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Social Cognition and Interaction in Chronic Users of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy")

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Abstract

Background: The empathogen 3,4-methylenedioxymethamphetamine (MDMA) is the prototypical prosocial club drug inducing emotional openness to others. It has recently been shown that acutely applied 3,4-MDMA in fact enhances emotional empathy and prosocial behavior, while it simultaneously decreases cognitive empathy. However, the long-term effects of 3,4-MDMA use on socio-cognitive functions and social interactions have not been investigated yet. Therefore, we examined emotional and cognitive empathy, social decision-making, and oxytocin plasma levels in chronic 3,4-MDMA users.
Methods: We tested 38 regular but recently abstinent 3,4-MDMA users and 56 3,4-MDMA-naïve controls with the Movie for the Assessment of Social Cognition, the Multifaceted Empathy Test, and the Distribution Game and the Dictator Game. Drug use was objectively quantified by 6-month hair analyses. Furthermore, oxytocin plasma levels were determined in smaller subgroups (24 3,4-MDMA users, 9 controls).
Results: 3,4-MDMA users showed superior cognitive empathy compared with controls in the Multifaceted Empathy Test (Cohen's $d = .39$) and in the Movie for the Assessment of Social Cognition ($d = .50$), but they did not differ from controls in emotional empathy. Moreover, 3,4-MDMA users acted less self-serving in the Distribution Game. However, within 3,4-MDMA users, multiple regression analyses showed that higher 3,4-MDMA concentrations in hair were associated with lower cognitive empathy ($\beta_{MDMA} = -.34$, $t = -2.12$, $P < .05$). Oxytocin plasma concentrations did not significantly differ between both groups.
Conclusions: We conclude that people with high cognitive empathy abilities and pronounced social motivations might be more prone to 3,4-MDMA consumption. In contrast, long-term 3,4-MDMA use might nevertheless have a detrimental effect on cognitive empathy capacity.

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Significance Statement

Humans show increased empathy under the acute influence of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Even in animals, increased prosocial behavior was observed after MDMA application. These prosocial effects of MDMA have been proposed to be mediated by an increased oxytocin release. Given that chronic administration of MDMA leads to a long-lasting depletion of oxytocin in animal models, it was predicted that MDMA has a detrimental effect on the oxytocin system and consequently on social cognition also in human users. This study therefore investigated the chronic effect of MDMA on social cognition and oxytocin in human users. We observed superior cognitive empathy and more prosocial behavior in MDMA users compared with MDMA-naïve controls. However, higher MDMA hair concentrations were associated with worse cognitive empathy. We concluded that relatively pure MDMA users are a specific group of socially high-performing drug users but that heavy MDMA consumption might lead to decreased cognitive empathy.

Keywords: entactogen, empathogen, 2C-B, MDEA, MDA

Introduction

With an estimated 19.4 million past-year users, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") remains one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2016). MDMA is a synthetic substituted amphetamine derivate that blocks and reverses monoamine transporters leading to a rapid release of serotonin (5-HT) and noradrenalin and to a lesser extend dopamine (Rudnick and Wall, 1992; Kalant, 2001). As its main positive subjective effects are enhanced empathy, increased prosocial feelings, and a general sense of well-being, MDMA is regarded as the prototypical prosocial club drug (Vollenweider et al., 1998; Kamilar-Britt and Bedi, 2015). Consequently, in an international survey on drug users, MDMA was ranked highest in the condition of sociability (Morgan et al., 2013).

In animals, the acute effects of MDMA on social behavior have been researched extensively, whereby "adjacent lying" and "friendly following" were consistently reported to be increased in rats (Ando et al., 2006; Thompson et al., 2009). Together with decreased aggression and elevated social reward, literature consistently suggests a prosocial effect profile of MDMA in rodents (Kamilar-Britt and Bedi, 2015). Recently, social cognition has been broadly investigated in MDMA-challenge studies conducted on healthy human volunteers mostly focusing on measures of empathy. The concept of empathy has frequently been conceptualized as entailing cognitive and emotional components. Cognitive empathy, which comprises inferring or discriminating emotions of others together with Theory-of-Mind (ToM), which additionally implicates the ability to deduce the perspective of others, describes the ability to decode and understand another person's mental state (Baron-Cohen and Wheelwright, 2004; Blair, 2005) on a mere cognitive level without considering the person's emotional response. On the other side, emotional empathy is defined as the compassion or the empathizing with the emotions of others (Blair, 2005).

Regarding cognitive empathy, acute MDMA intake has repeatedly been shown to reduce the identification of negative emotional stimuli (Bedi et al., 2010; Hysek et al., 2012, 2014a, 2014b; Kirkpatrick et al., 2014) and one study additionally found an increased recognition of positive emotional stimuli (Hysek et al., 2012). These valence-dependent acute MDMA effects were—to our knowledge—exclusively found in the Face Emotion Recognition Task (Bedi et al., 2010; Hysek et al., 2014b) and the Reading the Mind in the Eyes Test (Hysek et al., 2012). In 2 other well-established social cognition tasks, namely the Movie for the Assessment of Social Cognition (MASC) and the Multifaceted Empathy Test (MET), cognitive empathy performance was not affected by acute MDMA intake (Kuypers et al., 2017). By contrast, emotional empathy ratings— driven by enhanced responses to emotionally positively charged stimuli—was shown to be increased in the MET under the acute influence of MDMA (Hysek et al., 2014b; Schmid et al., 2014). In summary, research on empathy performance suggests that acute MDMA intake decreases cognitive empathy but enhances emotional empathy (Kamilar-Britt and Bedi, 2015), even though these findings are limited to specific tasks. Interestingly, these acute prosocial effects of MDMA have been linked to central oxytocin (OXT) release, as several studies have found dose-dependent increases in blood plasma OXT levels right after MDMA administration (Wolff et al., 2006; Dumont et al., 2009; Hysek et al., 2012; Schmid et al., 2014). This increase in plasma OXT levels was shown to correlate with increased prosocial feelings in humans (Dumont et al., 2009).

Interestingly, no study has investigated social cognition in abstinent, long-term MDMA users to date. Thus, we measured cognitive and emotional empathy of relatively pure MDMA users and drug-naïve healthy controls with the MASC and the MET. To measure social decision-making, we additionally applied the Distribution Game and the Dictator Game (Charness and Rabin, 2002; Engelmann and Strobel, 2004). Given that acutely applied MDMA increases plasma levels of OXT (Dumont et al., 2009; Hysek et al., 2012) and that a former animal study documented lasting depletion of brain OXT after long-term MDMA administration (van Nieuwenhuijzen et al., 2010), we additionally investigated blood plasma OXT levels in a subsample of our participants. Finally, as a special feature of our study, we objectively determined drug use through quantitative hair analyses for several reasons. First, MDMA users often co-use other drugs (Schifano et al., 1998; Curran, 2000), and previous MDMA research has been criticized for measuring drug consumption only via self-reports (Cole, 2014). Second, drug users might be motivated to give a biased self-report or simply over- or underestimate their own consumption because of consistently shown memory alterations (Magura and Kang, 1996; Quednow et al., 2006; Wunderli et al., 2017).

Because MDMA has been shown to impair OXT neurotransmission in rats when given chronically (van Nieuwenhuijzen et al., 2010) and because OXT and emotional empathy seem to be functionally linked (Thompson et al., 2007; Kirkpatrick et al., 2014), we hypothesized that chronic MDMA users show a deficit in emotional empathy and display lowered plasma levels of OXT. Alternatively, such deficits could also be preexistent given that

the main motivator for MDMA use is to enhance prosocial feelings like feeling closer to other people (Morgan et al., 2013) and to increase emotional empathy (Hysek et al., 2014b). Thus, recreational MDMA users might compensate (or self-medicate) a deficit in emotional empathy and lower OXT levels by their drug intake. Lastly, we expected higher MDMA use to be associated with lower cognitive empathy, as it was shown by an inverse correlation between lifetime MDMA use and Reading the Mind in the Eyes Test performance in one of our previous studies (Preller et al., 2014).

Methods

Participants

Within the context of the Zurich Cocaine Cognition Study (ZuCo²St) (Vonmoos et al., 2013b; Quednow, 2016), we recruited 53 long-term MDMA users and 56 MDMA-naïve healthy controls by means of online media and flyer advertisements. Candidates underwent a standardized telephone screening to assess their study eligibility prior to testing. All tested participants were aged between 18 and 60 years and had sufficient German language skills. We included only MDMA users whose self-reported drug use was confirmed by hair analyses and whose MDMA hair concentration values exceeded their cocaine and amphetamine concentrations—the most common concomitant drugs in our sample. Primary stimulant users with only a co-consumption of MDMA were thus excluded, as stimulants have been shown to strongly affect social cognition (Quednow, 2017). Furthermore, because of deficient/missing hair samples, 2 MDMA users were excluded. Following this procedure, 38 participants were identified as MDMA-preferring users and included in the analyses (see supplementary Table 1 for detailed hair analyses). The MDMA group was matched with 56 MDMA-naïve healthy controls for age, sex, verbal intelligence, years of education, depression scores, and weekly cannabis consumption (Table 1).

Inclusion criteria for the drug using group were MDMA as the primary drug, MDMA use of at least 100 standard doses (one MDMA standard dose corresponds to 100 mg crystalline MDMA or one ecstasy pill) or weekly consumption during the last year (>50 occasions), and a current abstinence period of <6 months. Exclusion criteria for the MDMA groups were any acute or previous Axis-I DSM-IV adult psychiatric disorders with the exception of MDMA, alcohol, and nicotine abuse and a history of depression (acute major depression was excluded). The general exclusion criteria encompassed current or previous neurological disorders or head injuries, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, the use of any medication affecting the central nervous system, and a lifetime history of opioid use. Additionally, all participants who reported daily (or more frequent) cannabis consumption were excluded. Controls were also excluded if they fulfilled the diagnostic criteria for any Axis-I DSM-IV psychiatric disorder, including any form of substance use disorder (except nicotine and cannabis) or any other current or previous regular illegal drug use.

All participants were asked to abstain from illegal substances for at least 3 days and from alcohol for at least 24 hours prior to testing. Drug urine screenings were employed to control for compliance with the abstinence period (Table 1). The study was approved by the Cantonal Ethics Committee of Zurich. All participants gave written informed consent and were compensated for their participation. Both MDMA users and MDMA-naïve healthy controls were already published in Wunderli et al. (2017); however, polydrug users with hair concentrations of stimulants (e.g., cocaine and amphetamine) exceeding the values of MDMA were excluded from the present analysis. Moreover, the present MDMA user sample did not overlap with the samples of previous publications from the ZuCo²St, including cocaine users and stimulant-naïve controls (e.g., Preller et al., 2013, 2014; Vonmoos et al., 2013b; Hulka et al., 2014). However, about 75% of the present control group has been reported in these previous publications, but all participants from the ZuCo²St and the present study were investigated with the same procedure in the same environment and by the same study team.

Assessment Measures

Clinical Assessment

Trained psychologists conducted the Structured Clinical Interview for Axis-I DSM-IV disorders. Depressive symptoms were assessed with the Beck Depression Inventory (Beck et al., 1961), because depression might impact social cognition (Schreiter et al., 2013) and ADHD symptoms with the ADHD Self-Rating Scale (ADHD-SR) corresponding to DSM-IV criteria (Rosler et al., 2004) given that ADHD and drug use were shown to mutually amplify ToM deficits (Wunderli et al., 2016). Premorbid verbal intelligence (verbal IQ) was estimated with a German vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest) (Lehrl et al., 1995). To assess the personality structure of our sample, we further applied the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) and the Temperament Character Inventory (TCI) (Cloninger, 1994).

Drug Use Assessment

Self-reported drug use was assessed with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). In addition, to objectively quantify the severity of participants' drug use during the past months, hair samples were taken from the posterior vertex region of the head to determine the concentration of 17 common drugs and their metabolites by liquid chromatography-tandem mass spectroscopy. To exclude acute intoxication at testing sessions, urine drug screenings were employed by semiquantitative enzyme multiplied immunoassays (for technical details, see supplementary Methods 1).

Assessment of Empathy and Social Decision-Making

MET

The MET is a computer-based test that consists of 40 pictures of people in emotionally charged situations (Dziobek et al., 2008). Based on the idea that empathy is a multidimensional construct consisting of cognitive and emotional empathy (Davis, 1983), the MET requires the participant to deduce the mental state of the depicted person by choosing which of 4 words best describes the person's mental state (cognitive empathy) and to indicate his/her empathic concern (explicit emotional empathy) and arousing rate (implicit emotional empathy) on a rating scale (1–9). To avoid multiple testing, we combined (summed up) the implicit and explicit emotional empathy measures (for both negative and positive stimuli) from the MET to an overall emotional empathy score (Table 2).

MASC

The MASC was developed with the aim to operationalize social cognition as close to real life as possible and therefore consists of a 15-minute video that shows 4 characters spending an

Table 1. Demographic Data and Drug Use (Means and SDs)

	Controls	MDMA Users	Value	P	df
n	56	38			
Age, y	25.8 (6.1)	25.9 (6.2)	-0.09	.93	92
Years of school education	11.0 (1.6)	10.4 (1.9)	1.7	.10	92
Verbal intelligence	103.9 (8.2)	102.7 (8.3)	0.70	.48	92
BDI score	3.5 (3.8)	4.2 (4.4)	-0.73	.47	92
Sex (f/m)	26/30, 46.5 % f	18/20, 47.5% f	0.01	.93	1
Tobacco					
Smoking status (y/n)[a]	41/15, 73.2% y	30/8, 78.9% y	0.40	.53	1
Cigarettes per day[a]	7.3 (10.1)	7.2 (8.7)	0.01	.99	92
Years of use	6.0 (6.6)	5.3 (5.5)	0.60	.55	92
Alcohol					
Status (y/n)[a]	55/1, 98.2% y	38/0, 100.0% y	0.69	.41	1
Grams per week[a]	117.9 (132.0)	151.1 (121.9)	-1.2	.22	92
Years of use	8.7 (6.5)	6.3 (6.1)	1.8	.07	92
Cannabis					
Status (y/n)[a]	30/26, 53.5% y	29/9, 76.3% y	5.0	**.03**	1
Grams per week[a]	0.44 (1.0)	0.60 (1.1)	-0.67	.51	92
Years of use	3.3 (3.7)	4.7 (5)	-1.6	.11	92
Cumulative dose (grams)	195.7 (504.6)	606.8 (1061)	-2.5	**.01**	92
Positive urine testing (n/y)[b]	48/7, 12,5% y	31/7, 18,4% y	0.57	.45	1
Last consumption (days)	23.1 (32.9), n = 30	17.5 (32.9), n = 29	0.43	.51	57
MDMA					
Status (y/n)[a]	0/56, 0.00% y	38/0, 100.0% y	94.0	**<.001**	1
Tablets per week[a,c]	0.00 (0.00)	0.90 (0.80)	-	-	-
Years of use	0.00 (0.00)	6.7 (6.1)	-	-	-
Cumulative dose (grams)	0.10 (0.40)	229.3 (277.2)	-6.2	**<.001**	92
Last consumption (days)	-	25.1 (20.9), n = 38	-	-	-
Positive urine testing (y/n)[b]	0/56, 0.00% y	0/38, 0.00% y	-	-	-
Hair analysis pg/mg	0.00 (0.00)	4705 (8521)	-	-	-
Amphetamine					
Status (y/n)[a]	0/56, 0.00% y	22/16, 57.9% y	42.3	**<.001**	1
Grams per week[a]	0.00 (0.00)	0.03 (0.05)	-	-	-
Years of use	0.00 (0.00)	1.9 (2.9)	-	-	-
Last consumption (days)	-	29.7 (33.8), n = 22	-	-	-
Cumulative dose (grams)	0.01 (0.03)	26.5 (107.3)	7.4	.07	92
Positive urine testing (y/n)[b]	0/56, 0.00% y	0/38, 0.00% y	-	-	-
Hair analysis pg/mg[e]	0.00 (0.00)	192.3 (689.5)	-	-	-
Cocaine					
Status (y/n)[a]	0/56, 0.00% y	20/18, 52,6% y	37.4	**<.001**	1
Grams per week[a]	0.00 (0.00)	0.11 (0.28)	-	-	-
Years of use	0.00 (0.00)	2.3 (3.6)	-	-	-
Last consumption (days)	-	29.3 (35.3), n = 20	-	-	-
Cumulative dose (grams)	0.02 (0.05)	52.3 (150.6)	21.3	**.01**	92
Positive urine testing (y/n)[b]	0/55, 0.00% y	1/37, 0.03% y	1.5	.23	1
Hair analysis pg/mg	0.00 (0.00)	578.8 (1344)	-	-	-

BDI, Beck's Depression Inventory.
Significant *P* values are shown in bold. Statistical tests: independent *t* tests for quantitative data, $\chi 2$ tests for frequency data. Consumption per week, duration of use, and cumulative dose are averages within the total group. Last consumption is an average only for persons who reported to have used the drug within the past 6 months. In this case, sample size (n) is shown. One urine sample (control), the ADHD-SR data for one participant (MDMA user), the years of scool education for one particant (MDMA user), and the duration of MDMA use for one participant were missing.
[a]During the past 6 months.
[b]For cutoffs, see supplementary Methods 1.
[c]In 100-mg tablets.

evening together. The video stops 45 times and questions about the characters' feelings, thoughts, and intentions are asked (Dziobek et al., 2006). For each question, 4 different answers are presented, whereof one answer represents the correct answer. The wrong answers represent 3 different mistakes: (1) instead of mentalizing, the subject explained the situation by physical causation (no ToM), (2) the subject undermentalized (less ToM), and (3) the subject overmentalized (too much ToM). The correct number of answers is the main outcome measure of the MASC. Additionally, we built the cognitive empathy domain score (CES) by averaging the MET cognitive empathy score and the MASC sum score after they were z-transformed on the means and SDs of the control group to a combined measure of cognitive empathy.

Table 2. Emotional and Cognitive Empathy (Means and SEs)

	Controls	MDMA Users	F	*df, dferr*	*P_group*	*p_IQ*	*p_sex*	*p_group_x_sex*
n	56	38						
MASC								
MASC sum correct[a]	34.8 (0.43)	36.4 (0.53)	6.0	1, 89	**.02**	.11	.81	.26
MASC sum no TOM	1.9 (0.23)	1.3 (0.28)	2.5	1, 89	.12	.34	.60	.33
MASC sum less TOM	3.3 (0.28)	3.4 (0.35)	0.03	1, 89	.87	.46	.30	.98
MASC sum too much TOM	5.1 (0.30)	3.9 (0.36)	6.2	1, 89	**.01**	.36	.08	.36
MET								
Emotional Empathy Sum Score (EES)	10.7 (0.31)	10.2 (0.37)	1.2	1, 88	.27	.93	**.006**	.35
EES over positive pictures	10.3 (0.37)	9.6 (0.45)	1.6	1, 88	.21	.44	**.04**	.24
EES over negative pictures	11.1 (0.31)	10.8 (0.37)	0.52	1, 88	.47	.46	**.003**	.65
Cognitive empathy sum score[a]	23.8 (0.48)	25.3 (0.57)	3.8	1, 88	**.05**	**.001**	.38	.52
CE over positive pictures	12.5 (0.31)	13.6 (0.37)	5.6	1, 88	**.02**	**.002**	.23	**.05**
CE over negative pictures	11.4 (0.36)	11.7 (0.43)	0.35	1, 88	.56	.09	.88	.39

CE, cognitive empathy, MASC, Movie for the assessement of social cognition, MET, Mulftifacetet empathy test.
Significant *P* values are shown in bold. Statistical test: 2-way ANCOVA with the factors group and sex and the covariate verbal IQ.
[a]Used for the cognitive empathy domain score.

Distribution Game and Dictator Game

The Distribution Game and Dictator Game have been described in detail before (Hulka et al., 2014). Notably, in these 2 monetary distribution games, the participants actually had the chance to gain real money (0.25 Swiss francs per 1 point). In brief, the Distribution Game involves 2 players. The participant, every time in the position of player A, is requested to choose 1 of 10 possible point distributions. In the first distribution, both players receive the same amount of 25 points, which represents the only completely fair distribution. In the most unfair distribution, player A receives 40 points (Payoff A) and player B only one point (Payoff B).

The Dictator Game, which always followed the Distribution Game, involved the same 2 players, whereby player A was asked to distribute 50 points among himself (Payoff A) and player B (Payoff B). In accordance with a previously published paper from the ZuCo²St (Hulka et al., 2014), we z-transformed the measures of the Distribution and Dictator Game on the means and SD of the control group and equally integrated them into the composite Payoff A and Payoff B scores.

For both games, we analyzed Payoff A as the main dependent variable.

Assessment of Blood Plasma OXT Levels

The blood was collected in 5-mL BD Vacutainer K2EDTA tubes (Vacutainer Systems, Becton Dickinson) and immediately mounted on ice. Right after blood collection, the samples were centrifuged at 4000 rpm for 10 minutes at 4°C to separate the plasma. After pipetting the plasma, it was stored at -80°C until it was analyzed according to procedures employed in previous studies (Neumann et al., 2013; Bosch et al., 2015).

Statistical Analysis

We performed the statistical analyses with SPSS 23.0 for Windows. Quantitative data were either analyzed by means of Student's *t* tests (only demographic data), Mann-Whitney tests, or 2-way ANCOVA. Frequency data were analyzed by means of Pearson's chi-square tests. We used an alpha level of .05 for all statistical tests. In the ANCOVAs applied to compare empathy between MDMA users and controls, we introduced group and sex as fixed factors, and verbal IQ as a covariate, because it was consistently shown that men are less empathic that women (Fukushima and Hiraki, 2006; Knickmeyer et al., 2006; Singer et al., 2006; Rueckert and Naybar, 2008) and because verbal IQ has been proposed to be linked to empathy measures before (Lawrence et al., 2004). Analyzing social decision-making with ANCOVAs, sex was used as a second covariate to verbal IQ given that age is correlated with prosocial behavior (Hulka et al., 2014). We investigated the association between clinical measures and empathy and the association between plasma OXT values and empathy within MDMA users with correlation analyses (Pearson's product-moment and Spearman's rank correlation, respectively) whereby we applied a significance threshold of $P < .01$ to avoid alpha error accumulation. To be able to assess the strength of group differences and their practical significance between controls and MDMA users, Cohen's *d* effect sizes were calculated based on the means and pooled SDs of the 2 groups (Cohen, 1988).

To analyze potential cofactors of cognitive empathy, we regressed the CES on the demographic variables age, sex, years of education, and verbal IQ (forced entry) over all participants and over MDMA users only. To analyze drug effects (within MDMA users) on cognitive empathy, we regressed CES on the MDMA hair analyses while retaining those demographic variables in the model that were significantly associated with CES. Because our MDMA user group showed, although minimal, co-consumption of other drugs, we additionally added amphetamine and cocaine hair analyses together with self-reported measures of cannabis, alcohol, and nicotine consumption into the model according to previously published investigations of MDMA users (Wunderli et al., 2017). Because some of the drug use variables displayed a right-skewed distribution, we log-transformed ($\log_{10}$) these data after adding the constant 1 to those variables that included 0 values.

Based on a posthoc power analysis (after participant's drug use was confirmed by hair analyses) with G*Power 3.1.9.2 (Faul et al., 2007), the main effects of the ANCOVAs in this study have an alpha-error probability of 5% and a power of 80% (assumed 6% variance explained by special effect, 24% variance explained by the covariates, and 70% error variance). The power analysis for our regression model investigating MDMA's effect on cognitive empathy within MDMA users revealed a power of 80% (one-tailed, assumed 13% variance explained by predictor, 12% by verbal IQ and 75% residual variance) (Shamay-Tsoory et al., 2004; Toussaint and Webb, 2005).

Results

Demographic Characteristics and Drug Use

As intended by the application of our matching procedure, the groups did not differ significantly in sex distribution, age, verbal IQ, years of education, and depression scores (Table 1). For objective drug-use measures, the median hair drug concentration for the MDMA users (n = 38) was 2116 pg/mg and the middle 50% of hair analyses fell between 881 and 3530 pg/mg, whereas none of the controls had MDMA in their hair.

Moreover, 26 of the 38 investigated MDMA users showed only minimal amphetamine and cocaine hair concentrations below the commonly accepted cutoff values (Society of Hair, 2004) of 200 and 500 pg/mg, respectively (supplementary Table 1). The remaining 12 MDMA users displayed amphetamine and/or cocaine hair concentrations above the mentioned cutoff values, but in each case also showed considerably higher MDMA hair concentrations. Therefore, we included all 38 (preferred) MDMA users to increase the power of our analyses (for detailed hair analyses of all MDMA users, see supplementary Table 1). For self-reported cannabis parameters, MDMA users did not differ from controls for weekly cannabis use during the past half-year, duration of use, duration since last consumption, and in the amount of positive urine analyses. However, MDMA users reported a larger lifetime dose of cannabis. Finally, MDMA users did not differ from controls in any tobacco or alcohol use measures.

Social Cognition

For cognitive empathy, 2-way ANCOVAs revealed a significant main effect of group on the CES ($d = .62$) (Figure 1). Both measures constituting the CES also differed between groups, the MASC sum score ($d = .50$) and the MET sum score ($d = .39$), indicating a better cognitive empathy performance of MDMA users compared with drug-naïve controls (Table 2). These group differences were driven by a superior emotion identification of the MDMA users for emotionally positively charged pictures in the MET ($d = .47$) and a reduced tendency to overmentalize (overinterpreted perspective-taking) in the MASC ($d = .51$). A significant group*sex interaction was not found for the MASC sum score, the cognitive empathy performance in the MET, or the CES (Table 2).

Regarding emotional empathy (MET), no significant group and group*sex interaction effects occurred ($P > .24$). However, the factor sex showed a significant impact. As expected, women showed higher emotional empathy ratings ($d = .58$) for positively ($d = .43$) as well as negatively charged pictures ($d = .63$) (Table 2; Figure 2).

Social Decision-Making

Averaged across the Distribution Game and the Dictator Game, MDMA users (mean combined Payoff A = 63.2 ± 13.5 SD) exhibited less self-serving behavior than controls (67.9 ± 14.0) as indicated by a significant difference in the combined score Payoff A ($F(1,90) = 3.99$, $P < .05$, $d = .41$). The effect was mainly driven by the Distribution Game, in which MDMA users acted less self-serving ($d = .56$) (Figure 3). Accordingly, in this game, 53% of the MDMA users chose the only fair point distribution (50:50 for player A and B) as opposed to 25% of the controls ($\chi^2 = 7.50$, $p = .006$, $\varphi = .28$).

Clinical Measures

MDMA users reported significantly more ADHD symptoms than controls ($d = .66$) (Table 3). In the BIS-11, the MDMA users displayed higher trait impulsivity (total score) compared with controls ($d = .53$). Likewise, significant main group effects were found for the subscales attentional impulsiveness ($d = .41$) and non-planning impulsiveness ($d = .47$). In the TCI, MDMA users differed from controls in novelty seeking (NS) scores ($d = .57$), driven by the subscore disorderliness (NS4) ($d = .52$) (Table 3). Correlation analyses showed that severity of ADHD symptoms correlated significantly with BIS-11 attentional impulsiveness but not with TCI NS and NS4 scores. Finally, the BIS-11 total score was robustly correlated with TCI NS score (supplementary Table 2).

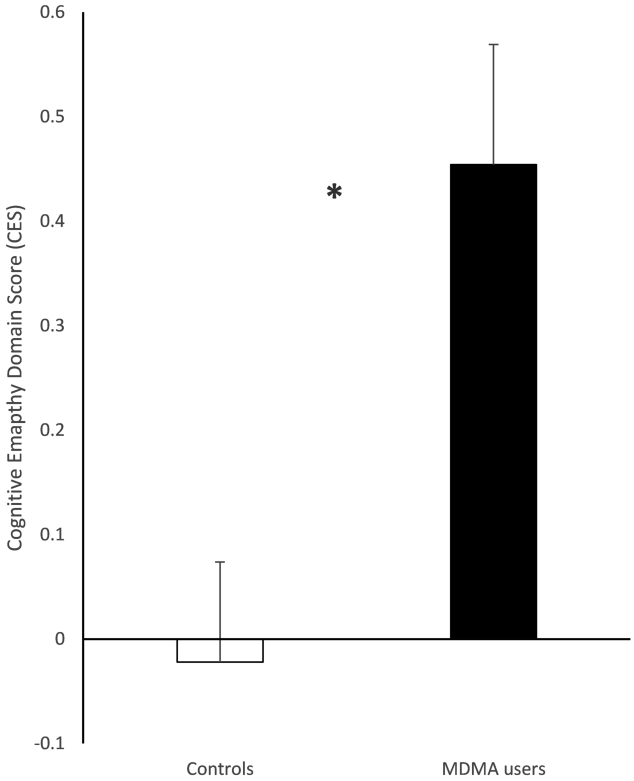

Figure 1. Differences in a combined cognitive empathy score between controls (n = 56) and 3,4-methylenedioxymethamphetamine (MDMA) users (n = 37). Estimated means and SEs of the cognitive empathy domain score (CES). *$P < .05$.

Regression Models

To analyze potential cofactors on cognitive empathy, we regressed the CES on demographic variables (age, sex, years of education, and verbal IQ). This analysis over all participants (n = 94) revealed significance for the verbal IQ coefficient ($\beta = .344$, $t = 3.31$, $P < .001$) only (supplementary Table 3). In a second step, we additionally introduced a grouping variable (MDMA users vs controls) into the model. This grouping variable significantly predicted cognitive empathy ($\beta = .301$, $t = 3.11$, $P < .01$). The amount of explained variance (corrected) increased significantly ($P < .01$) from 9% in the model without the grouping variable to 17% in the model with the grouping variable ($R^2_{corr} = 0.17$, $F_{5,87} = 4.70$, $P < .001$).

Within MDMA users (n = 38), again, verbal IQ was the only demographic variable significantly associated with cognitive empathy ($\beta = .408$, $t = 2.33$, $P < .05$). To analyze the effect of MDMA on cognitive empathy, we therefore regressed the CES on the MDMA hair analysis and the verbal IQ score. Interestingly, of the 2 predictors, only higher MDMA hair concentration significantly

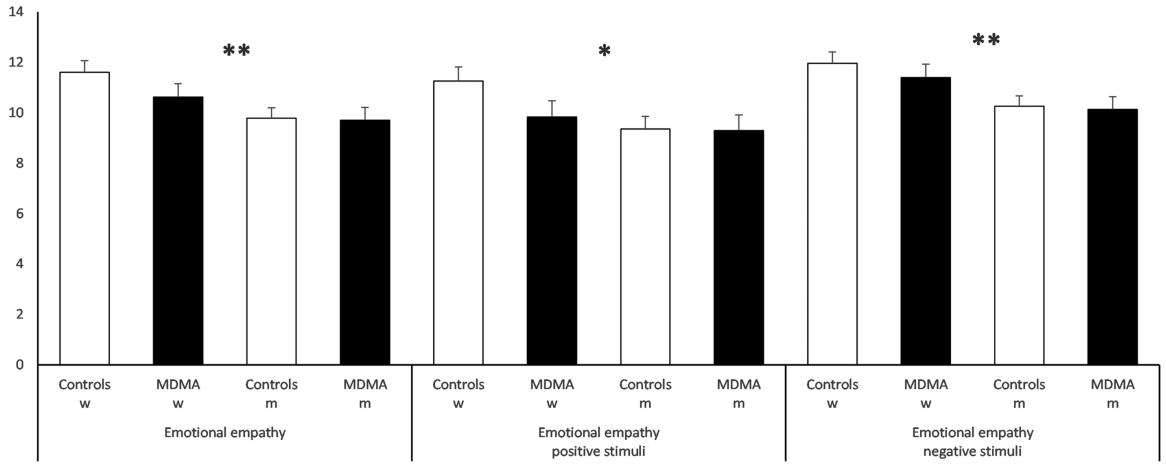

Figure 2. Differences in emotional empathy between women (n = 43) and men (n = 50). Estimated means and SEs of emotional empathy ratings for all emotionally charged pictures, emotionally positively charged pictures, and emotionally negatively charged pictures. *P < .05, **P < .01.

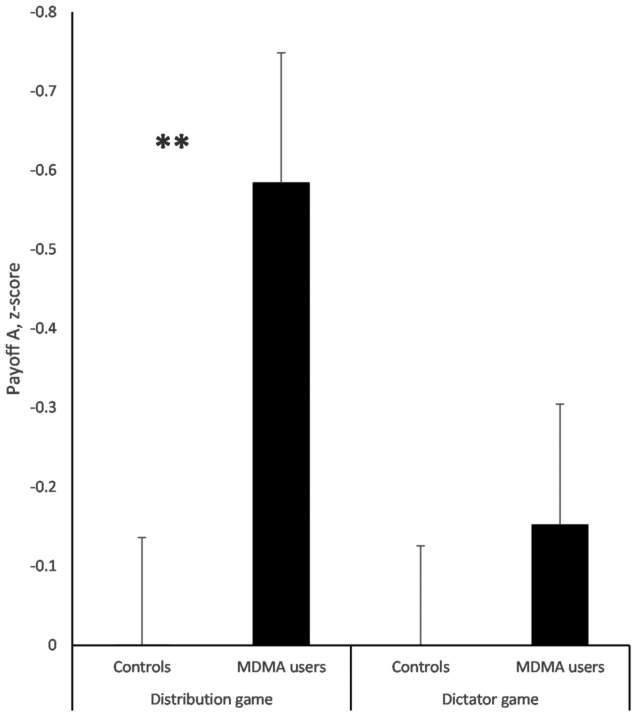

Figure 3. Differences in self-serving behavior between controls (n = 56) and 3,4-methylenedioxymethamphetamine (MDMA) users (n = 38). Estimated means and SEs of the z-transformed payoff A (points participants gave to themselves) in the Distribution game and the Dictator game. **P < .01.

predicted lower cognitive empathy (β = -.324, t = -2.13, $P < .05$) (Figure 4; supplementary Table 4). Consequently, we excluded verbal IQ in a second step. The change in F was nonsignificant ($P = .09$). In a third step, we added amphetamine and cocaine hair concentration values, self-reported lifetime cannabis consumption (in grams), as well as the duration of alcohol and nicotine consumption into the model. Because no objective measures were available for cannabis, alcohol, and nicotine consumption, self-reported variables were used to operationalize the influence of these substances. Importantly, the amount of explained variance did not increase ($P = .60$) by adding these drugs into the model, and none of the coefficients predicted cognitive empathy except for MDMA ($P < .05$). In conclusion, group differences in cognitive empathy cannot be explained, for example, by the co-use of stimulants of the MDMA users. Finally, MDMA hair concentration predicted neither emotional empathy nor prosocial behavior in MDMA users (β = .194, t = .947, $P = .35$ and β = .251, t = 1.008, $P = .32$, respectively).

Oxytocin and Empathy

Blood plasma OXT levels were available for 9 controls and 24 MDMA users only. A Mann-Whitney test indicated no group difference in blood plasma OXT levels between controls (median = 13.56 pg/mL) and MDMA users (median = 18.29 pg/mL), even though MDMA users unexpectedly showed moderately higher levels (U = 139.0, $P = .22$, $d = .42$) (Figure 5). Within the MDMA users, blood plasma OXT levels did not correlate significantly with any MDMA use parameters. Moreover, women's OXT levels were ranked higher than those of men ($r_s = -.35$, $P < .05$). Finally, in accordance with the gender effects on both emotional empathy and OXT plasma concentrations, we found that higher OXT levels were positively correlated with higher emotional empathy ($r_s = .44$, $P < .03$) in MDMA users.

Discussion

The aim of the study was to investigate empathy and social decision-making in objectively verified long-term MDMA users taking this drug as their main drug of choice. Detailed psychiatric diagnostics, hair toxicology, and matching were used to minimize the influence of psychiatric comorbidities and polydrug use. We showed that MDMA users display superior cognitive empathy compared with MDMA- and stimulant-naïve healthy controls on one hand but that within MDMA users, increased MDMA hair contamination is associated with a decrease in cognitive empathy on the other hand. Additionally, MDMA users acted more pro-social than controls in the social decision-making tasks. Finally, the OXT system is likely not affected after long-term MDMA consumption, as peripheral OXY plasma levels were not significantly changed even though moderately elevated (d = 0.42). In sum, these data suggest that recreational long-term MDMA users do not compensate for emotional empathy deficits by consuming MDMA (as no deficit was found), but rather show better cognitive empathy and pronounced prosocial behavior.

Table 3. Clinical Measures

	Controls	MDMA	*F*	*df, dferr*	*P*
n	56	38			
ADHD self-report rating scale (ADHD-SR)					
ADHD-SR sum score	7.7 (0.8)	12.0 (1.0)	10.7	1, 88	**.001**
Barratt Impulsiveness Scale (BIS-11)					
BIS-11 total score	62.0 (1.2)	66.8 (1.4)	6.5	1,89	**.01**
FI attentional impulsiveness	14.3 (0.4)	15.6 (0.5)	4.0	1,89	**.05**
FII motor impulsiveness	21.9 (0.5)	23.2 (0.6)	2.9	1,89	.09
FIII nonplanning impulsiveness	25.9 (0.6)	28.0 (0.7)	4.8	1,89	**.03**
Temperament and Character Inventory					
Self-directedness	33.8 (0.77)	32.4 (0.93)	1.4	1, 88	.24
Cooperativeness	33.5 (0.69)	32.2 (0.83)	1.4	1, 88	.23
Self-transcendence	10.8 (0.82)	12.1 (0.98)	0.92	1, 88	.34
Harm avoidance	12.8 (0.76)	11.2 (0.91)	2.0	1, 88	.16
Reward dependence	17.1 (0.48)	15.9 (0.58)	2.6	1, 88	.11
Persistence	4.0 (0.28)	3.2 (0.33)	3.3	1, 88	.07
Novelty seeking total score (NS)	22.3 (0.69)	25.4 (0.83)	7.8	1, 88	**.007**
NS1 exploratory excitability	7.8 (0.27)	8.5 (0.32)	2.6	1, 88	.11
NS2 impulsiveness	4.4 (0.32)	5.3 (0.38)	2.7	1, 88	.11
NS3 extravagance	5.7 (0.27)	6.3 (0.32)	1.7	1, 88	.20
NS4 disorderliness	4.3 (0.25)	5.3 (0.3)	6.3	1, 88	**.01**

Estimated means and SEs. 2-way ANCOVA (verbal IQ score as covariate, group, and sex as factors). The ADHD-SR data for one participant (MDMA user) are missing. Significant *P* values are shown in bold.

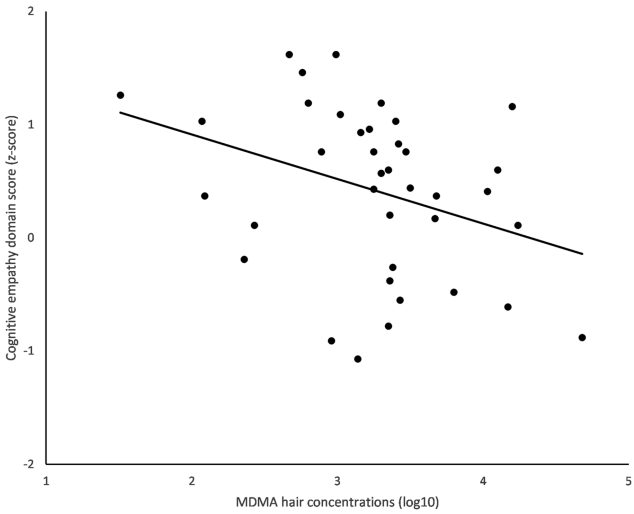

Figure 4. Regression of cognitive empathy on 3,4-methylenedioxymethamphetamine (MDMA) hair concentrations (pg/mg). Regression of the CES z-score on the MDMA hair concentrations (log_{10}) of the MDMA users (n = 38), $r(36) = -.34$, $P < .05$, 2-way. Higher hair values were associated with lower cognitive empathy.

In line with previous studies investigating MDMA and stimulant users in general (Morgan, 1998; Butler and Montgomery, 2004; Vonmoos et al., 2014), our sample of main MDMA users showed increased trait impulsivity (BIS-11) together with higher novelty seeking scores (TCI) compared with drug-naïve controls. This characterizes our sample of MDMA users as a typical recreational drug user sample as proposed before (Rounsaville, 2004; Vonmoos et al., 2013a; Maier et al., 2015). However, our sample of MDMA users might be special given that it encompasses 26 relatively pure and stimulant-free MDMA users (Table 1). Thus, our findings of a superior cognitive empathy and prosocial behavior in MDMA users might be valid only for relatively pure MDMA users and not for the more typical type of polydrug MDMA users (Schifano et al., 1998). Moreover, cognitive empathy and prosocial behavior were not correlated with ADHD symptoms, impulsivity, and novelty seeking (supplementary Table 2). Thus, our finding of superior cognitive empathy and prosocial behavior cannot be explained by elevated impulsivity and novelty-seeking in MDMA users. Interestingly, the higher cognitive empathy of the MDMA users in this study were mainly driven by a superior identification of positive emotions in the MET compared with controls. Therefore, one might conclude that either MDMA chronically induces a "positivity bias" with regard to cognitive empathy or that people with a predisposed emotional "positivity bias" prefer MDMA as a recreational drug. In line with our findings, Hysek et al. (2012) showed that MDMA acutely enhances the ability to interpret stimuli with positive emotional valence correctly. Moreover, also the emotional empathy for positive stimuli is increased acutely (Hysek et al., 2014b). Thus, the valence of emotional stimuli is of critical importance when considering acute and chronic effects of MDMA on measures of empathy.

Using the same test battery, we have previously shown that relatively pure recreational and addicted cocaine users show impaired cognitive empathy (Hulka et al., 2013) and emotional empathy (Preller et al., 2014), which stands in strong contrast to the findings in MDMA users presented here. Hence, although their personality traits (impulsivity and novelty seeking) resemble those of stimulant users, the group of relatively pure MDMA users seems to be a unique group of socially high-performing drug users. This notion is further supported by our results regarding social decision-making as MDMA users, which, contrary to cocaine users (Hulka et al., 2014), acted more prosocial in the neuroeconomic games compared with controls. If this increased prosocial behavior of the MDMA users is a preexisting trait or rather a consequence of regular MDMA consumption cannot be explained by a cross-sectional study as the present one. Nevertheless, it seems plausible that repeated experiencing of interpersonal closeness leads to more prosocial behavior. Moreover, together with emotional empathy (empathic concern for others), cognitive empathy (mental and emotional perspective-taking) has previously been shown to correlate with affiliation motivation (Hill, 1987). More specifically, the underlying

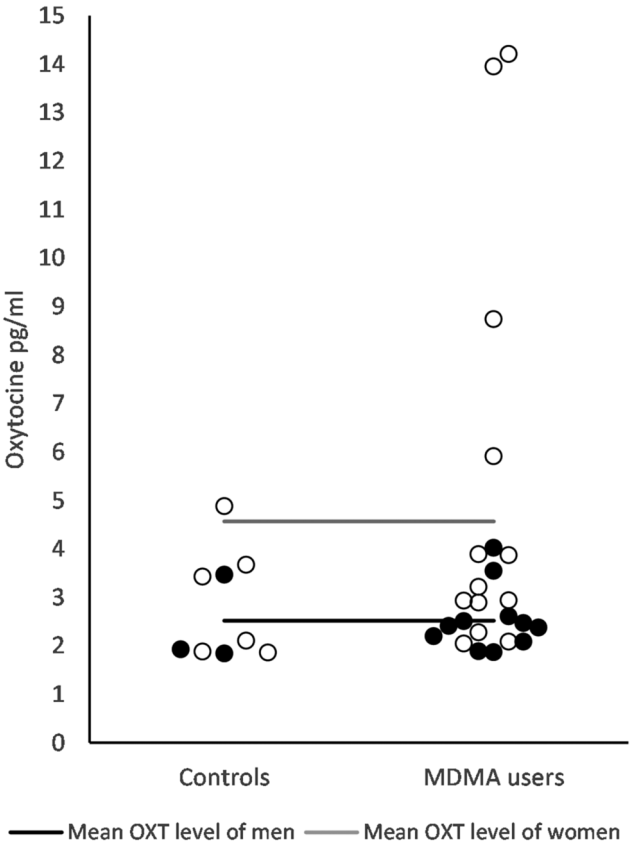

Figure 5. Mean peripheral blood plasma oxytocin (OXT) levels (pg/mL) of controls (n = 9) and 3,4-methylenedioxymethamphetamine (MDMA) users (n = 24). Groups did not differ signifianctly ($P > .05$, $d = .42$). Circles represent female and dots represent male participants.

dimensions of positive stimulation, the tendency to receive gratification from harmonious relationships and from a sense of communion (Hill, 1987), correlated highest with cognitive empathy. Thus, it seems likely that MDMA users display high affiliation motivation and that they use MDMA in social environments to satisfy this need for affiliation by MDMA's acute effect of enhanced emotional empathy (Hysek et al., 2014b).

The results of the regression analysis for demographic variables emphasize our finding of superior cognitive empathy in MDMA users in 2 ways: first, the group contrast remains significant, even when the variables age and years of school education are held constant in addition to verbal IQ and sex. Second, almost one-half of the explained variance in cognitive empathy is explained by the group contrast. Notably, within MDMA users, our regression model was most efficient when only the hair toxicology analysis of MDMA was entered into the model, indicating a possible detrimental chronic effect of MDMA on social cognition as it was predicted from animal studies before (Boot et al., 2000; McGregor et al., 2008; van Nieuwenhuijzen et al., 2010). We are aware that causal interpretations of drug effects derived from a cross-sectional investigation are speculative. Nevertheless, the present results are in line with earlier studies from our group showing dose-dependent impairment of executive functions in MDMA users (Quednow et al., 2006, 2007). In fact, cognitive empathy has been shown to correlate with executive functioning before (Eslinger et al., 2011) and in our sample, a domain score of executive functions, according to Vonmoos et al. (2013b) and Wunderli et al. (2016), was positively correlated with the MASC sum score ($r(92) = .227$, $P < .05$). Additionally, low recall consistency, as a measure for executive functioning, has been correlated with decreased glucose metabolism in the right dorsolateral prefrontal cortex in MDMA users in a recent PET study (Bosch et al., 2013). Given that adaptations in serotonin transporter density (McCann et al., 1998; Kish et al., 2010) as well as $5HT_{2A}$ receptor density (Reneman et al., 2002) in the prefrontal cortex have been reported in MDMA users, changes in the prefrontal 5HT system might be responsible for the demonstrated decrease in cognitive empathy that went along with increased MDMA hair concentrations. Finally, it would be interesting to investigate cognitive empathy in an MDMA user sample in a longitudinal study in which premorbid cognitive empathy scores are gathered and empathy scores together with sustained drug use are measured over time to answer the question if the changes shown here are predisposed or MDMA-induced.

This study has some limitations. First, the common practice to measure drug use by means of self-reported drug assessments has been criticized before (Cole, 2014). Therefore, we objectively quantified our participants' drug use via hair toxicology analyses but still had to rely on self-reports for alcohol, nicotine, and cannabis consumption. Being aware of this problem, we aimed to minimize the influence of these drugs by matching the groups accordingly. Second, we cannot rule out that the superior cognitive empathy of MDMA users is in fact a consequence at least of light or moderate MDMA consumption. Likewise, the implicated detrimental effect of MDMA on cognitive empathy is based only on the correlation between past drug use (hair analyses) across the last 3 to 6 months and current cognitive empathy. We therefore suggest that future research investigates this relationship in a longitudinal study. Third, our sample comprises 26 stimulant-free, pure MDMA users and might therefore not be generalizable to the prototypical recreational polydrug MDMA user. Fourth, our exploratory investigation of blood plasma OXT is based on a rather small sample size (n = 24 users vs n = 9 controls). Moreover, peripheral OXT levels might not reflect the status of the neural OXY system (Kagerbauer et al., 2013). Therefore, the possibility of a long-term MDMA consumption effect on neural OXT systems still cannot be ruled out. We suggest that blood plasma OXT values of long-term MDMA users are compared with MDMA-naïve controls in a bigger sample in which sex is distributed evenly between groups. Moreover, an OXY receptor radioligand should be developed to investigate the status of the cerebral OXY system in human MDMA users by positron emission tomography.

Taken together, our data suggest that primary MDMA users show personality traits comparable with recreational stimulant users, but in contrast to those show superior cognitive empathy and more pro-social behavior than drug-naïve, healthy controls. Primary MDMA users might therefore be described as socially high performing drug users. However, because severe chronic MDMA consumption seems to have a toxic effect on cognitive empathy, we suggest that the superior cognitive empathy of MDMA users is not a consequence of MDMA use, but rather a predisposition for it. We conclude that main MDMA users do not consume MDMA to compensate for emotional empathy deficits but are more prone to MDMA consumption because of pronounced cognitive empathy likely going along with high affiliation motivation.

Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* online.

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Statement of interest

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