA (125 mg or 1.5 mg/kg) in previous studies (Bedi et al., 2010; Hysek et al., 2013; Hysek et al., 2014). A lower dose of MDMA (0.75 mg/kg) had no effect in the same FERT (Bedi et al., 2010). Overall, these findings support the view that MDMA at a dose of 125 mg could be a useful adjunct in psychotherapy of PTSD to reduce the perception of negative emotions and facilitate therapeutic alliance (Mithoefer et al., 2010; Oehen et al., 2013).

Our data are consistent with the positive mood bias in emotion recognition observed with other serotonergic drugs MDMA also increased emotional classification deficits, reflected by a neutral response bias as previously shown for a higher dose of MDMA (Bedi et al., 2010). A similar alteration in affect recognition, in which faces were more often mistakenly judged as neutral, particularly in response to sad facial expressions, was also found after moderate alcohol consumption (Kamboj et al., 2013). Drugs that facilitate social approach behavior may do so by partially decreasing the correct identification of threat-related or negative facial emotion signals. In contrast, the 40 mg dose of methylphenidate used in the present study had no effects on emotion recognition. However, we previously showed that a higher dose (60 mg) increased the recognition of sad and fearful faces (Hysek et al., 2014). Methylphenidate also enhanced the recognition of anger and fear in subjects with attention-deficit/hyperactivity

disorder (Williams et al., 2008). A similar negative bias in emotion processing was seen with higher doses of amphetamine (Wardle et al., 2012). Because methylphenidate and amphetamine stimulate the dopamine and norepinephrine systems, the findings indicate that pronounced activation of these neurotransmitters may be associated with a negative bias in mood processing, whereas 5-HT stimulation may result in a positive bias that facilitates prosocial behavior.

Deficits in ToM and social cognitive capabilities are expected to affect social interaction. The MASC is considered sensitive to the detection of even subtle mind-reading difficulties (Dziobek et al., 2006). In the present study, a low dose of MDMA or methylphenidate had no effects on mental perspective-taking on the MASC. This suggests that the subjects were fully capable of correctly inferring mental states in others when under the acute influence of the drug. Consistently, neither MDMA nor methylphenidate had an effect on cognitive empathy on the MET in the present low-dose study or previous high-dose study (Hysek et al., 2013). Furthermore, the high dose of MDMA did not alter mind-reading accuracy overall on the Reading the Mind in the Eyes Test (Hysek et al., 2012a). However, methylphenidate increased correct answers to control questions on the MASC, consistent with enhanced cognitive performance (more careful responding). No data are available on the effects of a high dose of MDMA or methylphenidate on the MASC. In contrast, acute alcohol consumption has been shown to impair ToM (identification of faux pas; (Mitchell et al., 2011). Finally, MDMA had no effect on the moral judgment of moral dilemmas on the MJT compared with placebo. Citalopram made subjects more likely to judge harmful actions as unacceptable compared with placebo but only in emotionally salient personal scenarios (Crockett et al., 2010). Although we expect MDMA to enhance the 5-HT system more than citalopram, we found no effects on moral judgment. A possible explanation could be that MDMA also stimulates the noradrenergic system. The stimulation of norepinephrine using atomoxetine did not alter moral judgment (Crockett et al., 2010), consistent with the lack of an effect of methylphenidate on moral decisions in the present study. Finally, we previously showed that high-dose MDMA increased prosocial behavior on the SVO in men (Hysek et al., 2013), consistent with a role for 5-HT in

prosocial behavior (Crockett, 2009). However, low-dose MDMA had no effect on prosociality in the same test in the present study, suggesting that higher doses are needed to enhance prosocial behavior. Notably, the SVO was administered 4 h after drug intake, which may have been too late after low-dose MDMA administration.

Low-dose MDMA increased the plasma concentrations of cortisol, prolactin, and oxytocin, as previously shown for the high dose (Hysek et al., 2013). These hormones are known markers of the serotonergic effects of MDMA (Hysek et al., 2013). In contrast, methylphenidate did not change the plasma concentrations of prolactin or oxytocin.

Only MDMA and not methylphenidate produced empathogenic effects, such as increased ratings in happiness, openness, trust, and closeness to others. The empathogenic effect of the 75 mg dose of MDMA was moderate and significantly lower than the 125 mg dose. The hallucinogen-like effects of MDMA were also dose-dependent. The data showed that the characteristic subjective MDMA effects only fully developed at the 125 mg and only partially at the 75 mg dose.

The doses of MDMA and methylphenidate used in the present study produced comparable cardiovascular stimulation (rate $\times$ pressure product). Methylphenidate significantly and dose-dependently increased body temperature, which has not been described previously. Low-dose MDMA did not significantly increase body temperature, whereas the high dose did.

The present study has clear limitations. First, we used only single doses of MDMA and methylphenidate, and we found only subtle effects on social cognition. Formally, it is not possible to compare effects of two drugs if only single doses are used. Second, we used many test and made no statistical corrections for the resulting multiple comparisons. However, we made specific predictions based on previous studies for the effects of MDMA on a selection of primary endpoint measures. Most importantly, we previously used different and higher doses of both MDMA and methylphenidate (Hysek et al., 2013; Hysek et al., 2014) and documented overall very similar effects using several identical outcome measures. Additionally, we included a pooled analyses of the present with our previous similar data and dose-response analyses to confirm and validate our present findings. The assessment of different aspects of

social cognition also enhanced the validity of the study. Nevertheless, it has to be noted that drug-effects on aspects of social cognition appear to be rather subtle and larger studies would be needed to confirm our preliminary findings. Third, we administered several test one after another and without counterbalancing the order within the session. Drug effects may have been stronger during the first (FERT, MET, MJT) compared to the last (MASC, SVO) tests administered. Thus, weaker drug effects may have contributed to the negative findings in the MASC and SVO. Although the present study only addressed drug-induced influences on social cognition in tasks in a laboratory setting, remaining unknown is whether MDMA or methylphenidate use alters social cognitive abilities and behavior in real-world interactions. Finally we assessed the social cognitive and endocrine effects only once after drug administration and may have missed drug-induced changes or correlations at other time points.

In conclusion, the positive bias in emotion recognition and increase in emotional empathy induced by even a low dose of MDMA likely contribute to its popularity as a recreational drug.

Conflict of interest

The authors declare no conflict of interest.

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FIGURE LEGENDS

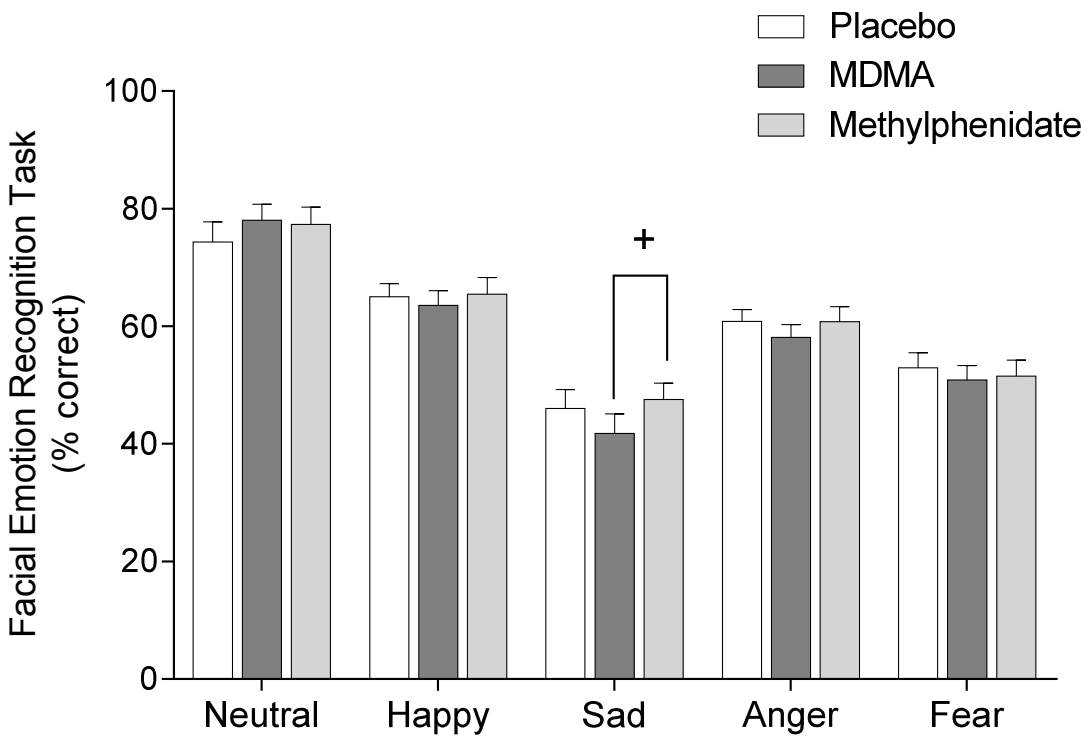

Figure 1. Facial Emotion Recognition Task. No significant effects of methylphenidate or MDMA on facial emotion recognition were found. However, MDMA tended to impair the recognition of sad faces compared with methylphenidate (^{+}p = 0.056, nearly significant difference between MDMA and methylphenidate). The data are expressed as mean ± s.e.m. in 30 subjects.

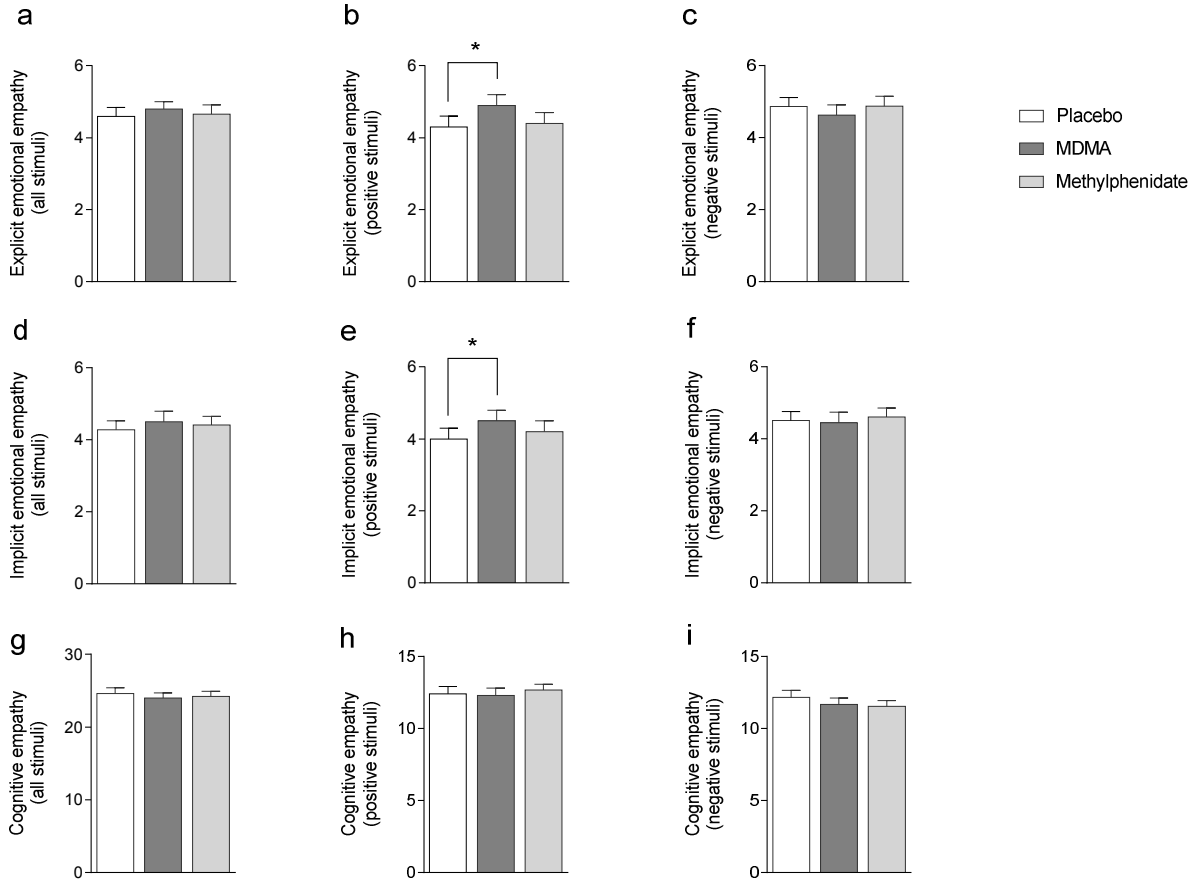

Figure 2. Multifaceted Empathy Test. MDMA increased explicit (b) and implicit (e) emotional empathy for positive stimuli but not for negative stimuli (c, f) or for all stimuli together (a, d). No effects of MDMA on cognitive empathy were found (g-i). No effects of methylphenidate on emotional (a-f) or cognitive (g-i) empathy were found. The data are expressed as mean ± s.e.m. in 30 subjects. *$p < 0.05$, significant difference compared with placebo.

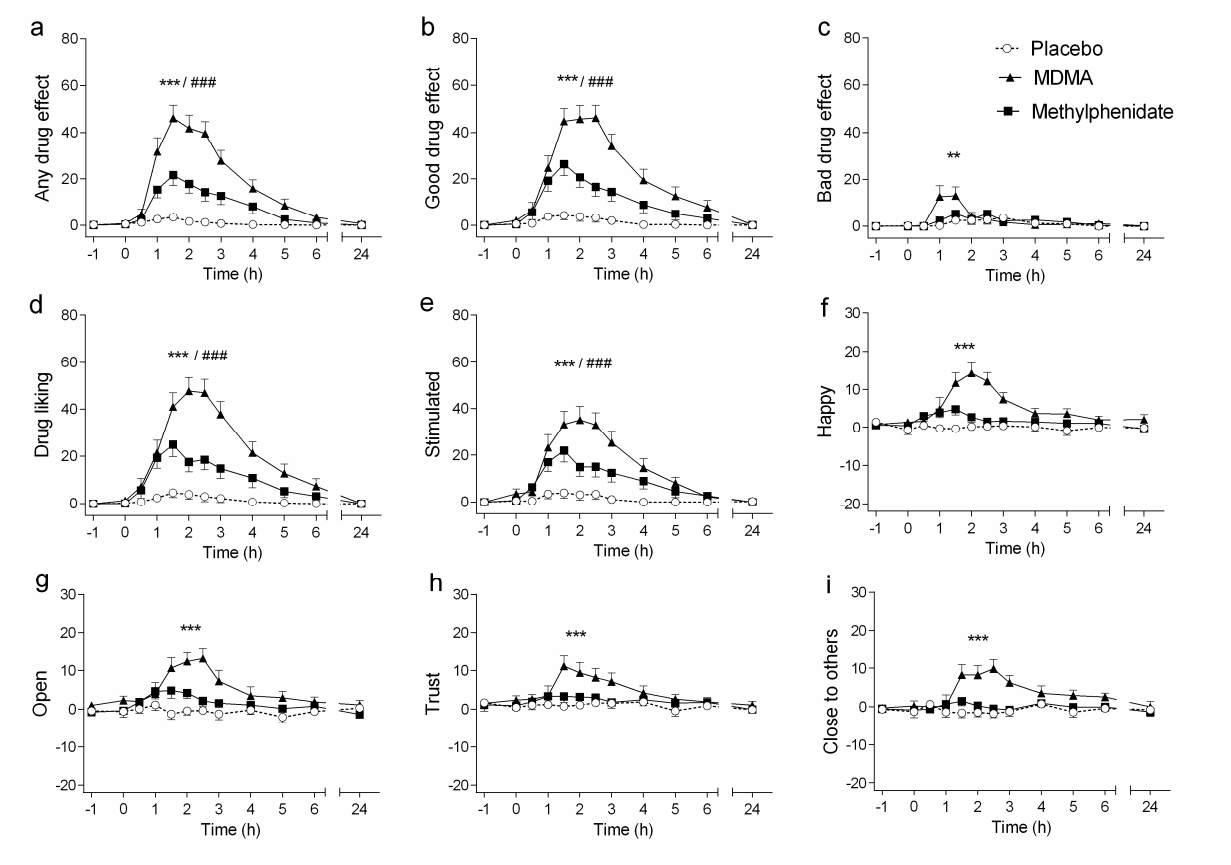

Figure 3. Visual Analog Scale. MDMA, methylphenidate, and placebo were administered at t = 0 h. Both MDMA and methylphenidate increased ratings of "any drug effect" (a), "good drug effect" (b), "drug liking" (d), and "stimulated" (e) compared with placebo. MDMA produced more pronounced effects than methylphenidate. Additionally, only MDMA and not methylphenidate produced "empathogenic" subjective effects, including significant increases in "happy" (f), "open" (g), "trust" (h), and "close to others" (i) compared with placebo. MDMA also produced minimal but significant increases in "bad drug effect" (c). The data are expressed as mean ± s.e.m. in 30 subjects. $^{**}p < 0.01$, $^{***}p < 0.001$, MDMA compared with placebo; $^{\#\#\#}p < 0.001$, methylphenidate compared with placebo.