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Multifaceted empathy of healthy volunteers after single doses of MDMA: A pooled sample of placebo-controlled studies

Kim PC Kuypers¹, Patrick C Dolder², Johannes G Ramaekers¹ and Matthias E Liechti²

Abstract

Previous placebo-controlled experimental studies have shown that a single dose of MDMA can increase emotional empathy in the multifaceted empathy test (MET) without affecting cognitive empathy. Although sufficiently powered to detect main effects of MDMA, these studies were generally underpowered to also validly assess contributions of additional parameters, such as sex, drug use history, trait empathy and MDMA or oxytocin plasma concentrations. The present study examined the robustness of the MDMA effect on empathy and investigated the moderating role of these additional parameters. Participants ($n = 118$) from six placebo-controlled within-subject studies and two laboratories were included in the present pooled analysis. Empathy (MET), MDMA and oxytocin plasma concentrations were assessed after oral administration of MDMA (single dose, 75 or 125 mg). Trait empathy was assessed using the interpersonal reactivity index. We confirmed that MDMA increased emotional empathy at both doses without affecting cognitive empathy. This MDMA-related increase in empathy was most pronounced during presentation of positive emotions as compared with negative emotions. MDMA-induced empathy enhancement was positively related to MDMA blood concentrations measured before the test, but independent of sex, drug use history and trait empathy. Oxytocin concentrations increased after MDMA administration but were not associated with behavioral effects. The MDMA effects on emotional empathy were stable across laboratories and doses. Sex did not play a moderating role in this effect, and oxytocin levels, trait empathy and drug use history were also unrelated. Acute drug exposure was of significant relevance in the MDMA-induced emotional empathy elevation.

Keywords

MDMA, cognitive empathy, emotional empathy, sex, pooled data analysis

Introduction

The psychoactive substance in ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), is known for its empathogenic effects such as increased happiness, openness, trust and closeness to others (Kirkpatrick et al., 2014b; Schmid et al., 2014). Previous placebo-controlled experimental studies have also shown that a single dose of MDMA can increase sociability and different aspects of empathy (Kamilar-Britt and Bedi, 2015). Behavioral tasks of empathy measure an individual's response to faces showing a positive or negative emotional expression. Participants are asked to identify the emotion (as a measure of cognitive empathy (CE)) and/or rate how much they feel for those persons or how aroused they are by the emotion (as a measure of emotional empathy (EE)). Commonly used tasks for assessing cognitive empathy are the Facial Emotion Recognition Test (FERT) and the Reading the Mind in the Eyes Test (RMET). The Multifaceted Empathy Test (MET) measures both cognitive and emotional empathy (Dziobek et al., 2008). In comparison with the FERT and RMET, the MET displays more complex and more realistic and ecologically valid emotional stimuli.

Overall, MDMA studies have shown mixed effects with regard to CE across different tasks. MDMA (75 or 125 mg) did not affect recognition of positive or negative emotions in the MET, but reduced recognition of negative emotions in the FERT (Bedi et al., 2010; Hysek et al., 2014a; Schmid et al., 2014).

Results from the RMET were also not consistent. Two studies reported no acute effects of (MDMA 1.5 mg/kg or 75 mg; Bedi et al., 2010; Kuypers et al., 2014), whereas one study (Hysek et al., 2012a) reported enhancement of recognition of positive emotions, a decrease in recognition of negative emotions, and no effect on the recognition of neutral emotions after a single MDMA dose of 125 mg. Interestingly, findings using the MET, the paradigm with the most realistic stimuli, have shown a consistent pattern, that is, no effect of MDMA on accuracy of

¹Department of Neuropsychology & Psychopharmacology, Faculty of Psychology & Neuroscience, Maastricht University, the Netherlands

²Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel and University of Basel, Switzerland

Corresponding author:

Kim PC Kuypers, Department of Neuropsychology & Psychopharmacology, Faculty of Psychology & Neuroscience, Maastricht University, P.O. Box 616, 6200 MD Maastricht, Maastricht, 6200 MD, the Netherlands.

Email: k.kuypers@maastrichtuniversity.nl

emotion recognition (Hysek et al., 2014a; Hysek and Liechti, 2012; Kuypers et al., 2014, 2016; Schmid et al., 2014, 2015).

Findings on MDMA effects on EE, as assessed by the MET, have been consistent across studies. MDMA (75 or 125 mg) either enhanced EE for both positive and negative emotions (Hysek et al., 2012a; Kuypers et al., 2014) or only for positive emotions (75 mg; Schmid et al., 2014). Research has also shown that MDMA produced an increase in peripheral oxytocin levels that seems to coincide with the increase in EE. Oxytocin is implicated in social behavior and it was suggested that MDMA's effects on empathy could in part be attributed to this effect on oxytocin (Dumont et al., 2009). However MDMA-induced changes in EE were not related to oxytocin plasma levels in two independent studies (Hysek et al., 2014a; Kuypers et al., 2014).

Placebo-controlled MDMA studies investigating effects on empathy have used relatively small samples sizes ($n = 16-32$) that were sufficiently powered to detect main effects of MDMA, but were generally underpowered to also assess the effect of moderators such as sex, drug use history, trait empathy, and MDMA or oxytocin plasma concentrations. For example, one study ($n = 32$) tested the role of sex in the effect of MDMA on EE (Hysek et al., 2014a) since studies have shown that females often perform better than males on behavioral ('state') and self-report measures ('trait') of empathy. Emotional empathy was enhanced after 125 mg of MDMA, mainly in men; that is, MDMA increased empathy ratings in men up to the higher placebo levels of women (Hysek et al., 2014a). However, assuming a small to moderate effect size, this study may have been too small to detect a reliable effect, a dose-response study is missing, and replication is needed. Besides sex, other factors might moderate the MDMA effect on empathy, for example the blood concentration of MDMA and lifetime ecstasy use. Individual MDMA concentrations are mainly determined by the MDMA dose per body weight and the individual's function of CYP2D6, the main enzyme involved in the metabolism of MDMA (de la Torre et al., 2012; Schmid et al., 2016). Studies have previously shown that physiological measures correlated positively with plasma MDMA concentrations (Schmid et al., 2014), and some have shown modest evidence for tolerance to the subjective overall effects of MDMA in more experienced users (Kirkpatrick et al., 2014a). Accordingly, the previous and actual exposure to MDMA may also influence its effects on empathy.

Some research suggests that aspects of social cognition are rather subtle and, therefore, larger studies would be needed to confirm previous findings from smaller sample studies (Schmid et al., 2014). Previously, Kirkpatrick and colleagues (2014a) showed that pooling data across laboratories increased the robustness and reproducibility of pharmacological effects of MDMA across different laboratories using similar methodology (Kirkpatrick et al., 2014a). The present study merged data from studies collected in two different laboratories that used the same methodology (double-blind, placebo-controlled, within-subject study design, and using the same empathy test). The primary aim was to determine the robustness of the MDMA effect on empathy in a large pooled sample including data from two different research teams and from participants with different amounts of previous ecstasy use. In addition, pooling data across these studies provided sufficient statistical power to assess the moderating role of contributing factors such as sex, plasma concentrations of MDMA and oxytocin, trait empathy, and lifetime MDMA use on the behavioral empathic response.

Methods

Participants

Six placebo-controlled within-subject studies investigating the effect of MDMA on empathy were included in the present pooled analysis. To our knowledge, these are all completed studies that used MDMA and the same version of the MET. Four studies were conducted in Basel, Switzerland (Hysek et al., 2014a; Hysek and Liechti, 2012; Schmid et al., 2014, 2015) and two in Maastricht, the Netherlands (Kuypers et al., 2014, 2016). The six studies were all individually approved by either the Ethics Committee of Basel, Switzerland (Hysek et al., 2014a; Hysek and Liechti, 2012; Schmid et al., 2014, 2015) or the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University (Kuypers et al., 2014, 2016) and conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent to participate in the studies and were paid.

Inclusion criteria were an absence of psychiatric history (personal or first-degree relative), good medical health as determined by a medical history and examination, blood analyses, and ECG, and a maximal lifetime history of illicit drug use of five times in the Basel studies, and minimally three experiences with ecstasy/MDMA in the Maastricht studies. The detailed inclusion and exclusion criteria have previously been published (Hysek et al., 2012b; Kuypers et al., 2014).

The pooled sample size included 118 participants. Characteristics of the participants and the studies are given in Table 1.

Procedure

The test days (placebo or MDMA) were separated by at least 7 days (i.e. a washout period). On the day prior to the each test day, the use of alcohol was prohibited. Participants were also asked to refrain from any other substance use during the study and participants were screened for drugs of abuse consumption in urine (THC, opiates, cocaine, amphetamines, methamphetamines) at the beginning of each test day. In addition, women were given a pregnancy test. When tests were negative they were allowed to proceed with the test day. Before administration of the study drugs, a blood sample was taken to determine baseline oxytocin levels.

Placebo or MDMA (Lipomed AG, Arlesheim, Switzerland; fixed dose of 75 mg in studies 3,5,6 or 125 mg in studies 1,2,4, prepared as capsules) was administered orally under double-blind conditions. Blood samples were taken prior to the empathy test, that is, between 90 and 120 min after administration to determine oxytocin levels and MDMA concentrations (Table 1). Subjective and cardiovascular effects were also assessed in all studies as reported elsewhere (Hysek et al., 2014a; Hysek and Liechti, 2012; Kuypers et al., 2014, 2016; Schmid et al., 2014, 2015).

Multifaceted Empathy Test and empathy questionnaire

The MET (Hurlmann et al., 2010) consists of 40 pictures of people conveying a complex emotional state that was positive in 50% of the pictures and negative in the other half. To assess CE, participants had to select the emotion word that matched the emotion picture out of four words. To assess EE, participants had to rate on a scale from 1 to 9 'how aroused this picture made them

Table 1. Characteristics of participants (Mean [\pm SD]) and methods per study.

Laboratory site	Study number	Demographics			Methods			Reference		
		Sample size N (M, F)	Age (years)	Weight (kg)	Ecstasy/MDMA use (times used in life)	MDMA dose (mg)	MDMA (mg/kg)		Time of blood sample after dosing (min)	Time of MET after dosing (min)
Basel	1	n = 16 (8, 8)	25.75 (3.25)	67.94 (12.37)	0.37 (.81)	125	1.90 (.39)	120'	180'	(Hysek and Liechti, 2012); MET data published in: (Hysek et al., 2014a)
	2	n = 16 (8, 8)	24.69 (2.55)	67.75 (7.58)	0.81 (1.05)	125	1.87 (.20)	120'	180'	(Hysek et al., 2014b); MET data published in: (Hysek et al., 2014a)
	3	n = 30 (15, 15)	23.93 (4.18)	70.03 (9.25)	0.57 (1.07)	75	1.09 (.13)	90'	90'	(Schmid et al., 2014)
	4	n = 16 (8, 8)	24.25 (2.21)	69.75 (7.94)	.37 (.50)	125	1.81 (.21)	120'	180'	(Schmid et al., 2015)
Maastricht	5	n = 20 (12, 8)	21.90 (2.45)	70.25 (13.09)	10.95 (8.97)	75	1.10 (.20)	90'	120'	(Kuypers et al., 2014)
	6	n = 20 (12, 8)	21.20 (2.63)	74.25 (10.01)	16.85 (23.21)	75	1.03 (.13)	90'	100'	(Kuypers et al., 2016)

feel' (implicit EE) and 'how concerned they were for the person' (explicit EE; Figure 1). Dependent variables were the number of correct classified pictures and the implicit EE and explicit EE ratings per valence.

The Interpersonal Reactivity Index (IRI) is originally a 28-item questionnaire referring to feelings and thoughts experienced in different situations. It consists of four discrete seven-item scales: 'Fantasy', F (tendency to imaginatively transpose oneself into fictional situations), 'Perspective-Taking', PT (tendency to spontaneously adopt the psychological viewpoint of others), 'Empathic Concern', EC (taps the respondents' feelings of warmth, compassion and concern for others), and 'Personal Distress', PD (assesses self-oriented feelings of anxiety and discomfort resulting from tense interpersonal settings). The first two scales are a measure of CE; the two latter a measure of EE (Davis, 1983). In the present study, the shortened version of the IRI was used, only including the data obtained in the placebo condition (Maastricht) or during the baseline (Basel). In this shortened version, negatively formulated items were left out, favoring its reliability (Paulus, 2009).

MDMA and oxytocin blood concentrations

MDMA and oxytocin concentrations were determined in blood samples collected before and after drug administration (Table 1). Blood plasma samples were frozen at -20°C until analysis; MDMA concentrations were determined according to Hysek et al. (2012b) and Pizarro et al. (2002) for the Basel and Maastricht site, respectively. Oxytocin concentrations were analyzed according to (Neumann et al., 2013) or using a fluorescent immunoassay kit (Phoenix Pharm. Inc Burlingame, CA) for the Basel and Maastricht site, respectively. Since oxytocin plasma levels were determined differently in different studies, a baseline %-change was calculated for oxytocin concentrations ($[\text{oxytocin concentrations before MET} - \text{oxytocin concentrations at baseline} / \text{oxytocin concentrations at baseline}] \times 100$).

Statistical analyses

To assess the effect of MDMA on state cognitive and EE, MET data were subjected to a mixed generalized linear model (GLM) repeated-measures analysis of variance (ANOVA) with Treatment (2 levels; Placebo and MDMA) and Valence (2 levels, positive, negative) as within-subjects factors and Study (6 levels) and Dose (2 levels) as between-subject factors. Sex was added in a second ANOVA as an additional between-subjects factor to assess its moderating influence on the MDMA effect. Main effects and two-way interaction effects between Treatment and additional factors (Valence, Study, Dose, and Sex) and Dose by Sex are reported.

To assess the role of Sex in trait cognitive and EE, data of the IRI entered a multivariate GLM with Study and Sex as fixed factors. To study the effect of Sex and Dose on MDMA blood concentrations a univariate GLM with Sex and Dose as fixed factors was conducted; In order to assess the effect of Study and Sex on MDMA blood concentrations, two separate univariate GLMs for MDMA dose (75 mg and 125 mg) were conducted. To assess the effects of MDMA on oxytocin concentrations, a repeated-measures GLM was conducted with Treatment as within-subjects factor and Study as between-subjects factor. In order to study the

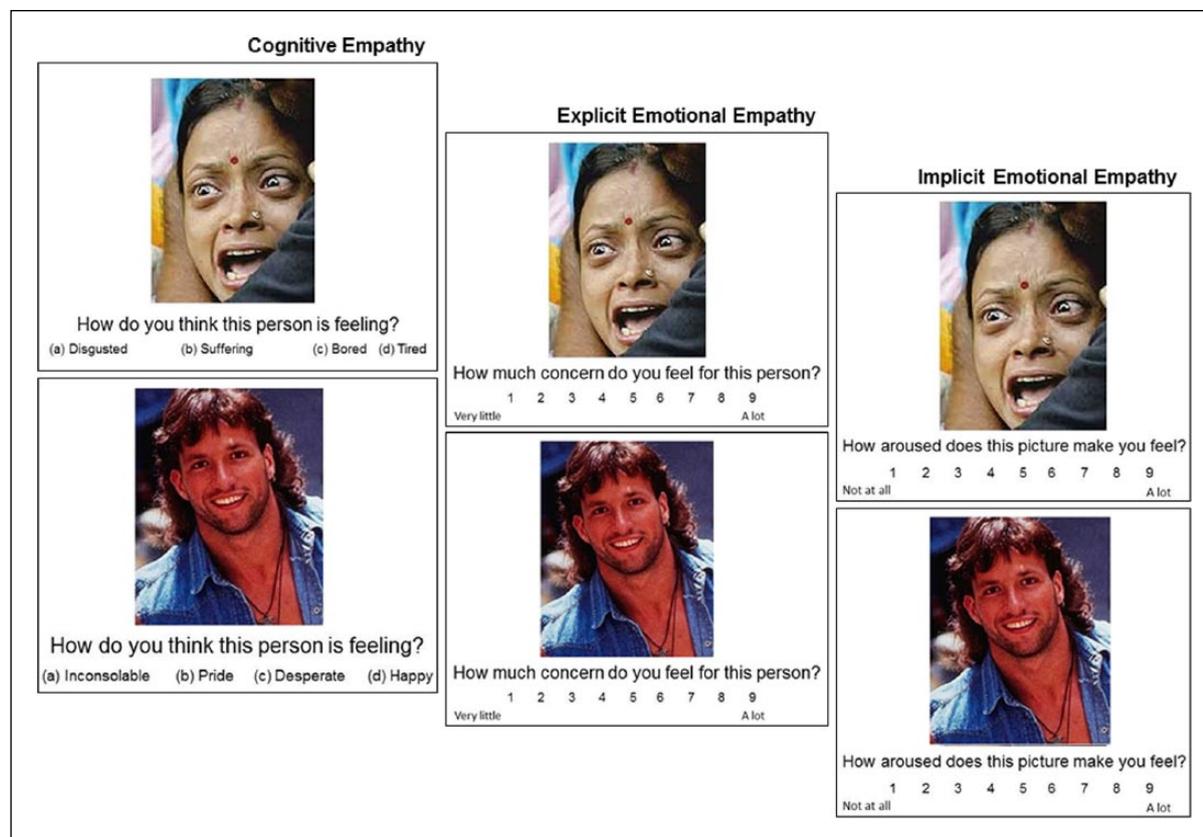


Figure 1. Example of a negative (top row) and a positive stimulus (bottom row) in the Multifaceted Empathy Test with questions assessing cognitive empathy, explicit emotional empathy and implicit emotional empathy respectively from left to right.

effect of Treatment and Sex on oxytocin concentrations separate for both MDMA doses, two separate repeated-measures GLMs for MDMA dose (75 and 125 mg) were conducted.

To study the relation between state empathy measures on the one hand and other parameters (trait empathy, MDMA blood concentrations, oxytocin blood concentrations, and lifetime ecstasy use) on the other hand, correlations were calculated. In case data were normally distributed, Pearson's correlations were reported; otherwise Spearman rank tests are reported.

The alpha criterion level of statistical significance for all analyses was set at $p = 0.05$; partial eta² (η^2) is reported in case of significant effects to demonstrate the effect's magnitude (0.01: small, 0.06: moderate; 0.14: large). In case of significant main effects, post-hoc t -tests were conducted. Analyses were performed with IBM SPSS Statistics for Windows, Version 24.0.

Results

Multifaceted empathy test

Cognitive empathy. ANOVA revealed a main effect of Valence ($F_{1,112} = 22.80$; $p < 0.001$; partial $\eta^2 = 0.17$) on CE, demonstrating a higher accuracy for positive emotions compared with negative emotions (Figures 2(h) and 2(i)). There were no effects of Treatment (Figure 2(g)), Study, Dose, or their interactions on CE. Adding Sex as a factor to the ANOVA did not change the outcome, that is, positive stimuli were better recognized than

negative stimuli, independent of Treatment, Study, Dose or Sex (Figure 2(h) and 2(i)).

Emotional empathy. Analysis revealed a main effect of Treatment ($F_{1,112} = 7.23$; $p = 0.008$; partial $\eta^2 = 0.06$) on explicit EE (Figure 2(a)). Participants felt more concern for people depicting emotions when they were under the influence of MDMA compared with placebo. Additionally the Valence by Treatment interaction ($F_{1,112} = 11.15$; $p = 0.001$; partial $\eta^2 = 0.09$) indicated that the MDMA-induced concern for positive emotions was higher compared with concern for positive ($t_{117} = 4.27$; $p < 0.001$) and negative ($t_{117} = 2.45$; $p = 0.02$) emotions in the placebo condition (Figure 2(b) and 2(c)). Adding Sex to the model revealed a main effect of Sex ($F_{1,106} = 6.41$; $p = 0.01$; partial $\eta^2 = 0.06$) on explicit EE demonstrating that females felt more concern for the depicted emotions compared with males (Figure 2(a)). However, Sex did not interact with Treatment (Figure 2(a)), supporting the hypothesis that the MDMA effect on EE is similar in both sexes.

Analysis of implicit EE revealed a main effect of Treatment ($F_{1,112} = 8.68$; $p = 0.004$; partial $\eta^2 = 0.08$, Figure 2(b)) and a Treatment by Valence interaction effect ($F_{1,112} = 9.13$; $p = 0.003$; partial $\eta^2 = 0.07$, Figure 2(e) and 2(f)). Under the influence of MDMA, participants were more aroused by the emotional content of the stimuli (Figure 2(d)). The interaction demonstrated that MDMA made the participants feel more aroused by positive ($t_{117} = 4.48$; $p < 0.001$) and negative ($t_{117} = 2.34$; $p = 0.02$) stimuli compared with positive stimuli in the

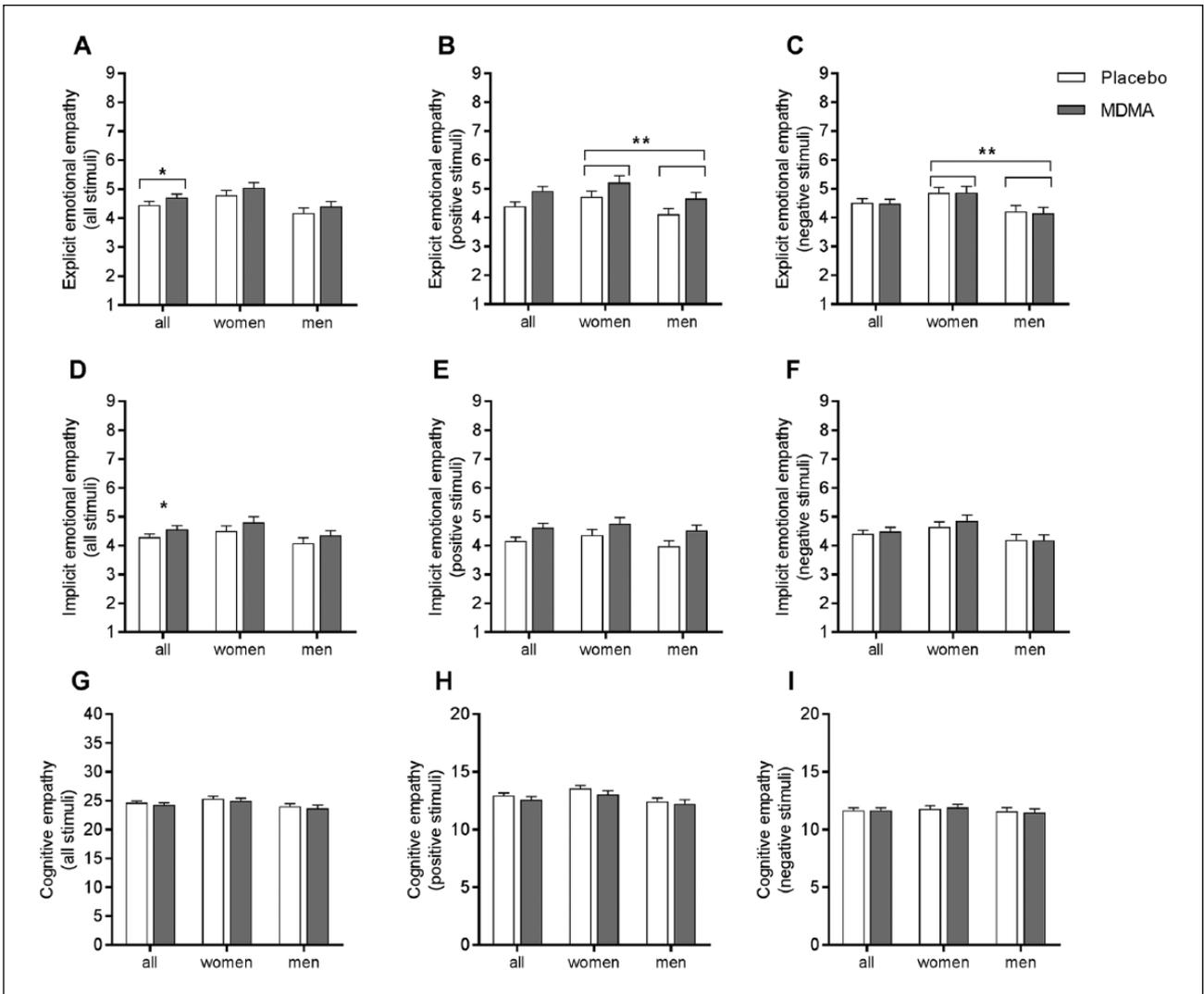


Figure 2. Mean (\pm SE) of cognitive and emotional empathy in the MET, for positive (upper panel) and negative emotions (lower panel) in placebo and MDMA conditions for men and women, pooled over 6 studies; Panels A to I depict respectively explicit emotional empathy ratings for all stimuli (A), positive stimuli (B), negative stimuli (C); implicit emotional empathy ratings for all stimuli (D), positive stimuli (E), negative stimuli (F), and number of correct recognized items (cognitive empathy) for all stimuli (G), positive stimuli (H), and negative stimuli (I); *indicates a main effect of Treatment and **indicates a main effect of Sex at $p = 0.05$ for both.

placebo condition (Figure 2(e) and 2(f)). Adding Sex to the model did not change the effects; there was no significant main effect of Sex on implicit EE or a significant Sex by Treatment interaction (Figure 2(d)).

There were no significant main effects of Study or Dose or other significant interaction effects with Treatment on EE (Table 2).

Interpersonal reactivity index

Multivariate GLM revealed a main effect of Sex on both EE scales, that is, ratings on empathic concern ($F_{1,102} = 7.06$; $p = 0.009$) and personal distress ($F_{1,102} = 13.37$; $p < 0.001$) were higher in women compared with men. There was no effect of Sex on CE (Figure 3 and Table 3).

MDMA and oxytocin blood concentrations

MDMA blood concentrations. Univariate GLM analysis revealed main effects of Sex ($F_{1,108} = 10.79$; $p = 0.001$; partial $\eta^2 = 0.09$) and Dose ($F_{1,108} = 146.75$; $p = 0.001$; partial $\eta^2 = 0.58$), and their interaction ($F_{1,108} = 18.00$; $p = 0.001$; partial $\eta^2 = 0.14$) on MDMA blood concentrations. The Dose effect demonstrated that MDMA blood concentrations were significantly higher in the 125 mg dose group compared with the 75 mg group. The Sex effect showed that concentrations were significantly higher in females compared with males. The interaction between Sex and Dose was explained by females having a disproportionate increase in MDMA blood concentrations in the 125 mg MDMA dose compared with the 75 mg MDMA ($t_{50} = -10.96$; $p < 0.001$) dose and the 125 mg dose in males ($t_{38} = -6.17$; $p < 0.001$). To assess whether MDMA blood concentrations were comparable

Table 2. Mean (\pm SD) of the MET scores per study.

Lab Site		Basel				Maastricht	
		Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
	Treatment condition						
Cognitive empathy							
All stimuli	MDMA	24.06 (4.09)	24.44 (5.99)	23.97 (4.01)	26.19 (3.97)	23.90 (3.57)	23.70 (3.52)
	Placebo	24.69 (3.07)	25.19 (3.88)	24.57 (4.47)	26.50 (2.94)	23.90 (3.06)	23.55 (3.27)
Positive stimuli	MDMA	12.37 (3.30)	13.00 (3.56)	12.30 (2.74)	13.44 (2.58)	12.75 (2.15)	12.15 (2.13)
	Placebo	13.19 (2.26)	13.00 (2.45)	12.40 (2.85)	13.81 (1.80)	13.05 (1.73)	12.85 (2.01)
Negative stimuli	MDMA	11.69 (1.78)	11.44 (3.05)	11.67 (2.45)	12.75 (2.35)	11.15 (2.85)	11.55 (2.04)
	Placebo	11.50 (1.63)	12.19 (2.43)	12.17 (2.67)	12.69 (1.85)	10.85 (2.68)	10.70 (2.15)
Explicit emotional empathy							
All stimuli	MDMA	4.85 (1.60)	5.17 (1.79)	4.76 (1.32)	4.71 (1.36)	4.26 (1.23)	4.56 (1.26)
	Placebo	4.13 (1.62)	4.67 (1.65)	4.59 (1.35)	4.77 (1.30)	3.94 (1.19)	4.60 (1.50)
Positive stimuli	MDMA	5.61 (1.98)	5.30 (2.03)	4.89 (1.64)	4.87 (1.53)	4.23 (1.61)	4.84 (1.62)
	Placebo	4.44 (1.85)	4.76 (1.17)	4.31 (1.57)	4.84 (1.19)	3.66 (1.35)	4.60 (1.56)
Negative stimuli	MDMA	4.09 (2.01)	5.04 (1.62)	4.63 (1.53)	4.55 (1.54)	4.28 (1.85)	4.27 (1.63)
	Placebo	3.81 (1.75)	4.58 (1.67)	4.87 (1.35)	4.71 (1.46)	4.23 (1.64)	4.60 (1.68)
Implicit emotional empathy							
All stimuli	MDMA	4.58 (1.71)	5.02 (1.90)	4.49 (1.41)	4.44 (1.13)	4.39 (1.21)	4.56 (1.26)
	Placebo	4.12 (1.60)	4.49 (1.68)	4.28 (1.37)	4.32 (1.16)	4.02 (1.21)	4.51 (1.45)
Positive stimuli	MDMA	4.95 (2.07)	5.00 (1.99)	4.50 (1.54)	4.53 (1.05)	4.26 (1.38)	4.71 (1.62)
	Placebo	4.14 (1.84)	4.58 (1.83)	4.03 (1.49)	4.10 (1.20)	3.75 (1.28)	4.47 (1.51)
Negative stimuli	MDMA	4.21 (1.79)	5.05 (1.86)	4.45 (1.56)	4.38 (1.36)	4.51 (1.52)	4.40 (1.59)
	Placebo	4.09 (1.54)	4.40 (1.61)	4.51 (1.36)	4.51 (1.34)	4.28 (1.47)	4.56 (1.58)

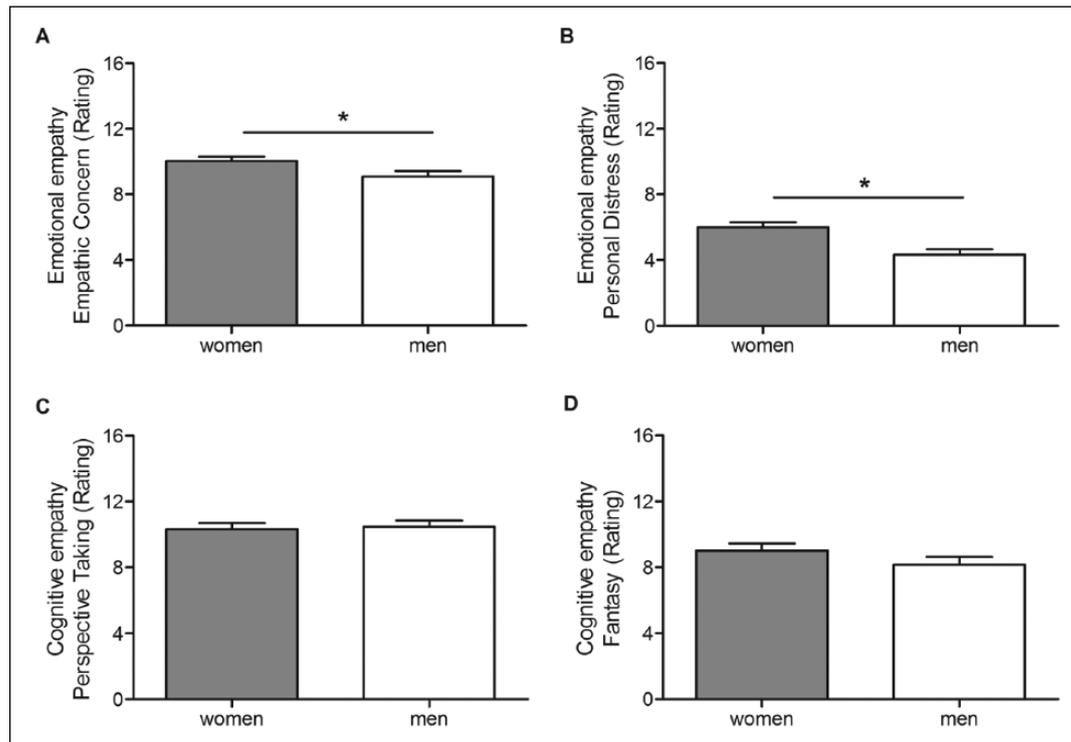
**Figure 3.** Mean (\pm SE) empathy trait ratings on emotional empathy subscales empathic concern (A) and personal distress (B) and cognitive empathy subscales perspective taking (C) and Fantasy (D) in the IRI for men and women, pooled over 6 studies; *indicates statistical sex significance at $p = 0.05$.

Table 3. Mean (\pm SD) of the IRI scores per study; PT = Perspective Taking; FS = Fantasy Scale; EC = Emotional Concern; PD = Personal Distress.

Lab site	Study number	Cognitive empathy		Emotional empathy	
		PT	FS	EC	PD
Basel	1	10.67 (2.46)	8.08 (2.39)	9.33 (2.06)	5.67 (2.19)
	2	11.50 (2.56)	9.00 (3.27)	10.19 (1.94)	5.62 (2.06)
	3	9.67 (2.83)	9.57 (2.88)	9.67 (2.17)	5.37 (1.97)
	4	10.81 (2.74)	9.31 (3.24)	9.06 (2.23)	4.81 (2.20)
Maastricht	5	10.20 (2.57)	7.85 (4.07)	9.85 (2.60)	3.85 (2.78)
	6	10.40 (2.91)	7.10 (4.41)	9.10 (2.49)	5.65 (3.13)

Table 4. Mean (\pm SD) oxytocin (%-change baseline) and MDMA blood concentrations per study.

Lab site	Study number	Oxytocin (pg/ μ L) (%-change baseline)		MDMA (ng/mL)
		MDMA	Placebo	
Basel	1	951 (1588)	62 (242)	217(59)
	2	487 (835)	56 (54)	222 (39)
	3	1354 (1428)	4 (29)	90 (35)
	4	1495 (1524)	-17 (25)	206 (52)
Maastricht	5	151 (276)	17 (34)	105 (42)
	6	140 (315)	-8 (55)	134 (69)

over studies using the same dose, two additional GLM analyses were run. The univariate GLM including the MDMA blood concentrations of the 75 mg condition revealed a main effect of Study ($F_{2,59} = 4.54; p = 0.02$; partial $\eta^2 = 0.13$); concentrations in Study 3 were significantly lower than concentrations in Study 6. There was no main effect of Sex or an interaction between Sex and Study on MDMA blood concentrations. A second univariate GLM including the MDMA blood concentrations of the studies using the 125 mg revealed a main effect of Sex ($F_{1,41} = 36.18; p < 0.001$; partial $\eta^2 = 0.47$), indicating that females had significantly higher MDMA blood concentrations compared with males. There was no main effect of Study or interaction effect between Sex and Study.

Oxytocin blood concentrations. Repeated-measures GLM analysis revealed significant main effects of Treatment ($F_{1,98} = 36.55; p < 0.001$; partial $\eta^2 = 0.27$) and Study ($F_{4,98} = 4.72; p = 0.002$; partial $\eta^2 = 0.16$) and a significant interaction ($F_{4,98} = 5.20; p = 0.001$; partial $\eta^2 = 0.18$) on the oxytocin response (oxytocin %-change baseline). MDMA caused an increase in oxytocin levels, measured between 90 and 120 min after MDMA administration, compared with placebo. There was a difference in oxytocin response between Studies 3 and 5 and Studies 4 and 5; responses in Study 3 and 4 were significantly higher compared to those in study 5. Adding Sex to the model did not change the findings; Sex did not affect the oxytocin responses, nor did it interact with Treatment. In order to study whether Treatment and Sex effects were different per dose of MDMA, two separate RM GLMs were conducted. Findings showed a main effect of Treatment on oxytocin blood concentrations for both the 75 mg dose ($F_{1,55} = 22.08; p < 0.001$) as well as the 125 mg ($F_{1,45} = 20.53; p < 0.001$) MDMA dose. There were no effects of Sex or Treatment by Sex interaction effects (Table 4).

Correlations

MET and IRI. Analyses showed low-to-moderate positive correlations between trait empathy and emotional empathy as measured by the MET in both treatment conditions, that is, MDMA and placebo. Overall, participants who rated themselves higher on cognitive and emotional empathy in daily life situations felt more concern and arousal when viewing pictures of people displaying positive and negative emotions. Trait empathy scales did not correlate with state measures of CE (Table 5).

MET and oxytocin levels. Spearman’s rho did not reveal significant correlations between oxytocin concentrations (%-baseline change) and responses on the positive or negative emotion in the MET, in the placebo and MDMA condition.

MET, MDMA blood concentrations and MDMA dose (mg/kg). Analyses showed low but significant correlations between EE for positive emotions and MDMA blood concentrations; that is, concern for positive emotions ($r_{110} = 0.26; p = 0.005$) and arousal for positive emotions ($r_{110} = 0.20; p = 0.04$) increased with increasing MDMA concentrations. MDMA blood levels did not significantly correlate with other parameters of the MET (i.e. CE for positive or negative emotions or EE for negative emotions). MDMA dose, expressed as mg MDMA per kg bodyweight, also correlated weakly with explicit EE (concern) for positive emotions ($r_{116} = 0.19; p = 0.04$).

As expected, MDMA blood concentrations and dose (mg/kg) of MDMA were strongly correlated ($r_{110} = 0.78; p < 0.001$); that is, the higher the amount of ingested MDMA per kg bodyweight, the higher the MDMA concentrations in blood. This positive correlation exists in both females ($r_{52} = 0.67; p < 0.001$) and males ($r_{63} = 0.41; p < 0.001$).

Table 5. Pearson correlations (r_{df} and p) between IRI scales and Emotional Empathy in the MET in the MDMA and placebo condition; CE = Cognitive Empathy; EE = Emotional Empathy; PT = Perspective Taking; FS = Fantasy Scale; EC = Emotional Concern; PD = Personal Distress; * indicates significance at $p = 0.05$.

Empathy Subscale	Concern	Arousal							
		Positive		Negative					
		MDMA	Placebo	MDMA	Placebo				
CE	PT	$r_{112} = 0.18; p = 0.05^*$	$r_{112} = 0.20; p = 0.04^*$	$r_{112} = -0.01; p = .93$	$r_{112} = -0.02; p = 0.79$	$r_{112} = 0.17; p = 0.07$	$r_{112} = 0.23; p = 0.01^*$	$r_{112} = 0.06; p = 0.55$	$r_{112} = 0.11; p = 0.23$
		$r_{112} = 0.29; p = 0.002^*$	$r_{112} = 0.32; p = 0.001^*$	$r_{112} = 0.16; p = 0.13^*$	$r_{112} = 0.20; p = 0.03^*$	$r_{112} = 0.29; p = 0.002^*$	$r_{112} = 0.29; p = 0.002^*$	$r_{112} = 0.30; p = 0.001^*$	$r_{112} = 0.19; p = 0.05^*$
EE	EC	$r_{112} = 0.25; p = 0.006^*$	$r_{112} = 0.34; p < 0.001^*$	$r_{112} = 0.22; p = 0.02^*$	$r_{112} = 0.30; p = 0.003^*$	$r_{112} = 0.26; p = 0.006^*$	$r_{112} = 0.26; p < 0.001^*$	$r_{112} = 0.25; p = 0.007^*$	$r_{112} = 0.36; p < 0.001^*$
		$r_{112} = 0.32; p < 0.001^*$	$r_{112} = 0.43; p < 0.001^*$	$r_{112} = 0.21; p = 0.02^*$	$r_{112} = 0.32; p = 0.001^*$	$r_{112} = 0.29; p = 0.002^*$	$r_{112} = 0.29; p = 0.002^*$	$r_{112} = 0.41; p < 0.001^*$	$r_{112} = 0.30; p = 0.001^*$
PD	PD								

MDMA and oxytocin blood concentrations. Analysis did not reveal a significant correlation between MDMA blood concentrations and oxytocin blood concentrations.

MET and IRI, and lifetime ecstasy use. Spearman's rho did not reveal significant correlations between lifetime ecstasy use (Table 1) and MET responses in the placebo and MDMA condition; that is, empathetic reactions were not associated with the number of times participants had previously used ecstasy/MDMA. Lifetime ecstasy use correlated negatively with two IRI scales, the Fantasy Scale ($r_{114} = -0.35; p < 0.001$) and Personal Distress ($r_{114} = -0.20; p = 0.03$). More experience with ecstasy use was associated with a lower ability for subjects to transpose themselves imaginatively into the feelings and actions of fictitious characters ('Fantasy') and lower feelings of personal anxiety and unease in tense interpersonal settings ('Personal Distress').

Discussion

The primary aim of the present study was to test the effect of MDMA on emotional and cognitive empathy in a large pooled sample from six studies. In addition, we aimed to assess whether the MDMA-induced empathy effect was moderated by sex, trait empathy, history of ecstasy use, and concentrations of MDMA and oxytocin in the circulation at the time of testing. We demonstrated that MDMA did not significantly influence CE in the MET, replicating the findings of the separate studies (Hysek et al., 2014a; Hysek and Liechti, 2012; Kuypers et al., 2014; Schmid et al., 2014, 2015). The scores were in the range of those found in other studies using healthy volunteers (Hurlmann et al., 2010; Thoma et al., 2011). We also demonstrated that MDMA enhanced both explicit and implicit EE, and this effect was especially evident for the positively valenced stimuli, that is, MDMA caused an increase in concern and arousal for people displaying positive emotions. This potentially reflects a mood-congruent response; individuals preferentially process emotional stimuli that are congruent with their current mood state (Mayer et al., 1995; Rusting, 1998) and this positive emotion bias could lead to more concern and arousal for people expressing alike emotions. Otherwise it could be explained as an increase in 'positive empathy', that is, the ability to share, celebrate, and enjoy others' positive emotions; a state which correlates with increased prosocial behavior, social closeness, and well-being (Morelli et al., 2015). It is worth noting that although we used a double-blind design, most participants realized which treatment they had been administered and expectations related to the MDMA effect ("I will/do feel good and more empathic now") may have influenced the behavioral task outcome. We think that it is rather unlikely that the subjective effects of MDMA can be separated from its behavioral effects in tasks such as the MET. Specifically, the low 75 mg dose produced robust subjective (mood) effects but only relative small effects on EE in the test. The MDMA-induced increase in EE was observed in men and women and at both doses. In contrast a previous study using a sub-set of the present data showed significant effects of MDMA on EE only in men (Hysek et al., 2014a) while we could now confirm this effect in both sexes using the larger sample. In the present study, the extent of arousal and concern was associated with the concentrations of MDMA in the blood as well as with the MDMA dose per kg body weight;

the higher the concentrations or doses of MDMA, the larger was the emotional response.

While Kirkpatrick and colleagues (2014a) previously showed moderate tolerance to the subjective drug effects in more experienced users (Kirkpatrick et al., 2014a), the present study did not detect a relation between lifetime ecstasy history and the behavioral effects of MDMA on the MET. Thus, MDMA appears to induce its empathogenic response repeatedly and irrespective of previous use. However, it is important to note that we did not include subjects with excessively high MDMA use as the range of previous use was 0 to 100 times. MDMA also caused an increase in circulating oxytocin. However, as previously demonstrated (Hysek et al., 2014a; Kuypers et al., 2014), MDMA-induced increases in plasma oxytocin were not related to increases in emotional responding.

In the IRI of the present study, women reported more empathic concern and personal distress in daily life situations compared with men. In the MET, women also reported more concern for the people expressing emotions in the pictures compared with men while they were not more aroused by the emotional content compared with men, as demonstrated by the lack of a sex effect on the implicit measure of EE. In other words, women report more concern for the people in the pictures and in daily life situations compared with men, although they seem physically equally aroused by the content. Although it is a general finding that females are more empathic than males, there is evidence that higher empathy levels are linked with higher potential to be aroused (Mehrabian et al., 1988). The implicit EE ('arousal') was included in the MET because it is less likely to elicit a social desirability bias; it should minimize the ability to self-reflect on a more abstract level (Dziobek et al., 2008). The discrepancy between implicit and explicit EE responses in females in the present study could reflect such a social desirability bias.

To our knowledge, all studies that tested the effects of MDMA on the MET were included in the present pooled analysis. The effects on empathy using the MET have been examined using a series of other substances including oxytocin (Hurlemann et al., 2010), LSD (Dolder et al., 2016), and alcohol (Dolder et al., 2017). Intranasal oxytocin was found to enhance EE for positive stimuli on the MET without affecting CE, similar to MDMA in the present study, but without producing subjective drug effects (Hurlemann et al., 2010). Similar to the serotonin releaser MDMA in the present study, the serotonin 5-HT_{2a} receptor agonist LSD also enhanced explicit and implicit EE for positive stimuli in the MET (Dolder et al., 2016). In contrast to MDMA, LSD impaired CE (Dolder et al., 2016). Of interest, LSD also increased oxytocin plasma levels similar to MDMA and LSD also produced MDMA-like positive mood effects in addition to its similar effects on the MET. Finally, a low dose of alcohol also increased explicit EE ratings for positive stimuli similar to MDMA, but alcohol did not alter levels of circulating oxytocin and also produced different subjective effects than MDMA (Dolder et al., 2017). Together, the findings indicate robust effects of MDMA on EE, but it appears that different substances produce similar empathy changes in the MET. It remains to be determined whether there are common neurochemical and neuroendocrine mediators of these substance-induced changes in empathy. The present study could not document any association

between circulating oxytocin and the MDMA-induced empathy response. However, oxytocin levels in plasma may not reflect levels in the brain (Neumann et al., 2013) and the absence of significant between-subject correlations (Hysek and Liechti, 2012) does not exclude a mediating role of oxytocin in the empathy response to MDMA.

There were no significant sex effects on trait or state measures of CE. There were also no significant effects of sex on oxytocin concentrations. For both empathy responses and oxytocin concentrations, these effects of sex were independent of treatments, that is, it did not moderate the MDMA effect on oxytocin concentrations in blood or EE. Thus, despite the higher blood concentrations in women in the 125 mg condition compared with the 75 mg condition and men, this did not translate into a difference in behavioral response. Previous studies found stronger positive and especially negative subjective responses to MDMA in women than men at doses adjusted for body weight (Allott and Redman, 2007; Liechti et al., 2001). It is therefore of interest to note that with regard to the empathic response similarly strong effects are observed in men and women despite the higher mg/kg MDMA doses used in women.

The present study has several limitations. The pooling of data from six different studies is attractive in terms of study power but revealed inconsistencies in the data. For example, the time of administration of the MET was consistently 180 min after the 125 mg dose but varied (90–120 min) after the 75 mg dose. MDMA concentrations were measured in different laboratories and at slightly different time points in relation to the MET. We also only report concentrations prior to the task and not the full pharmacokinetic profiles because this has been done elsewhere in detail (Hysek et al., 2012b, 2014a, 2014b; Schmid et al., 2014, 2016). In addition, the studies administered other tasks and participants may have been exposed to other demanding tasks before the MET in some studies but not in others. Study instructions may have differed slightly between studies. While this did not affect the main study outcome, it may have confounded the correlational findings, that is, the association between MDMA concentration and its effect on the MET. Oxytocin levels were also determined differently and the MDMA effect on absolute but also the %-change baseline oxytocin levels varied significantly between studies, indicating procedural differences or more generally non-reliable determinations of oxytocin. While this again did not affect the robust finding of increased oxytocin levels after MDMA compared with placebo, the association between oxytocin levels and the MET is likely affected. In contrast, it was a strength of the study that equal or similar numbers of male and female participants were included in the sub-studies, largely excluding confounding of sex differences by sub-study. On the other hand, interpretation of the presence or absence of sex differences in the effects of MDMA in the present study needs to account for the higher mg MDMA per body weight in women compared with men in the study. Because MDMA concentration and mg/kg dose were associated with greater empathy it is possible that a sex difference (greater effect in men) was masked by the greater dose of MDMA given to women.

In summary, the present pooled data analysis showed that MDMA effects on EE are stable across labs and doses. It also showed that sex does not play a moderating role in the MDMA-induced effects on EE.

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