Original Paper

Greater empathy in MDMA users

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Abstract

Background: 3,4-Methylenedioxymethamphetamine (MDMA) is widely known for its positive acute effects on social behaviour, such as increasing empathy, whilst also attenuating the negative impact of social exclusion. However there is a scarcity of research that investigates the long-term impact of recreational MDMA use on these fundamental social processes.

Method: Sixty-seven individuals were split into three groups based on their drug-use history: poly-drug MDMA users ($n=25$), poly-drug users who do not use MDMA ($n=19$), alcohol-only users ($n=23$), and were tested in an independent groups design. Participants completed both a self-report measure of emotional and cognitive empathy, along with the Multifaceted Empathy Task – a computerised assessment of empathy – and the Cyberball Game – a social exclusion paradigm.

Results: MDMA users had significantly greater subjective emotional empathy, and greater cognitive empathy on the computer task compared with the poly-drug users who do not use MDMA. There were no significant differences in subjective responses to social exclusion between the groups. Indices of MDMA use did not correlate with empathy.

Conclusions: Long-term MDMA users in this sample exhibited normal psychosocial functioning in regard to empathy and social pain and had higher subjective emotional empathy. This conflicts with previous suggestions that moderate, long-term MDMA use may cause heightened social distress, and is further evidence of the safety of the drug, which is relevant to considerations of its therapeutic use.

Keywords
MDMA, ecstasy, empathy, social pain, social cognition

Introduction

3,4-Methylenedioxymethamphetamine (MDMA) has recently been approved for Phase III clinical trials of post-traumatic stress disorder (PTSD), based on evidence from several studies that it improves clinical outcomes in PTSD when given as an adjunct to psychotherapy (Mithoefer et al., 2018; Oehen et al., 2013). When used alongside psychotherapy, MDMA has been suggested to enable patients to address painful emotions and memories without experiencing an overwhelming emotional response, which can help facilitate recovery (Feduccia and Mithoefer, 2018). Amongst recreational drug users, MDMA is used for its capacity to enhance social functioning (Heifets and Malenka, 2016). Investigative studies looking at the acute effects of MDMA on social cognition have reported heightened levels of compassion (Kamboj et al., 2015), trust (Dolder et al., 2018a; Stewart et al., 2014), generosity (Kirkpatrick et al., 2015), and empathy (Hysek et al., 2014a; Kuypers et al., 2014, 2017), mirroring the effects reported by recreational users (Peroutka et al., 1988; Siegel, 1986). In addition to augmenting prosocial processes, MDMA can also reduce the perception of negative emotions (Dolder et al., 2018a; Hysek et al., 2012, 2014a, 2014b), lessen responses to negative social events by acutely reducing responses to social threat (Bedi et al., 2009; Wardle and de Wit, 2014), and alleviate the impact of social exclusion i.e. 'social pain' (Frye et al., 2014). These effects of MDMA in boosting prosocial processes whilst reducing the experience of social pain have highlighted the therapeutic potential of this psychoactive substance.

Both empathy and the experience of social pain are key social processes that have been investigated under the acute influence of MDMA. The two are connected; as empathy for others is affected by socially painful events (DeWall and Baumeister, 2006), and impairments in the ability to empathise can lead to social difficulties (Krull et al., 2018). Several acute drug studies have found that MDMA can increase empathy (Hysek et al., 2014a; Kuypers et al., 2014, 2017; Schmid et al., 2014), with particular enhancements to the emotional component (experiencing the emotional state of others) more so than the cognitive component (understanding the perspective of others). Cognitive empathy has been likened to 'theory of mind', and encompasses the ability to transpose oneself into the perspective of others and to accurately identify their emotional state (Baron-Cohen and Wheelwright, 2004; Blair, 2005). Meanwhile emotional empathy has been likened to sympathy and emotional contagion, signifying to the ability to spontaneously experience the emotions of others (Blair, 2005; Nummenmaa et al., 2008). MDMA has also been found to reduce the drop in mood and self-esteem experienced after being socially excluded during the Cyberball Game (Frye et al., 2014). Social exclusion is considered one facet of the experience of social pain.

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Following an acute dose MDMA elicits serotonin, dopamine and noradrenaline release, but its actions at the 5-HT transporter, along with its induction of the release of hormones like oxytocin, are thought to be responsible for the drug's prosocial effects (Francis et al., 2016; Hysek et al., 2014a; Thompson et al., 2007; van Wel et al., 2012; Vizeli and Liechti, 2018). The exact role of oxytocin on the prosocial effects of MDMA is less clear, however, as some studies have found it to be unrelated to empathy (Kuypers et al., 2017). It is well-known that, in the short term, MDMA impacts upon the serotonergic system, and preclinical and neuroimaging studies have suggested that a 40–70% reduction in the density of the 5-HT transporter may occur with chronic MDMA use (Roberts et al., 2016). Though recent work has indicated that these effects may be more modest: imaging studies have generally recruited exceptionally heavy MDMA users in order to maximise the likelihood of detecting an effect (individuals that consume 720% more MDMA than the average user) (Szigeti et al., 2018). These exceptionally large levels do not necessarily reflect what is used by recreational users on the whole, where serotonergic depletion may not be so extreme (Szigeti et al., 2018). Moreover, it is unknown whether pre-existing group differences or a reversible neuroadaptation account for the reduction in density of 5-HT transporter markers seen in chronic MDMA users. Increasing serotonergic activity via agonists and selective serotonin reuptake inhibitors have shown positive effects on social functioning and empathy (Crockett et al., 2010; Dolder et al., 2016; Preller et al., 2016), and concurrently blocking 5-HT activity using a serotonin antagonist has shown to obstruct the prosocial effects of MDMA in animals (Morley et al., 2005). Since serotonin may be involved in the empathogenic effects of MDMA, serotonergic depletion over long-term use may plausibly have a downstream effect on empathy and other social processes; however, this may only be the case in extreme users.

To our knowledge, only one human study has investigated this potential link. This study investigated processes of empathy among chronic MDMA users and reported heightened cognitive empathy in this group, thus indicating an increased ability to discriminate the emotional states of others (otherwise known as theory of mind) (Wunderli et al., 2018). However, this increased cognitive ability was only present in lower-level users, and in fact cognitive empathy appeared to deteriorate with heavier use. Alongside empathy, empirical research into whether chronic use of MDMA affects the experience of social pain has not been conducted – despite concerns that prolonged use of this drug could heighten levels of social distress (Parrott, 2007). However, the acute effects of MDMA on empathy and openness are thought to help the extinction of traumatic memories as well as overall engagement during psychotherapy, and it is hoped that this will promote long-term changes in reducing distress (Bedi, 2018). Thus, given the recent developments in the therapeutic use of the drug, it is important for researchers to fully characterise the acute and chronic effects of MDMA in order to facilitate informed clinical use of this novel treatment.

The current study thus aimed to investigate whether repeated use of MDMA was associated with any changes to social functioning. The study specifically looked at empathy and responses to socially painful events, due to their clinical relevance, and a low level of repeated MDMA use was targeted to map more closely on likely therapeutic use. We aimed to recruit a poly-drug using group who did not use MDMA, to control for differences between illicit-drug users and non-drug users. In this study we use the term 'MDMA' to refer to street MDMA (otherwise known as ecstasy), which is generally taken in powder or crystal form and referred to by users as MDMA. However, we understand that street MDMA can vary in purity and quantity compared with pharmaceutical MDMA given in acute studies. In line with evidence of serotonergic dysfunction from earlier studies of MDMA, it was hypothesised that chronic MDMA use would reduce empathic processes and heighten sensitivity to social pain, compared with non-MDMA poly-drug users and alcohol-only users. However, given recent findings (Wunderli et al., 2018) and suggestions from recent reviews (Bedi, 2018), it may also be possible that empathy increases and there is a reduction in social pain with repeated MDMA use.

Method

Design and participants

The current study used an independent groups design; we examined differences between three groups (MDMA poly-drug users; non-MDMA poly-drug users; alcohol-only users). All three groups completed all study procedures.

Seventy-five participants (25 male; 50 female) between the ages of 18 and 43 (M=21.41, SD= 3.27) were recruited from a community sample via advertisements on posters and word of mouth, along with snowball sampling. The study was advertised as looking at the long-term effects of drug and alcohol use on social perception, and thus participants were not aware the study was specifically investigating MDMA use, empathy, or social pain. To be included in the MDMA group, individuals were required to have used MDMA at least once a month for the past 10 months, and/or more than 10 times in their lifetime. To be in the poly-drug using condition participants were required to have used any illicit substance excluding MDMA at least once a month for the past 10 months, and/or more than 10 times in their lifetime. All participants were asked to abstain from drugs and alcohol for 24 hours prior to study participation. Exclusion criteria were having autism spectrum disorder, a neurological disorder, a severe mental health problem (schizophrenia, bipolar disorder, etc.). Individuals with mild depression and anxiety (assessed by asking whether participants had previously sought treatment) were not excluded from the study. One participant was removed from this and all subsequent analyses on empathy indices due to the subsequent discovery that they had Asperger's syndrome. The study was approved by the institutional ethics committee and written valid informed consent was received from all participants.

Measures

The Multifaceted Empathy Test (MET) (Dziobek et al., 2008). This is a computerised task that measures and discriminates between both cognitive and emotional empathy. The task involved showing participants 40 photographs of people with emotionally charged expressions, which were given in eight blocks each consisting of 10 pictures. In four of these blocks, participants were required to identify the correct mental state of the subject in each scene by picking one from a choice of four emotion labels (cognitive empathy). In the other four blocks, participants were asked to rate how much they empathised with the individual in each scene on a nine-point Likert scale (1 = not at all; 9 = very

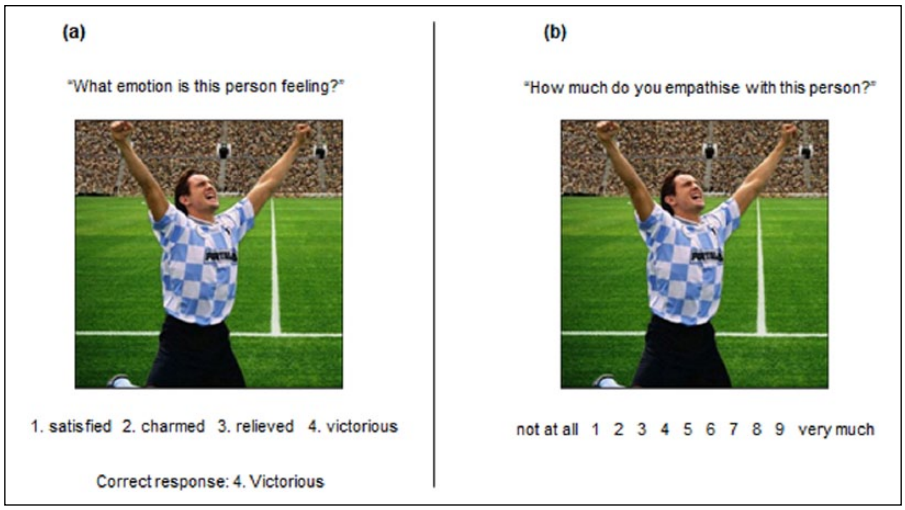

Figure 1. Conditions assessing either cognitive or emotional empathy in the MET: (a) for assessing cognitive empathy, participants were required to pick one of four emotion labels; (b) for assessing emotional empathy, participants were asked to rate how much they empathised with the subject in the photo. Image reproduced from Dziobek I, Rogers K, Fleck S, et al. (2008) Dissociation of cognitive and emotional empathy in adults with asperger syndrome using the multifaceted empathy test (MET). *J Autism Dev Disord* 38: 464–473 with permission.

much) (emotional empathy) before being presented with the next trial, i.e. the task is self-paced. An example of both block types is shown in Figure 1. The task lasted approximately 15 minutes.

The Cyberball Game (Williams et al., 2012). This is a computerised game that uses ball tosses between the participant and fictitious virtual players, and has been reliably shown to simulate the experience of social rejection. Participants were told that they were playing with two other participants on a virtual network in a mental visualisation experiment. Unbeknown to them, the two other players were not real and were programmed to socially exclude them. There were two conditions (inclusion status) that simulated either social inclusion or social exclusion. Conditions were counterbalanced between participants, and each condition included a block of two games that lasted approximately 3 minutes each. There were 30 ball throws for each game, and participants received exactly one-third (10 ±1 of 30) of all ball throws during the inclusion condition, and only one-sixth (5 ±1 of 30) of all ball throws in the exclusion condition. The task took approximately 15 minutes to complete, and responses were recorded via affective measures taken between each game (described below).

Post-Ostracism Cyberball Questionnaire (POCQ) (Williams et al., 2002). This 25-item scale was used to assess positive and negative affect, belongingness, self-esteem, control, meaningful existence, anger, and hurt feelings. Responses were recorded on a five-point Likert scale (1 = not at all; 5 = very much). It also incorporated three manipulation checks to ensure participants identified whether they had been included or excluded (for Cronbach's α s, see Supplemental material (SM); SM1).

Questionnaires

Interpersonal Reactivity Index (IRI) (Davis, 1980). This 28-item scale assesses trait empathy, and differentiates between subjective emotional and cognitive empathy. Emotional empathy is characterised by subscales 'empathic concern' and 'personal distress', which respectively refer to the ability to feel sympathy and concern towards another individual's emotional state (other-oriented), and the preoccupation by one's own feelings of distress and anxiety upon seeing other's distress (self-oriented). Cognitive empathy is characterised by the subscales 'perspective taking' and 'fantasy', which respectively refer to the ability to understand the point of view of others, and the ability to imagine the mental states of fictional characters (such as in books or movies). Responses were recorded on a five-point Likert scale (A = does not describe me well; E = describes me very well) (for Cronbach's α s, see SM1).

Drug and alcohol use history. In an interview, participants were asked about their drug-use history by going through each substance and asking whether it had been used in the past and, if yes, when they last used it, whether it was used regularly, and amount used in a typical session. Participants also gave information about their drug use over the past two weeks by answering for each day, 1) if any substances were used and what these were, and 2) the amount of these substances used per session. Participants who met the criteria for the chronic MDMA user group were asked further questions about their MDMA use.

Testing took place during the day in a testing laboratory at the University of Exeter, and the test took approximately 1 hour. Figure 2 gives a timeline of the testing in the current study.

On arrival, participants read the participant information sheet and provided written informed consent. They then completed both the subjective questionnaire (IRI) and computerised task (MET) that measured empathy. Upon completion of these measures, participants played the Cyberball Game, where affective measures (POCQ) were taken following each individual game. Once all computer tasks and associated measures were completed, participants provided an extensive history of their licit and illicit drug use.

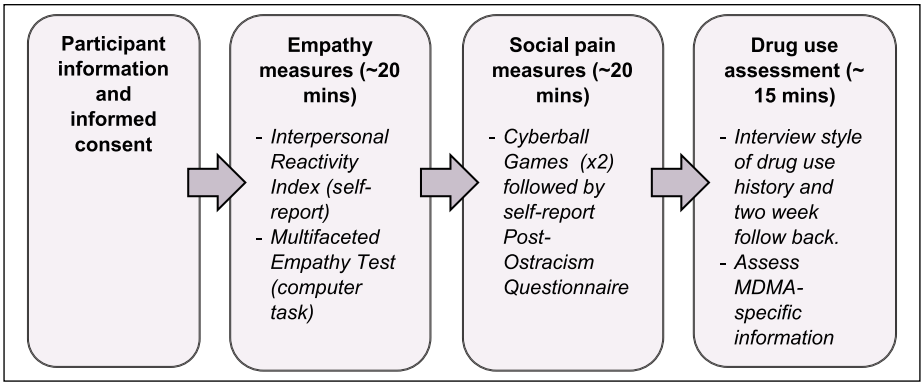

Figure 2. Study timeline.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 23. Data were checked for outliers, homogeneity of variance, skewness and kurtosis. Assumptions of normality were tested using the Shapiro–Wilk test and histogram plots.

Group differences in both cognitive and emotional empathy using the subjective questionnaire (IRI) and a computerised task (MET) were assessed using a one-way ANOVA, with group (MDMA users; non-MDMA drug users; alcohol-only users) as the between-subjects variable. For the IRI, all four subscales (empathic concern, personal distress, perspective taking, fantasy scale) were assessed independently. For the MET, cognitive empathy was calculated by summing the total of correct responses participants made when identifying emotions, whilst emotional empathy was calculated as the mean overall score of empathy ratings over the emotional images. For the Cyberball paradigm, group differences in the dependent variables were assessed using mixed measures ANOVA, with group as the between-subjects variable, and inclusion status (inclusion game, exclusion game) as the within-subjects variable. Chi-squared tests were used to assess dichotomous, categorical dependent variables. Where data was found to be non-normally distributed, transformations were applied, namely the Kruskal–Wallis test. Pearson's correlations were used to assess exploratory relationships between key psychological variables and drug use, and all post hoc tests were amended for multiple comparisons using Holm–Bonferroni corrections.

Results

Demographics and drug use (Table 1)

The three groups were matched in age, gender, years in education, and history of substance use problems. There was a trend to suggest there may be a group difference in history of mental health problems, with the MDMA poly-drug user group appearing to have a higher prevalence of historical treatment for mental health problems, but this did not reach the threshold for significance. Drug-use history and recent use (in the two weeks prior to testing) were also assessed between the two groups (Table 1), where information regarding the number of years that each substance has been used for, the number of days each substance (licit and illicit) is used per month, the amount of the substance that is used per session, the number of individuals that have used each substance in the last two weeks, and the total amount of units used in the last two weeks is reported. There were minor reports of MDMA use in the non-MDMA poly-drug user group; however there were no recent reports of MDMA use except for one isolated occasion 14 days prior to testing. The number of individuals who have used the substance is reported alongside regular use for each substance, which was calculated as the number of individuals who had used that substance for over a year and used it within the year. A chi-squared test was used to assess group differences in regular use and significance values were adjusted for multiple comparisons using Holm–Bonferroni corrections.

Empathy

Subjective empathy (Interpersonal Reactivity Index; IRI). For emotional empathy, there was a significant group difference in empathic concern ($F(2,64) = 6.42$, $p = .003$, $\eta^2 = .17$), where Holm–Bonferroni corrected *t*-tests revealed MDMA users scored significantly higher than the non-MDMA drug users ($t(42) = 3.54$, $p = .004$, $\eta^2 = 0.23$) (Figure 3), but not significantly different from the alcohol-only users ($t(46) = 2.19$, $p = .066$, $\eta^2 = 0.09$). There were no differences between non-MDMA drug- and alcohol-only users ($t(40) = 1.46$, $p = .152$, $\eta^2 = 0.05$). On the personal distress subscale, there were no significant group differences ($F(2,64) = 1.74$, $p = .185$, $\eta^2 = .05$).

For cognitive empathy, there was a trend to suggest a significant group differences on the subscales of fantasy ($F(2,64) = 3.06$, $p = .054$, $\eta^2 = .09$). There were no significant group differences in perspective taking ($F(2,64) = 1.06$, $p = .352$, $\eta^2 = .03$) (Figure 3).

Computerised task (Multifaceted Empathy Test; MET). When looking at cognitive empathy, there was a significant difference in group ($F(2,64) = 3.69$, $p = .031$, $\eta^2 = .10$). Holm–Bonferroni corrected *t*-tests revealed that the MDMA user group scored significantly higher than the non-MDMA user group ($t(42) = 2.85$, $p = .028$, $\eta^2 = .16$) but no differently to the alcohol-only group ($t(46) = 1.39$, $p = .342$, $\eta^2 = .04$), and there were no differences

Table 1. Demographic information, drug-use history and recent drug use between the three groups (*M* and SDs).

	MDMA poly-drug users ($n=25$)	Non-MDMA poly-drug users ($n=19$)	Alcohol users only ($n=23$)	F or χ^2	p-value
Age	21.3 (1.6)	21.1 (2.9)	20.8 (1.3)	0.38	.684
Gender (male, female)	12,13	5,14	5,18	4.26	.119
Years in education	16.0 (1.8)	16.5 (1.0)	16.6 (1.1)	1.06	.351
History of mental health problems (n=yes)	8	1	3	5.38	.068
History of substance use problems (n=yes)	1	0	0	2.90	.574
Alcohol (n = used, n = regular)	**25, 23**	**19, 17**	**23, 21**	0.09	1.00
Years used	6.7 (0.46)	6.1 (0.67)	5.7 (0.50)		
Days per month	10.6 (0.96)	9.0 (1.2)	7.3 (0.85)		
Units per session	12.1 (0.98)	10.7 (0.84)	10.1 (1.0)		
Used in past two weeks (n =yes, units)	25, 52.2 (27.4)	18, 23.0 (32.5)[a]	22, 33.0 (40.9)[a]		
MDMA (n = used, n = regular)	**25, 23[b]**	**13, 0**	**5, 0**	65.0	<.001***
Years used	3.1 (0.35)	1.0 (n/a)[a]	0.0		
Days per month	2.0 (0.31)	1.0 (1.8)	0.0		
Units per session	0.5 (0.25)[a]	0.5 (0.67)[a]	0.0		
Used in past two weeks (n= yes, units)	10, 0.2 (0.40)[a]	1, 0.5 (0.00)	0.0		
Tobacco (n = used, n = regular)	**24, 20**	**18, 6**	**10, 0**	32.9	<.001***
Years used	5.5 (3.0)[a]	5.5 (4.0)[a]	3.5 (0.50)		
Days per month	21.5 (27.0)[a]	9.0 (11.0)[a]	3.0 (22.8)[a]		
Units per session	2.0 (3.0)[a]	2.0 (1.8)[a]	1.0 (2.5)[a]		
Used in past two weeks (n=yes, units)	8, 34.5 (73.5)[a]	5, 30.0 (81.5)[a]	0.0		
Cannabis (n = used, n = regular)	**23, 15**	**18, 3**	**8, 0**	23.61	<.001***
Years used	4.8 (0.44)	2.8 (0.86)	0.0		
Days per month	3.5 (10.3)[a]	1.0 (2.0)[a]	0.0		
Units per session	0.5 (0.75)[a]	0.37 (0.08)[a]	0.0		
Used in past two weeks (n=yes, units)	12, 0.5 (2.0)[a]	1, 0.2 (0.0)	0.0		
Cocaine (n = used, n = regular)	**22, 4**	**11, 3**	**2, 0**	4.09	.518
Years used	1.8 (0.37)	1.0 (0.00)	0.0		
Days per month	2.0 (5.0)[a]	1.0 (3.0)[a]	0.0		
Units per session	0.58 (0.10)	0.51 (0.11)	0.0		
Used in past two weeks (n=yes, units)	3, 0.25 (n/a)[a]	2, 0.63, (n/a)[a]	0.0		
Ketamine (n = used, n = regular)	**15, 5**	**5, 0**	**0, 0**	9.08	.066
Years used	1.0 (3.0)[a]	n/a	0.0		
Days per month	2.0 (3.0)[a]	1.0 (2.5)[a]	0.0		
Units per session	0.25 (0.29)[a]	0.25 (n/a)[a]	0.0		
Used in past two weeks (n=yes, units)	4, 0.45 (45.0)[a]	3, 0.25 (n/a)[a]	0.0		
Amphetamines (n = used, n = regular)	**8, 1**	**1, 0**	**0, 0**	1.71	1.00
Years used	2.5 (2.5)[a]	0.0	0.0		
Days per month	4.0 (n/a)[a]	0.0	0.0		
Units per session	0.33 (3.6)[a]	0.0	0.0		
Used in past two weeks (n=yes, units)	1, 4.5 (0.0)	0.0	0.0		
Benzodiazepines (n = used, n = regular)	**6, 1**	**0, 0**	**0, 0**	1.71	1.00
Years used	1.5 (n/a)[a]	0.0	0.0		
Days per month	n/a	0.0	0.0		
Units per session	0.2 (n/a)[a]	0.0	0.0		
Used in past two weeks (n=yes, units)	1, 1.5 (0.0)	0.0	0.0		

(Continued)

Table 1. (Continued)

	MDMA poly-drug users ($n=25$)	Non-MDMA poly-drug users ($n=19$)	Alcohol users only ($n=23$)	F or χ^2	p-value
Hallucinogens (n = used, n = regular)	**17, 5**	**4, 1**	**2, 0**	6.32	.210
Years used	2.1 (0.42)	2.5 (1.5)	0.0		
Days per month	0.50 (n/a)	1.0 (n/a)	0.0		
Used in past two weeks (n = yes, units)	0.0	0.0	0.0		

Note. Units used are as follows: grams for MDMA, cannabis, cocaine and ketamine; units for alcohol; number of cigarettes for tobacco. Units for hallucinogens were excluded due to inconsistency in units for the different hallucinogenic drugs (i.e. grams of mushrooms, tabs of LSD).

[a]Non-normally distributed data where the median and interquartile range are reported.

[b]For regular use of MDMA, there was one missing value for two individuals which is why $n=23$ for regular users.

n/a = missing data or not enough data for calculating the interquartile range ($n>3$), or the standard deviation ($n>1$).

Within the MDMA poly-drug user group, the greatest amount of MDMA used in a single session was 0.50 grams (IQR = 0.76). Participants were also asked whether they felt their interactions with other people changed as a consequence of their MDMA use; 54.5% reported yes and were asked to briefly elaborate. Further information regarding their MDMA use (such as other drugs used alongside MDMA, and descriptions on how they felt their interactions changed) can be found in SM2 and SM3.

*$p<.05$, **$p<.01$, ***$p<.001$.

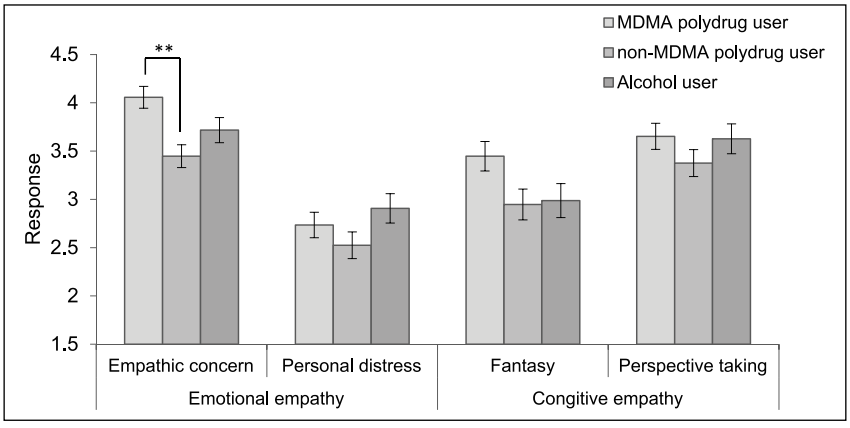

Figure 3. Cognitive and emotional empathy measured by the Interpersonal Reactivity Index (IRI). The MDMA poly-drug users rated significantly higher than non-MDMA poly-drug users for empathic concern (emotional empathy subscale), and there was a trend to suggest a difference with the alcohol users, too. Additionally, there was a trend to suggest a significant group difference in fantasy (cognitive empathy subscale). **$p<.01$.

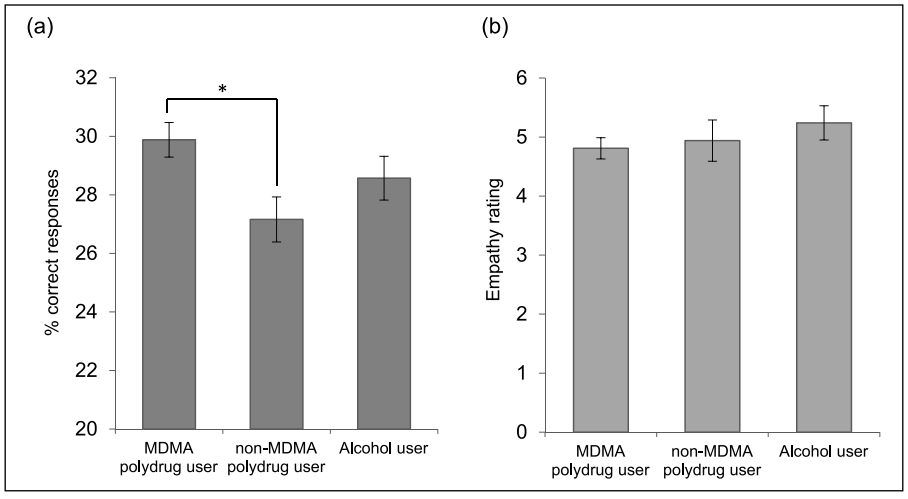

Figure 4. Results from the Multifaceted Empathy Test: (a) cognitive empathy was significantly greater for MDMA poly-drug users when compared with non-MDMA poly-drug users, and (b) there were no significant differences in ratings of emotional empathy between the groups. *$p<.05$.

Table 2. Statistical assessments on outcome measures for Cyberball.

	Inclusion status	MDMA poly-drug user	Non-MDMA poly-drug user	Alcohol-only user	*F*-statistic		*p*-value	η^2
Positive affect	Inclusion	3.41 (0.88)	3.51 (0.85)	3.68 (0.62)	Group	0.98	.383	0.04
	Exclusion	2.17 (0.75)	2.65 (0.93)	2.41 (0.83)	Inclusion status	7.84	.007**	0.10
					Group* inclusion status	0.97	.385	0.03
Negative affect	Inclusion	1.59 (0.74)	1.63 (0.67)	1.37 (0.41)	Group	1.48	.236	0.02
	Exclusion	2.49 (1.03)	2.77 (0.83)	2.38 (0.87)	Inclusion status	13.68	<.001***	0.08
					Group* inclusion status	0.13	.877	<0.01
Self-esteem	Inclusion	3.19 (0.99)	3.31 (0.95)	3.46 (0.76)	Group	1.66	.847	<0.01
	Exclusion	2.08 (0.78)	2.46 (0.92)	2.12 (0.76)	Inclusion status	24.38	<.001***	0.09
					Group* inclusion status	1.95	.151	0.01
Control	Inclusion	2.38 (0.81)	2.86 (1.04)	2.59 (0.69)	Group	3.28	.044*	0.07
	Exclusion	1.34 (0.44)	1.87 (0.72)	1.43 (0.53)	Inclusion status	15.19	<.001***	0.16
					Group* inclusion status	0.25	.783	0.01
Perceived number of ball throws	Inclusion	34.62 (11.00)	34.57 (8.17)	33.33 (4.52)	Group	0.65	.528	0.02
	Exclusion	13.52 (6.21)	14.83 (7.81)	12.21 (6.84)	Inclusion status	38.14	<.001***	0.34
					Group* inclusion status	0.16	0.823	<0.01

Note. df for main effects = 1, 62, for interaction = 2, 62; *** $p < .001$.

between the non-MDMA drug users and alcohol-only users ($t(40) = 1.30$, $p = .342$, $\eta^2 = .04$) (Figure 4). There were no significant group differences in emotional empathy ($F(2,64) = 0.71$, $p = .496$, $\eta^2 = .02$) (Figure 4).

Social pain

A mixed repeated measures ANOVA compared the effect of group (MDMA users, non-MDMA drug users, and alcohol-only users) and inclusion status (inclusion, exclusion) on the following dependent variables: 1) positive affect, 2) negative affect, 3) self-esteem, 4) control, and 5) perceived percentage of ball throws received (manipulation check). The other subscales (sense of belongingness, meaningful existence, anger, and hurt feelings) were highly skewed and did not improve following a log transformation. Thus, these were converted to change scores (inclusion minus exclusion) and analysed using one-way ANOVA's, where there were no statistical group differences (see SM4).

There were significant overall decreases in positive affect, self-esteem, control, and perceived percentage of ball throws from inclusion to exclusion (Table 2). There were also significant increases in negative affect from inclusion to exclusion. There were no significant main effects of group, and no significant interactions between group or inclusion status on any of these indices. All analyses co-varied for order of Cyberball games due to significant order × condition × inclusion status interactions.

Exploratory analyses

Thirteen cases were identified where MDMA was used in the two weeks prior to testing. Due to the acute effects of MDMA on emotional empathy on the MET, a Pearson's correlation was conducted between recent MDMA use (grams used in the last two weeks) with emotional empathy, which was not statistically significant ($r = 0.44$, $n = 11$, $p = .177$).

Ecstasy use (number of days used per month) in the MDMA poly-drug user group was not correlated with empathic concern on the IRI ($r = -0.20$, $n = 24$, $p = .343$), nor was it significantly correlated with cognitive empathy on the MET ($r = -0.19$, $n = 24$, $p = .371$). Empathic concern on the IRI and emotional empathy on the MET were significantly correlated ($r = 0.42$, $n = 67$, $p < .001$), however perspective taking on the IRI and cognitive empathy on the MET were not ($r = -0.11$, $n = 67$, $p = .398$).

Due to minor reports of MDMA use in the non-MDMA poly-drug and alcohol-only groups, we conducted an exploratory analysis looking at whether there was a significant difference between those who have used MDMA in the past and those who have never used MDMA on empathic concern on the IRI, finding that there was no significant difference between those who reported yes ($M = 3.82$, SD = 0.60) or no ($M = 3.67$, SD = 0.62, $F(1,65) = 0.88$, $p = .351$, $\eta^2 = 0.01$). A further analysis looked at the effect of group on empathic concern excluding any individuals who had reported ever using MDMA in the non-MDMA poly-drug users and alcohol-only users groups, finding that there was a near-significant effect on emotional empathy between the MDMA poly-drug ($M = 4.07$, SD = 0.51), non-MDMA poly-drug ($M = 3.47$, SD = 0.80), and alcohol-only group ($M = 3.74$, SD = 0.56) that became insignificant upon correcting for multiple comparisons ($F(2,46) = 3.29$, $p = .092$, $\eta^2 = 0.13$).

Discussion

The current study investigated the long-term effects of repeated MDMA use on empathy and the experience of social pain. Higher

levels of subjective emotional empathy in people who regularly used MDMA were observed when compared with non-MDMA poly-drug users. On the MET, cognitive empathy was found to be greater in MDMA users when compared with non-MDMA poly-drug users, mirroring the findings of previous research (Wunderli et al., 2018). However, no group differences were observed in emotional empathy during the MET or in cognitive empathy using the subjective measure. For the social pain measure, although there were significant declines on mood and self-esteem after being socially excluded, no differences were observed between the three groups in response to social exclusion.

The main novel finding of the study is of enhanced self-reported emotional empathy in people with reported repeated use of MDMA. This was confined to the empathic concern scale, which suggests a greater concern for others in these individuals compared with poly-drug users who do not take MDMA. Increased levels of cognitive empathy in long-term MDMA users were also observed, replicating the findings of the previous study by Wunderli and colleagues (2018). The current project recruited long-term but mild users (a minimum of 10 times), in order to reflect doses that may be used in a therapeutic setting. Wunderli and colleagues (2018) studied heavier users and observed that cognitive empathy was inversely related to hair concentrations of MDMA, i.e. heavier use was associated with poorer cognitive empathy, suggesting that lighter MDMA users had greater cognitive empathy. The current study only assessed light MDMA users and thus the finding of improved cognitive empathy in light users is consistent with the Wunderli et al. study. However, we did not find a correlation with self-reported MDMA use and cognitive empathy in our users, which may be due to the unreliability of subjective estimates. Furthermore, the current study differs from Wunderli and colleagues (2018) in that differences in empathy were only observed between the long-term MDMA users when compared with non-MDMA drug users, and not when compared with alcohol-only users. Furthermore, the similarity in scores between the alcohol-only and the non-MDMA poly-drug group also suggest that there is no simple linear relationship between substance use and degree of subjective emotional empathy.

Studies have found that MDMA enhances emotional but not cognitive empathy (Hysek et al., 2014a; Kuypers et al., 2014, 2017; Schmid et al., 2014), and our study extends these findings to suggest that enhancement of emotional empathy may be a longer-lasting consequence of MDMA use. Differences observed in emotional empathy may be down to pre-existing group differences that draw some users to take the substance; an explanation that is difficult to rule out without prospective studies. Although it did not meet the threshold for significance, there was a trend to suggest a greater incidence of mental health problems in the MDMA group, which is consistent with previous work in MDMA users (Verheyden et al., 2003). Historical mental health problems may also play a role in empathy differences between groups, though previous literature has suggested empathy deficits in those with depression (Hoffmann et al., 2016), which conflicts with this explanation.

Greater self-reported emotional empathy following repeated doses of MDMA may be down to users having experienced heightened emotional experiences under the acute effects of the drug. For example, in the popular press there is an often reported reduction in football violence that corresponded with an increase in MDMA use among fans, which has been attributed to the prosocial effect of the drug in reducing aggression (Gilman, 1994). As such, it may be that autobiographical memories of such experiences facilitate a longer-term increase in prosocial emotion among individuals in the MDMA user group.

Heightened emotional empathy in MDMA users versus non-MDMA users in the current study was only observed using the subjective measure, and was not observed in the computerised task despite the two measures being correlated. The discrepancy in findings between the IRI and the MET may have been influenced by multiple factors. One potential explanation is that the questionnaire measures 'trait' empathy, which is more stable over time, whilst the computerised task (the MET) measures 'state' empathy, which is more fluid. Many previous studies have used the MET to assess state empathy (Dolder et al., 2016, 2017, 2018b; Hysek et al., 2014a; Kuypers et al., 2017; Pokorny et al., 2017; Vizeli and Liechti, 2018). It is thus possible that differences in how both the IRI and the MET operationalise empathy could explain why significant differences in emotional and cognitive empathy were observed in one measure and not the other. For example, for emotional empathy, the MET is looking at the spontaneous ability to adopt the emotional state of someone on the screen (i.e. emotional contagion), whilst the IRI requires introspection and memory to more broadly assess sympathy and distress for others. As the study was relatively small and the effects between the groups expected to be subtle, it is possible that the IRI was slightly more sensitive to these subtle group differences as it assessed emotional empathy more broadly, compared with the MET.

Repeated MDMA use was not found to impact on the experience of social exclusion: users did not differ from the two control groups. Together with findings from the empathy measures, this could suggest that repeated MDMA use at this level may not have a negative impact on social functioning. Indeed, our findings tentatively suggest that repeated MDMA use, at a low level, is associated with increased concern and sympathy for others as well as improved cognitive empathy. However, the ability to draw conclusions from the Cyberball Game in our study is limited, as there are no differences between the three groups on responses to social exclusion (i.e. the MDMA group is no less or more sensitive). It is also possible that the absence of any effect of group on the Cyberball needs measures (self-esteem, meaningful existence, sense of belonging, and control) are due to the questions fitting a two-factor structure, rather than the current four-factor structure, as recently suggested (Gerber et al., 2017). Nonetheless, if chronic MDMA use causes serotonergic dysfunction and/or changes in psychological wellbeing, then this may only occur at high, repeated doses.

The findings of this study also contradict previous suggestions that long-term MDMA use may cause heightened social distress (Parrott, 2007). This is useful for understanding the utility of MDMA therapeutically, as many psychological disorders are associated with impaired empathy e.g. schizophrenia (Lysaker et al., 2013), alcohol use disorder (Dethier and Blairy, 2012), and chronic pain (Song et al., 2018). Although they did not show social distress, a large proportion of the MDMA users did report experiencing a lowered mood in the days following MDMA, all of whom believed this was due to using MDMA. This is possibly misleading: when used therapeutically, observed low mood following MDMA is no different to placebo, suggesting that it is perhaps the drug set and setting associated with recreational use that is causing a consequent lowering of mood (Mithoefer et al., 2011). For example,

recreational use is related to sleep deprivation and adulterants that are added to street MDMA, which would not be present when using MDMA therapeutically. Understanding the longer-term effects of MDMA could further enable clinicians to decipher whether such a treatment could have therapeutic uses beyond PTSD, indeed recent work is underway testing MDMA in patients with autism spectrum disorder (Danforth et al., 2016, 2018) and in alcohol use disorder (Sessa, 2018).

The present study inevitably had several limitations. We relied solely on self-report measures of drug use, and the use of objective measures e.g. hair analysis or urine drug screen would be advisable in future. Another limitation is that the cross-sectional design of the study does not rule out alternative explanations for the differences in empathy, for example, pre-existing differences in empathy prior to MDMA use. A strength of the current study was that it recruited low-level MDMA users, who were fairly mild users but used the substance regularly. Mild users have largely been overlooked in the literature (Szigeti et al., 2018), however these levels are more likely to mirror the levels that could be used in therapeutic settings. Another strength is the inclusion of a non-MDMA poly-drug user group; this is unlike other studies and was incorporated to elucidate any specific effects of MDMA (as MDMA users are likely to have used other substances), in addition with comparing them with drug-naïve controls. All three groups were matched on all demographic variables, but the two drug-using groups were not well matched on regular drug use (excluding MDMA). As the study was fairly small it is also possible that this three-group design may have been underpowered to detect other important group differences, for example, the number of mental health problems between groups.

In summary, the current study suggests that mild, repeated use of MDMA is not associated with any impairment to interpersonal functioning. Rather, it was associated in the present sample with enhanced levels of subjective emotional empathy, which has not been reported before, as well as greater cognitive empathy on a computer task, which replicates previous findings. Based on this research it is not possible to identify whether differences in empathic processes precede or are a consequence of MDMA use, nonetheless these data strengthen the argument that MDMA may be used safely in a therapeutic setting without negative repercussions on empathy and sensitivity to social pain. Future work could investigate whether there are any protective effects of mild MDMA use in clinical populations, for example in those with affective disorders, or autism spectrum disorders.

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