ORIGINAL INVESTIGATION

Depression, impulsiveness, sleep, and memory in past and present polydrug users of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)

Lynn Taurah · Chris Chandler · Geoff Sanders

Received: 3 March 2013 / Accepted: 11 September 2013

Abstract
Rationale Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a worldwide recreational drug of abuse. Unfortunately, the results from human research investigating its psychological effects have been inconsistent.
Objectives The present study aimed to be the largest to date in sample size and 5HT-related behaviors; the first to compare present ecstasy users with past users after an abstinence of 4 or more years, and the first to include robust controls for other recreational substances.
Methods A sample of 997 participants (52 % male) was recruited to four control groups (non-drug (ND), alcohol/nicotine (AN), cannabis/alcohol/nicotine (CAN), non-ecstasy polydrug (PD)), and two ecstasy polydrug groups (present (MDMA) and past users (EX-MDMA). Participants completed a drug history questionnaire, Beck Depression Inventory, Barratt Impulsiveness Scale, Pittsburgh Sleep Quality Index, and Wechsler Memory Scale-Revised which, in total, provided 13 psychometric measures.
Results While the CAN and PD groups tended to record greater deficits than the non-drug controls, the MDMA and EX-MDMA groups recorded greater deficits than all the control groups on ten of the 13 psychometric measures. Strikingly, despite prolonged abstinence (mean, 4.98; range, 4–9 years), past ecstasy users showed few signs of recovery. Compared with present ecstasy users, the past users showed no change for ten measures, increased impairment for two measures, and improvement on just one measure.
Conclusions Given this record of impaired memory and clinically significant levels of depression, impulsiveness, and sleep disturbance, the prognosis for the current generation of ecstasy users is a major cause for concern.

Keywords MDMA · Ecstasy · Present users · Past users · Prolonged abstinence · Depression · Impulsiveness · Sleep · Memory · Long-lasting deficits

Introduction

Research interest in 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) has increased over the past 30 years in line with its abuse as a recreational drug. Although the years 2005–2010 saw some decline in ecstasy use in Europe, data from 2011 show an increase in some countries; the lifetime prevalence of ecstasy use among 15- to 16-year-old students was 1–4 % in Europe and estimated to be 7 % in the USA (EMCDDA 2012). The continuing popularity of ecstasy makes robust investigations of the long-lasting consequences of MDMA use a matter of urgency.

In both animal and human studies, within an hour of MDMA administration, there is an initial increase in 5HT levels followed by a significant reduction which can last up to 3 days (Green et al. 2003). Animal studies demonstrate that MDMA causes nonrepairable damage to selective serotonergic neurons causing the nerve terminals and axons to degenerate (Fischer et al. 1995); if regeneration occurs, as it does in some brain regions, it is incomplete (Insel et al. 1989; Kirilly 2010; Ricaurte et al. 2000). The neuronal damage can last for periods ranging from months to years following cessation of MDMA use (Battaglia et al. 1988; Hatzidimitriou et al. 1999). Whether the reduction in 5HT is permanent or levels return to

L. Taurah · C. Chandler · G. Sanders
School of Psychology, London Metropolitan University, London, UK

L. Taurah (✉)
School of Psychology, Faculty of Life Sciences and Computing, London Metropolitan University, 166-220 Holloway Road, London N7 8DB, UK
e-mail: l.taurah@londonmet.ac.uk

baseline is hotly debated in human studies (Green et al. 2012; Morgan 2000). Therefore, while there is good evidence that the neurotoxicity of MDMA causes long-lasting compensatory alterations in specific brain regions of animals, there is insufficient evidence that related effects occur in humans. However, as the acute behavioral and pharmacological effects of MDMA are similar in animals and humans (Green et al. 2003), it is plausible to suggest the adverse behavioral effects of ecstasy may be long-lasting in humans.

Human studies of ecstasy use have pointed to acute deficits in mood (Curran and Travill 1997; Falck et al. 2008; Roiser and Sahakian 2004), impulsiveness (De Win et al. 2006), sleep (Allen et al. 1993; Carhart-Harris et al. 2009), and memory (Blagrove et al. 2011; Daumann et al. 2004; Gouzoulis-Mayfrank et al. 2005). However, a major problem with previous human ecstasy research is a failure to use adequate control groups to account for polydrug use in ecstasy users. Arguably, the psychological deficits attributed to ecstasy could be caused by the consumption of other recreational drugs, including alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine, either alone or in combination with ecstasy (Fisk and Montgomery 2009; Hernandez-Rabaza et al. 2010). Over the last two decades, ecstasy studies have also suffered from biased sampling of participants and a reliance on small samples (Curran 2000; Parrott 2001; Rogers et al. 2009). These methodological limitations make it difficult to draw adequate conclusions.

The aim of the present study was to investigate the potentially long-lasting behavioral and psychological consequences of ecstasy use in human participants who were using substances recreationally but had no history of substance dependency. To date, no human study has investigated the consequences of prior ecstasy use after a prolonged abstinence of more than 2 years. However, MDMA has been a recreational drug of abuse since the early 1980s so there are likely to be many previous users who have subsequently abstained from MDMA for a longer period.

Presently, this study is (1) the largest to monitor behaviors in ecstasy polydrug users, (2) the first to test a wide range of behaviors associated with 5HT (depression, impulsiveness, sleep, and memory), (3) the first to compare present polydrug ecstasy users with past users after an abstinence of 4 or more years, and (4) the first with robust controls for other recreational substances.

Participants and methods

Participants

On the basis of a power calculation, a sample of 997 participants (mean age, 25.1 (±7.4)years; 523 (52 %) male) was recruited between 2002 and 2007 from various sources: Web Page (34 %), local newspaper advertisements (6 %), drug advisory centers (22 %), snowballing technique (37 %), and unspecified (1 %). The advertisement, which was used for all recruitment sources, invited participation in "a large-scale nonbiased research investigation of the effects of recreational drug use on everyday life". In the advertisement and subsequent briefing, alcohol, cannabis, cocaine, and nicotine were named as examples but ecstasy, MDMA, depression, impulsiveness, sleep, and memory were not mentioned. Volunteers were asked to contact an email address or to telephone and leave contact details on a dedicated answering machine. Prior to making appointments, they were told there would be no reward for participation and general feedback would be available but that no individual feedback would be given. Appointments were made to ensure that all data were collected by the same experimenter (LT) at the same site in similar research rooms.

Participants were recruited to four control and two ecstasy groups:

1. ND—people who had never used recreational drugs ($n=182$)
2. AN—people who used either alcohol and/or nicotine ($n=172$)
3. CAN—people who used cannabis with or without alcohol and/or nicotine ($n=163$)
4. PD—a polydrug group who had used any of the following illicit substances (amphetamine, cocaine, heroin, and ketamine) but had never used MDMA ($n=169$)
5. MDMA—a present ecstasy polydrug group who had used ecstasy at least once in the last 6 months but not for at least 3 weeks (mean, 4 weeks) before testing to avoid short-term effects ($n=154$)
6. EX-MDMA—a past ecstasy polydrug group who had abstained from ecstasy for a minimum of 4 years (mean, 4.98; range, 4–9 years; $n=157$)

In general, each of the recruitment sources contributed equally to the AN, CAN, and PD groups although fewer ND and ecstasy volunteers were recruited via the newspaper advertisements.

Until arrival at the laboratory, the precise experiences of potential participants differed somewhat among the recruitment sources. To attract visits, the customized website which featured the advertisement also had articles and other information of interest to recreational drug users including a forum. Local newspapers simply carried the advertisement. The drug centers offered advice, not treatment, and staff drew the attention of clients to the advertisement. For the snowballing route, existing participants were encourage to recruit people they knew without saying more about the study than had been reveal to them in the advertisement and briefing. When potential participants made contact via email or telephone, the nature of the study was described without reference to ecstasy, MDMA, or the psychometric variables of interest. Callers

were assured that participation would be confidential. They were told the study would involve simple tests and take no longer than 2 h. If the contacts volunteered to join the study, an appointment was arranged. Approximately 50 % of the people who made an appointment did not attend for testing. A possible reason for this high dropout rate and its implications are addressed in the "Discussion" section.

All participants reported good health with no previous psychiatric history and they were all employed or in full time education at the time of the study (Table 1). After complete description of the study to the participants, written informed consent was obtained. In total, 1,133 people volunteered, but 136 (12 %) were lost from the study; a few withdrew after attending for testing, but the majority were discarded because they failed to meet the strict "knowledge of effects" criterion for inclusion in the ecstasy groups (see "Measures" section below).

Measures

All participants completed a Drug History Questionnaire (DHQ) developed in a pilot study (Taurah 2011) which included tests of reliability and validity for six drugs. Reliability was suitable for research purposes (Bland and Altman 1997) with a mean Cronbach's alpha of 0.81 (alcohol=0.66, amphetamine=0.77, cannabis=0.74, cocaine=0.91, ecstasy=0.86, and heroin=0.89). The DHQ was also a valid measure of drug-related behavior: comparison with the Maudsley Addiction Profile (Marsden et al. 1998) revealed a mean Pearson's correlation coefficient of 0.82 (alcohol=0.71, amphetamine=0.83, cannabis=0.72, cocaine=0.93, ecstasy=0.83, and heroin=0.91).

The DHQ explored basic demographics (age, educational background, and ethnicity), health, personal drug and medical history, and a family drug history. It has 47 main questions, 18 with subquestions, and, administered as an interview, the DHQ took on average 40 min to complete. Four health questions with "yes"/"no" answers focused on the psychometric measures to be used later in the study by asking participants if they experienced depression, impulsiveness, sleep disturbance, and memory problems. Drug-related questions explicitly asked about possible recreational use of ecstasy, alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine. Frequency of use was measured by exploring regular drug use, irregular drug use, and periods of abstinence. Participants were encouraged to focus on periods of irregular use and abstinence by the use of memory cues. We adopted a modified version of the Time-Line Follow-Back (Sobell et al. 1979), using flash cards (Marsden et al. 1998) to prompt memory of personal events, periods of rehabilitation, stressful events, period of time spent with drug using friends/family, and/or nondrug using friends/family. For each of the illicit substances recorded, all routes of administration were monitored (i.e., oral, smoking, insufflation, injection, inhalation, and suppository).

Lifetime drug exposure for each of the seven substances was calculated by the formula (number of grams/units/joints per single occasion)×(number of single occasions per week)×(number of months per year)×(total number of years). The formula was adjusted for the different type of drug exposure in terms of dose as well as the different routes of administration, i.e., cannabis (number of joints), alcohol (number of units), ketamine (grams), cocaine (grams), ecstasy (pills), heroin (grams), and amphetamine (grams). If a participant used several different doses and routes of administration, these were converted to the standard measures listed above, e.g., pills were converted to grams for ecstasy. Any periods of irregular drug use were added to the calculation and any periods of abstinence were deducted to provide a final frequency of drug use score. Participants' exposure to ecstasy was verified by the use of a strict "knowledge of effects" criterion in the DHQ; potential participants were asked to identify 14 subjective and physiological effects of ecstasy (Verheyden et al. 2003) out of a possible 47 effects. If the participants presenting as ecstasy polydrug users selected any of the 33 non-ecstasy effects or failed to select all of the 14 ecstasy effects they were excluded from the study. In a previous pilot study (Taurah 2011), none of the non-ecstasy users had met this "knowledge of effects" criterion and this remained true for the non-ecstasy users in the present study. None of the non-ecstasy users but all of the ecstasy users included in the study chose all 14 MDMA effects and none of the non-MDMA effects.

The participants completed four psychometric tests: the short-form of the Beck Depression Inventory Second Edition (BDI-II; Beck et al. 1961), the Barratt Impulsiveness Scale 11th Edition (BIS-11) (Patton et al. 1995), the Pittsburgh Sleep Quality Inventory (PSQI; Buysse et al. 1989), and the Wechsler Memory Scale-Revised (WMS-R; Wechsler 1987). These tests provide scores on a total of 13 psychometric measures: BDI Global and two subscales (somatic and cognitive), BIS-11 Global and three subscales (attention, motor, and nonplanning), PSQI Global, and the five components of the WMS-R (general, verbal, visual, attention, and delayed memory).

Procedure

Participants completed the items in the same order: the DHQ, the WMS-R (general, verbal, visual, attention, and first part of the delayed), the BDI, the BIS-11, the PSQI, and the final part of the WMS-R Delayed. The study, which followed the British Psychological Society Guidelines, was approved by the local University Ethics Committee. Written briefing and debriefing documents, including the experimenter's contact details, were given to the participants. On average, participants took 2 h to complete the study.

Table 1 Biographical data and details of lifetime drug use for the four control and two MDMA groups

	Group	ND		AN		CAN		PD		MDMA		EX-MDMA		Analysis		
		No drug use (N=182)		Alcohol and nicotine users (N=172)		Cannabis, alcohol, and nicotine users (N=163)		Non-MDMA polydrug users (N=169)		Present MDMA users (N=154)		Past MDMA users (N=157)		χ^2 (chi-squared) H (Kruskal–Wallis) t (t test)		
Biographical data		N	%	N	%	N	%	N	%	N	%	N	%	χ^2	df	p
Age range in years	18–25	78	43	73	42	73	45	77	46	71	46	11	7	149.55	10	<0.001
	26–34	67	37	77	45	65	40	71	42	71	46	66	42			
	35 older	37	20	22	13	25	15	21	12	12	8	80	51			
Sex	Male	89	49	89	52	85	52	82	49	102	66	104	66	22.74	5	<0.001
	Female	93	51	83	48	78	48	87	51	52	34	53	34			
Ethnicity	White (UK)	26	15	40	23	38	24	73	43	60	39	87	55	133.18	15	<0.001
	Black (UK)	46	25	48	28	46	28	23	14	38	25	27	17			
	Asian (UK)	73	40	40	23	51	31	34	20	50	32	17	11			
	Other	37	20	44	26	28	17	39	23	6	4	26	17			
Higher education	Yes	182	100	172	100	163	100	169	100	154	100	157	100	0	5	NS
	No	0	0	0	0	0	0	0	0	0	0	0	0			
Current employment	Yes	106	58	59	34	68	42	65	38	57	37	122	78	122.97	10	<0.001
	No	31	17	53	31	42	26	35	21	65	42	11	7			
	Student	45	25	60	35	53	33	69	41	32	21	24	15			
Current status	Married	78	43	49	28	21	13	24	14	37	24	74	47	329.74	10	<0.001
	Separated/divorced	0	0	10	6	21	13	3	2	0	0	61	39			
	Single	104	57	113	66	121	74	142	84	117	76	22	14			
Lifetime use of drugs[a]				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	H	df	p
Alcohol[b,c]				18,885	13,409	20,989	21,441	19,582	12,712	29,319	14,781	30,329	16,597	87.45	4	<0.001
Cannabis[b,c]						1,077.80	524.48	1,632.75	922.15	3,320.80	1,522.03	3,650.82	1,572.06	226.50	3	<0.001
Amphetamines[b,c]								72.72	73.72	204.99	136.23	200.60	111.07	161.04	2	<0.001
Cocaine[b,c]								27.67	30.31	82.39	74.47	56.46	40.51	93.10	2	<0.001
Heroin[b,c]								8.93	13.19	43.64	45.10	31.18	30.36	99.66	2	<0.001
Ketamine[b,c]								0.57	1.18	1.38	1.14	1.27	1.45	10.67	2	<0.005
Ecstasy										Mean	SD	Mean	SD	t	df	p
Initial age of exposure										18.25	3.11	23.47	5.97	8.20	309	<0.001
Initial dosage[c]										0.10	0.56	0.09	0.06	0.981	309	NS
Usual dosage per occasion[c]										0.17	1.14	0.09	0.05	6.14	309	<0.001
Lifetime exposure to ecstasy[b,c]										69.18	53.11	36.15	39.99	6.20	309	<0.001

[a] Post hoc paired comparisons were conducted with the Mann–Whitney U Test after group differences were confirmed with Kruskal-Wallis. The differences that were significant at p <0.05 or beyond were: alcohol—PD v MDMA, U=7,879.00, p <0.001; cannabis—CAN v PD, U=11,703.00, p =0.018, PD v MDMA, U=4,743.00, p <0.001; amphetamines—PD v MDMA, U=4,358.50, p <0.001; cocaine—PD and MDMA, U=5,708.50, p <0.001; heroin—PD v MDMA, U=6,054.00, p <0.001; ketamine—PD v MDMA, U=10,651.00, p <0.002

[b] Lifetime drug exposure was calculated by the formula (number of tablets/dose per single occasion)×(number of single occasions per week)×(number of months per year)×(total number of years) that the participant had used each drug. Any periods of abstinence were subtracted from the formula

[c] Ecstasy grams, cocaine grams, amphetamine grams, heroin grams, ketamine grams, alcohol units, and cannabis joints

Statistics

The data were analyzed using the Statistical Package for the Social Sciences Version 19. The biographical data were analyzed with chi-squared and the lifetime use of drugs with Kruskal–Wallis and Mann–Whitney for post hoc analyses. To meet the assumptions of the subsequent statistical analyses, the psychometric test data were checked for multicollinearity, non-normality, curvilinearity, and heteroscedasticity and, where necessary, the data were log transformed. One-way ANCOVAs were used to test for group differences in the scores for each of the 13 psychometric tests. Age, alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine were included as covariants. The homogeneity of the regression slope and independence were checked for each ANCOVA including the interaction term and the main effect. Post hoc analyses for the ANCOVAs were conducted using *t* tests with the Bonferroni correction. Effect sizes for the differences between groups were calculated using Cohen's *d* (Cohen 1988). Age and lifetime exposure to each of the drugs used were correlated with scores from each of the 13 psychometric tests. Subsequently, the relationships were further analyzed using multiple regression with lifetime exposure to ecstasy, age, alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine included as predictor variables. All tests were nondirectional.

Results

Patterns of drug use and perceived health

The participants' biographical data and details of their lifetime use of drugs are presented in Table 1. While premorbid IQ was not measured, participants did not significantly differ in their educational background, which suggests that intellectual ability was not a significant factor in the present study. It should be noted that, compared with past ecstasy users, present users began ecstasy use at a younger age and took larger doses; consequently they recorded higher lifetime ecstasy consumption. A notable proportion of the participants reported experiencing the four health issues of interest: depression, 38.1 %; impulsiveness, 19.1 %; sleep, 40.6 %; and memory, 16.9 %. However, Pearson Chi-square indicated that the frequency distributions of "yes"/"no" responses did not differ among the six groups (depression—χ^2 (5)=0.97, p=0.965; impulsiveness—χ^2 (5)=4.43, p=0.490; sleep—χ^2 (5)=4.60, p=0.467; and memory—χ^2 (5)=7.44, p=0.190).

Depression, impulsiveness, and sleep

As shown in Fig. 1 (see also Tables 2 and 3), a similar pattern of mean scores was obtained for the two ecstasy and four control groups across the global measures of depression (BDI), impulsiveness (BIS-11), and sleep quality (PSQI). The past and present ecstasy polydrug users both recorded higher mean scores for global BDI, BIS-11, and PSQI than the four control groups. There was no difference between the ecstasy groups in their mean scores for the BDI and PSQI

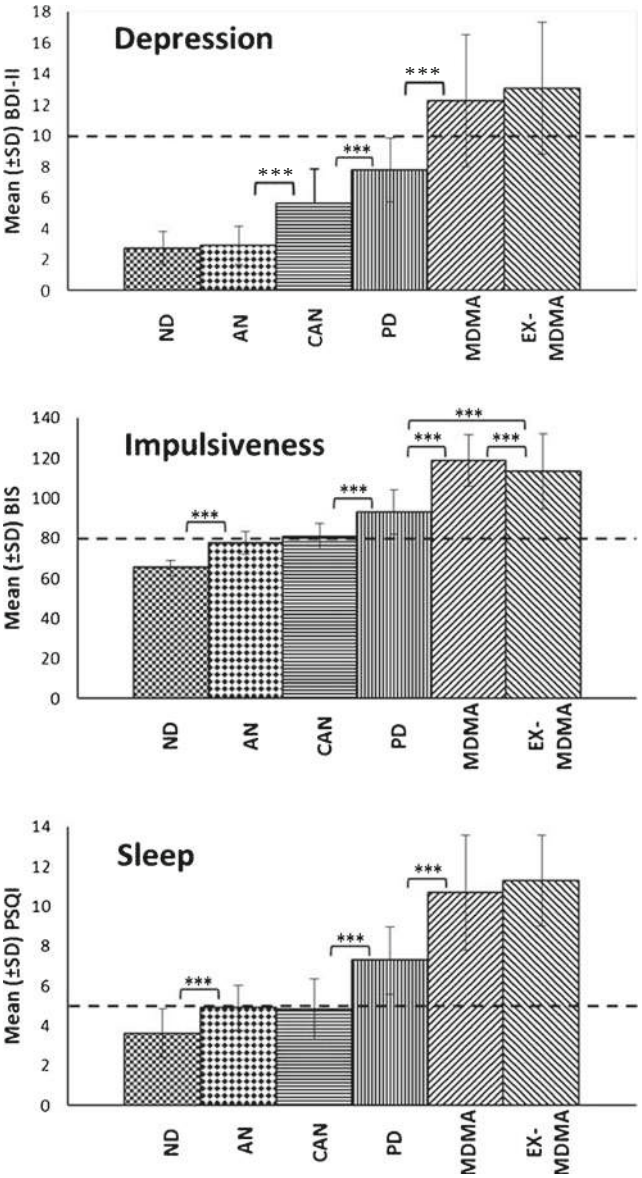


Fig. 1 Mean scores (±SD) on the Global Scales of the Beck Depression Inventory II (BDI-II), Barratt Impulsiveness Scale (BIS-11), and Pittsburgh Sleep Quality Inventory (PSQI) for the Control Groups (no drug (ND), N=182; alcohol and nicotine (AN), N=172; cannabis, alcohol, and nicotine (CAN), N=163; polydrug non-MDMA (PD), N=169) and the Ecstasy Groups (present users (MDMA), N=154; past users (EX-MDMA), N=157). The numerical values of the means and standard deviations are presented in Table 2. The *dashed horizontal line* indicates the clinical threshold level for each psychometric measure. Probability of difference between adjacent bars: *p<0.05, **p<0.01, ***p<0.001 (post hoc *t* tests with Bonferroni correction)

but, compared with present users, past users recorded lower mean scores for the BIS-11.

For the control groups, the BDI, BIS-11, and PSQI mean scores increased progressively, with the ND group recording the lowest scores, followed by the AN and then the CAN group, with the PD group recording the highest scores. Compared with the ND group, all of the drug control groups showed significant impairment except for AN on the BDI. Within this overall trend, CAN recorded a significant impairment on the BDI, AN on the BIS-11 and PSQI, and PD on the BDI, BIS-11, and PSQI (Fig. 1; Tables 2 and 3). The effect of drug use was even more marked in the ecstasy groups; both past and present ecstasy users recorded mean scores above the clinical thresholds for the BDI, BIS-11, and PSQI. The only control group to markedly exceed the clinical threshold was the PD for the BIS-11 and PSQI.

Performance on the subscales demonstrated which specific domains of depression and impulsiveness are particularly affected by ecstasy (Fig. 2; Tables 2 and 3). For three of the five subscales (BDI Somatic, BDI Cognitive, and BIS-11 Attention), the two ecstasy groups showed greater impairment in mean scores than the four control groups. The two exceptions were BIS-11 Motor where the present but not the past ecstasy users were significantly different from the polydrug controls and BIS-11 Non-Planning where neither ecstasy group was significantly different from the polydrug controls. In general, the mean scores of past and present ecstasy users tended not to differ with the exception of BIS-11 Non-Planning on which the past ecstasy group recorded higher mean scores than the present ecstasy group. There were no significant differences between the control groups on the BDI subscales but, compared with the ND group, AN showed significant impairment on the BIS-11 Motor, while the PD group showed greater impairment than CAN on the BIS-11 Attention, Motor, and Non-Planning subscales.

Memory

Memory scores from the WMS-R are shown in Fig. 2 (see also Tables 2 and 3). On the general, verbal, visual, and delayed memory tests both ecstasy groups recorded greater impairment than the polydrug and other control groups but did not themselves differ significantly. In contrast, past ecstasy users were more impaired than present users on Attention Memory but neither ecstasy group differed significantly from the PD group. Among the control groups, AN showed significantly greater impairment than ND on all five memory measures. The CAN group showed greater impairment than AN on general, verbal, and attention memory, no difference on delayed and significantly less impairment on visual memory. Compared with CAN, the PD group showed increased impairment for visual memory but not for any other memory measure.

Correlations and regression analyses

As shown in Table 4, correlations with the test scores were strong for lifetime ecstasy consumption (median, $r=0.72$; range, 0.26–0.92, all $p<0.001$) and age (median $r=0.75$; range, 0.37–0.80, all $p<0.001$). In contrast, these correlations were moderate for alcohol, cannabis, cocaine, and ketamine (median $r=0.49$–0.60; range, 0.22–0.94, all $p<0.01$) and nonsignificant for amphetamine and heroin.

Regression analysis showed that for seven of the test scores (BDI, BIS, PSQI Global; BDI Somatic; BIS motor, nonplanning, and attention) ecstasy was a dominant predictor (median beta, 0.76; range, 0.49–0.94). In contrast, for the memory scales ecstasy was a weak predictor (median beta, −0.04; range, −0.02 to 0.11). Age was a weak predictor (median beta, 0.08; range, 0.00–0.15) for all of the tests except BDI Cognitive (median beta, 0.44). Among the control drugs, heroin and amphetamine were either weak or nonsignificant predictors while the others (alcohol, cannabis, cocaine, and ketamine) were strong to moderate predictors for many of the tests (Table 4). However, the relationships among these drugs and the 13 psychometric test scores are complex and beyond the remit of the present report. Here, the emphasis is on ecstasy for which it is clear that the level of lifetime use is a strong predictor for impairment on the BDI, BIS-11, and PSQI but not for the WMS-R.

Discussion

At the time of writing, the present study is the largest to investigate the effects of ecstasy on a wide range of 5HT-related behaviors: depression, impulsiveness, sleep, and memory. It is also the first to use more robust control groups and, crucially, the first to compare present ecstasy users with past users who had not taken the drug for a prolonged period of time. In general, our findings confirm those from previous reports: ecstasy polydrug users have increased 5HT-related psychological disturbances in comparison to non-ecstasy polydrug users (Allen et al. 1993; Blagrove et al. 2011; Carhart-Harris et al. 2009; Curran and Travill 1997; Daumann et al. 2004; De Win et al. 2006; Falck et al. 2008; Gouzoulis-Mayfrank et al. 2005; Roiser and Sahakian 2004).

Overall, on ten of the psychometric measures, past and present ecstasy users showed greater impairment when compared with non-ecstasy polydrug users and the other control groups (Figs. 1 and 2; Tables 2 and 3). Thus, there is strong evidence for behavioral deficits associated with ecstasy use but, crucially, very limited evidence for a reduction in those deficits after the cessation of ecstasy intake even though the period of abstinence in our sample was prolonged (4+years). These findings are consistent with animal studies which indicate that MDMA induces selective damage to 5HT neurons

Table 2 Mean score, standard deviation (SD), and standard error of the mean (SEM) for the Beck Depression Inventory II (BDI), the Barratt Impulsiveness Scale (BIS-11), the Pittsburgh Sleep Quality Index (PSQI), and the Wechsler Memory Scale-Revised (WMS) for four control groups and past and present ecstasy users

Group		ND			AN			CAN			PD			MDMA			EX-MDMA		
Psychometric tests		No drug use (N=182)			Alcohol and nicotine users (N=172)			Cannabis, alcohol, and nicotine users (N=163)			Non-MDMA polydrug users (N=169)			Present MDMA users (N=154)			Past MDMA users (N=157)		
Main scales		Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
BDI	Global	2.74	1.06	0.08	2.94	1.25	0.10	5.67	2.17	0.17	7.81	2.06	0.16	12.27	4.27	0.34	13.07	4.27	0.34
BIS-11	Global	65.34	3.84	0.28	77.65	5.58	0.43	80.95	6.65	0.52	93.04	11.12	0.86	118.86	13.01	1.05	113.34	18.74	1.50
PSQI	Global	3.63	1.22	0.09	4.92	1.13	0.09	4.85	1.51	0.12	7.30	1.69	0.13	10.69	2.89	0.23	11.30	2.26	0.18
Subscales																			
BDI	Somatic	1.63	1.97	0.15	2.19	2.89	0.22	3.16	3.35	0.26	4.20	4.27	0.33	6.13	3.89	0.31	6.22	3.32	0.27
	Cognitive	0.69	1.34	0.10	0.78	1.17	0.09	1.01	1.43	0.11	1.07	1.37	0.11	4.83	2.86	0.23	4.69	2.88	0.23
BIS-11	Attention	31.65	5.28	0.39	31.19	5.56	0.42	31.42	5.52	0.43	35.82	6.97	0.54	42.45	3.61	0.29	42.48	3.52	0.28
	Motor	31.42	2.07	0.15	33.26	2.93	0.22	33.12	2.83	0.22	34.41	3.30	0.25	35.81	3.54	0.29	34.82	3.66	0.29
	Non-planning	50.12	5.10	0.38	49.63	5.65	0.43	48.98	5.56	0.44	53.81	8.58	0.66	52.11	7.19	0.58	54.82	6.09	0.49
Memory scales																			
WMS	General	108.55	6.08	0.45	105.59	3.88	0.30	99.66	5.77	0.45	99.53	5.74	0.44	86.95	4.15	0.33	87.09	4.47	0.36
	Verbal	111.00	6.13	0.45	106.31	4.95	0.38	103.93	4.87	0.38	103.05	5.75	0.44	88.33	5.39	0.43	88.90	5.54	0.44
	Visual	111.12	5.83	0.43	106.97	5.94	045	111.63	6.85	0.54	108.94	6.91	0.53	99.18	5.40	0.43	99.54	5.89	0.47
	Attention	111.35	7.63	0.57	105.99	3.23	0.25	112.01	7.39	0.58	110.96	7.15	0.55	112.92	6.81	0.55	110.57	7.88	0.63
	Delayed	110.86	7.29	0.54	105.47	3.88	0.30	106.54	3.15	0.25	105.92	3.57	0.27	87.68	4.83	0.39	86.83	4.25	0.34

Table 3 Group Differences for Scores on the Beck Depression Inventory II (BDI), Barratt Impulsiveness Scale (BIS-11), Pittsburgh Sleep Quality Index (PSQI), and Wechsler Memory Scale-Revised (WMS)

Paired Comparison				ND v AN		AN v CAN		CAN v PD		PD v MDMA		PD v EX-MDMA		MDMA v EX-MDMA	
Groups		Main effect of group (*df* 1,5) (*N*=997)		No drug use (*N*=182) v alcohol and nicotine users (*N*=172)		Alcohol and nicotine users (*N*=172) v cannabis, alcohol, and nicotine users (*N*=163)		Cannabis, alcohol, and nicotine users (*N*=163) v polydrug users (*N*=169)		Polydrug users (*N*=169) v present MDMA users (*N*=154)		Polydrug users (*N*=169) v past MDMA users (*N*=154)		Present MDMA users (*N*=154) v past MDMA users (*N*=157)	
		ANCOVA		*t* test	Cohen's	*t* test	Cohen's	*t* test	Cohen's	*t* test	Cohen's	*t* test	Cohen's	*t* test	Cohen's
Psychometric tests		*F*	*p*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*
BDI	Global	181.33	<0.001	1.00	0.17	<0.001	1.60	<0.001	1.01	<0.001	1.41	<0.001	1.66	0.16	0.19
BIS-11	Global	263.70	<0.001	<0.001	2.61	0.08	0.54	<0.001	1.36	<0.001	2.14	<0.001	1.36	<0.001	−0.35 *
PSQI	Global	209.15	<0.001	<0.001	1.10	1.00	−0.05	<0.001	1.53	<0.001	1.48	<0.001	2.03	0.06	0.24
BDI	Somatic	24.32	<0.001	1.00	0.23	0.12	0.31	0.07	0.27	<0.001	0.47	<0.001	0.53	1.00	0.02
	Cognitive	71.39	<0.001	1.00	0.07	1.00	0.18	1.00	0.04	<0.001	1.78	<0.001	1.70	1.00	−0.05
BIS-11	Attention	75.02	<0.001	1.00	−0.08	1.00	0.04	<0.001	0.70	<0.001	1.25	<0.001	1.27	1.00	0.01
	Motor	18.10	<0.001	<0.001	0.74	1.00	−0.05	0.002	0.42	0.001	0.41	1.00	0.12	0.07	−0.28
	Nonplanning	9.47	<0.001	1.00	−0.09	1.00	−0.12	<0.001	0.68	0.27	−0.22	1.00	0.14	0.003	0.41
WMS	General	221.71	<0.001	<0.001	−0.59	<0.001	−1.23	1.00	−0.02	<0.001	−2.54	<0.001	−2.44	1.00	0.03
	Verbal	202.75	<0.001	<0.001	−0.85	<0.001	−0.48	1.00	−0.17	<0.001	−2.64	<0.001	−2.51	1.00	0.10
	Visual	56.21	<0.001	<0.001	−0.71	<0.001	0.73 *	<0.001	−0.39	<0.001	−1.59	<0.001	−1.47	1.00	0.06
	Attention	9.93	<0.001	<0.001	−0.99	<0.001	1.13	1.00	−0.14	0.15	0.28	1.00	−0.05	0.04	−0.32
	Delayed	328.99	<0.001	<0.001	−0.97	0.58	0.30	1.00	−0.18	<0.001	−4.34	<0.001	−4.88	1.00	−0.19

[a] Post hoc paired comparisons were conducted with *t* tests using the Bonferroni adjustment after group differences were confirmed with one-way ANCOVAs

[b] Cohen (1988) suggested that an effect size of 0.2 was a small, 0.5 a medium, and 0.8 a large difference

[c] In each paired comparison, the left group was general less impaired than the right group. An asterisk indicates the two exceptions, where the right group was significantly less impaired than the left group at $p < 0.05$ or beyond (see Figs. 1 and 2 and Table 2 for the group means and standard deviations)

(Battaglia et al. 1988; Fischer et al. 1995; Hatzidimitriou et al. 1999; Insel et al. 1989; Kirilly 2010; Ricaurte et al. 2000). Our findings point to domain-specific 5HT behavioral consequences in humans for depression, impulsiveness, sleep, and memory, suggesting such 5-HT damage results in long-term behavioral consequences for humans. Not only are these negative effects of ecstasy persistent, they are also nontrivial. Both past and present ecstasy users recorded levels of global depression, impulsiveness, and sleep disturbance that were in the clinically significant range (Fig. 1).

Further support for the conclusion that ecstasy use is linked with impairment comes from the correlation and regression analysis (Table 4). Lifetime self-reported ecstasy exposure was significantly correlated with performance on all of the psychometric tests. However, the regression analysis revealed a more complex relationship. While lifetime ecstasy use was a strong predictor for depression, impulsiveness, and sleep, it was a weak predictor for memory for which several of the control drugs were moderate to strong predictors. Incidentally, although age correlated strongly with the test scores it was a weak predictor suggesting that the impairment we recorded with the present sample arises from drug use. However, age may become increasingly important as the ecstasy population grows older.

In summary, for global depression, impulsiveness, and sleep, ecstasy alone or in combination with another drug appears to be causing impairments. Alternatively, it may be that ecstasy users are predisposed to these impairments and therefore vulnerable to their appearance. Our data demonstrates the value of looking beyond the global scores because ecstasy did not predict performance on the BDI Cognitive subscale. For memory, ecstasy was a weak or nonsignificant predictor suggesting that the memory deficits were the result of one or more control drugs acting in combination with ecstasy.

Limitations of the research

The present study may suffer from the possibility of biased sampling and conclusions regarding cause and effect cannot be drawn. For example, non-drug users and ecstasy users may volunteer for different reasons and/or, compared with the other groups, ecstasy users may be particularly predisposed to the impairments we recorded. Our use of large samples and a variety of recruitment methods was designed to mitigate against such group differences but the possibility cannot be eliminated. Drug exposure was recorded retrospectively but this reliance on memory was addressed by using the detailed DHQ, which we have shown to be valid and reliable, and the strict "knowledge of effects" criterion for the inclusion of participants who claimed to have used ecstasy.

Readers should remember that ecstasy is an illegal drug and no one, not even the user, can know exactly how much of the drug has been taken. However, the differences between our control and ecstasy group scores provide strong evidence for the effects of ecstasy in both past and present users. Additional confidence in self-reported drug use comes from studies that have compared self-report with biological testing, e.g., Scholey et al. (2011) used hair analysis to demonstrate the reliability of self-report. Drug tests were not an option for the present study which included past ecstasy users after long-term abstinence.

As noted above, some 50 % of the people who offered to participate failed to attend their agreed appointment. This high dropout rate probably reflects the lack of financial or other reward and raises the question why, even over a 4+year period, so many people participated in the study. One reason may be that the participants were drawn largely from professional people and students who might be expected to have an intrinsic interest in drug use and an inclination to help a research study. However, it took longer to recruit the participants who did not use drugs than the recreational drug users, suggesting that users were more motivated to participate. Apart from a greater intrinsic interest it may be the users hoped to gain insight into health issues they attributed to their drug use even though they were told before participating that no individual feedback would be given. Hence, our sample may have been biased towards users who had experienced problems. If so, we would argue that such a bias should have applied to all of the drug use groups. Critically, there were no significant differences between groups in terms of their perceived experience of problems with depression, impulsiveness, sleep, and memory. Hence, the group differences we have reported are valid findings although the absolute levels of impairment may be higher than would be found in randomly selected samples of users.

Two major criticisms have been leveled at the findings of previous ecstasy studies and their interpretation. The first pointed to the somewhat marginal changes in scores for ecstasy users that have been reported. Critics have argued that the levels found in previous studies for depression (e.g., BDI Global scores of 7–9) and impulsiveness (e.g., BIS-11 Global scores circa 60) are within the normal range (Evenden 1999). However, for depression we recorded BDI Global mean scores of 12.3 and 13.1, respectively, for our present and past ecstasy users (Fig. 1, Table 2), scores which are clinically significant (Beck et al. 1961). For impulsiveness, BIS-11 Global scores of 80+ are considered beyond the normal range (Evenden 1999). Consequently, the BIS-11 Global mean scores of 118.9 and 113.3 recorded respectively for our present and past ecstasy users are well beyond the normal range. We should note that the cannabis control group (mean, 81.0) was marginally and the non-ecstasy polydrug group (mean, 93.0) was clearly above the normal range for the BIS-11 with scores which would be considered highly impulsive and problematic (Evenden 1999). The impulsiveness scores for the

other two control groups were within the normal range although the alcohol/nicotine controls recorded greater impulsiveness than the no drug group (Fig. 1; Table 2).

The large effects in our study compared with previous studies may be because our participants tended to be older and because we used a very strict "knowledge of effects" criterion for inclusion in the ecstasy groups. An additional or alternative reason may be that our sample was biased towards users who were already experiencing drug-related health problems. However, this bias is an unlikely explanation for the greater impairment in our findings compared with other reports because most other studies have also used opportunity samples recruited online, via posters in nightclubs, or advertisements in newspapers (Carhart-Harris et al. 2009; Curran and Travill 1997; Falck et al. 2008; Fisk and Montgomery 2009; Gouzoulis-Mayfrank et al. 2005; Roiser and Sahakian 2004).

The second criticism of the research to date is that changes in 5HT-related behaviors are caused by other drugs including cannabis and are not a consequence of ecstasy use per se (Shen et al. 2011). In the present study, we included recreational drug controls for AN, CAN, and for PD, and we argue that while these drugs were associated with impairments none of them alone was responsible for producing the large effects recorded by our past and present ecstasy polydrug users.

Compared with the ND controls, our AN, CAN, and PD groups were associated with significant impairments on the BIS-11 Global and Motor, PSQI, and all five WMS-R memory scales (Figs. 1 and 2; Tables 2 and 3). These findings are consistent with studies which suggest alcohol, cannabis, cocaine, and ketamine may be associated with deficits in some aspects of depression, impulsiveness, sleep, and memory (Bedi and Redman 2008; Morgan 2000; Parrott 2001) and this view is further supported by the moderate to high beta values obtained for these drugs in our regression analysis. However, when alcohol, amphetamine, cannabis, cocaine, heroin, and ketamine were entered as covariants in our ANCOVAs the deficits shown by the present ecstasy group compared with the control groups were still significant for depression, impulsiveness, sleep, and the domains of memory with the exception of attention memory. Strikingly, this was also true for the past ecstasy group. Thus, the elevated depression, increased impulsiveness, sleep disturbance, and memory impairment recorded for both past and present ecstasy groups are unlikely to be a result of exposure to alcohol, amphetamine, cannabis, cocaine, heroin, or ketamine alone. Nevertheless, at the time of testing the majority of participants in all but the ND group were still using the non-ecstasy recreational drugs of their choice. Consequently, the behavioral impairments recorded by our past and present ecstasy users may have arisen from the combination of ecstasy with other illicit drugs.

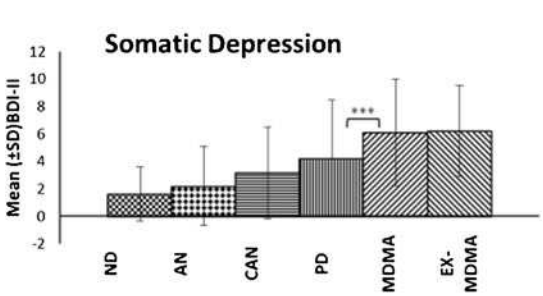
Fig. 2 Mean scores (±SD) on the Subscales of the Beck Depression Inventory II (BDI-II) and the Barratt Impulsiveness Scale (BIS-11) plus the Five Components of the Wechsler Memory Scale-Revised (WMS-R) for the control groups (no drug (ND), $N=182$; alcohol and nicotine (AN), $N=172$; cannabis, alcohol, and nicotine (CAN), $N=163$; polydrug non-MDMA (PD), $N=169$) and the Ecstasy Groups (Present Users (MDMA), $N=154$; past users (EX-MDMA), $N=157$). The numerical values of the means and standard deviations are presented in Table 2. Probability of difference between adjacent bars: $*p<0.05$, $**p<0.01$, $***p<0.001$ (post hoc t tests with Bonferroni correction)

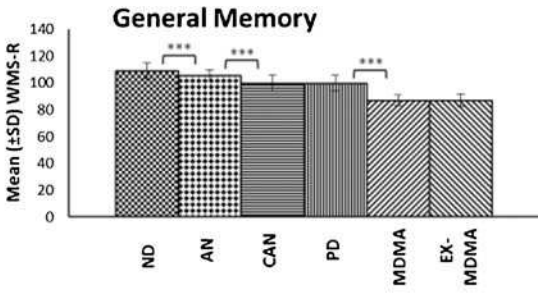
Future studies

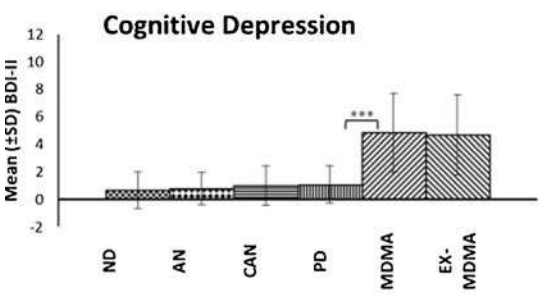
Although ecstasy users are typically polydrug users, there have been few studies to date that have addressed the issue of whether psychological deficits such as those we report are caused by ecstasy alone or in combination with other recreational drugs. One way of answering this question would be to include an ecstasy only group as did Gerra et al. (1998) and their data support our present finding that ecstasy users demonstrate deficits in mood and impulsiveness. A second such study, Halpern et al. (2011), failed to find executive functioning deficits when comparing ecstasy only participants with non-ecstasy users. Unfortunately, major concerns with these ecstasy only studies are small samples and weak effect sizes. As an alternative approach, animal studies comparing MDMA alone and MDMA in combination with co-used recreational drugs would go some way towards addressing this issue (see for example Hernandez-Rabaza et al. 2010).

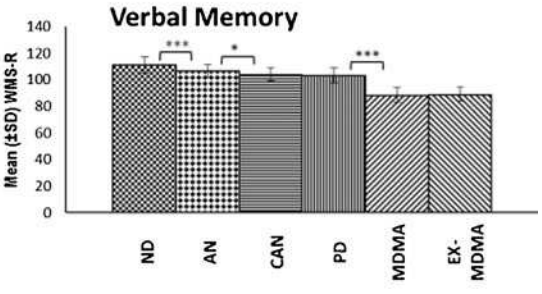
For the clinical picture, the issue of whether ecstasy-related impairments are caused by ecstasy alone or in combination with other illicit drugs is irrelevant because the majority of ecstasy users across the world are polydrug users. However, from a theoretical perspective, we cannot exclude the possibility that our results may be due to the acute and/or long lasting effects of other drugs used in combination with ecstasy. An additional consideration arises because the common recreational drugs promote the release of dopamine which is known to exacerbate the neurotoxic effects of ecstasy in animals (Granado et al. 2011). Consequently, future studies should investigate the possibility of a dopamine/ecstasy interaction in humans.

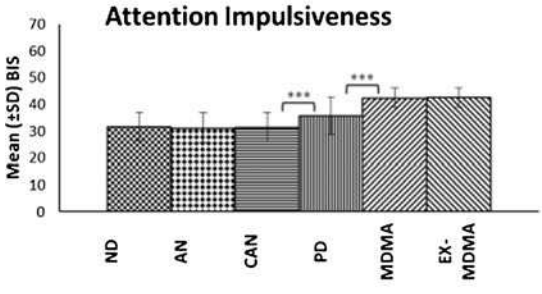
One of the objectives of our research was to understand what may happen in the future to young adults who have previously used ecstasy. We have shown that the adverse effects of ecstasy are long-lasting, persisting after prolonged abstinence. As past ecstasy polydrug users age, it is possible that life pressures may cause the behavioral impairments resulting from their previous exposure to ecstasy to increase, accelerating with the aging process and reaching clinically

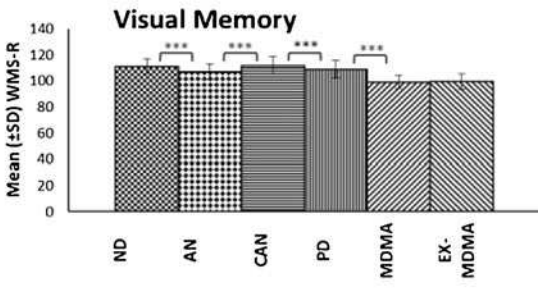

Somatic Depression
Mean (±SD)BDI-II
12
10
8
6
4
2
0
-2
***
ND
AN
CAN
PD
MDMA
EX-MDMA

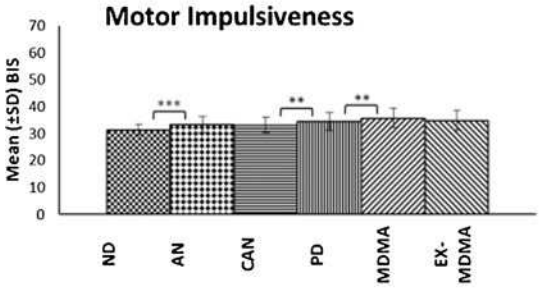

General Memory
Mean (±SD) WMS-R
140
120
100
80
60
40
20
0
***
***
***
ND
AN
CAN
PD
MDMA
EX-MDMA

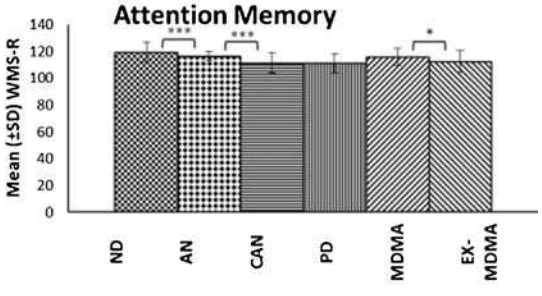

Cognitive Depression
Mean (±SD) BDI-II
12
10
8
6
4
2
0
-2
***
ND
AN
CAN
PD
MDMA
EX-MDMA

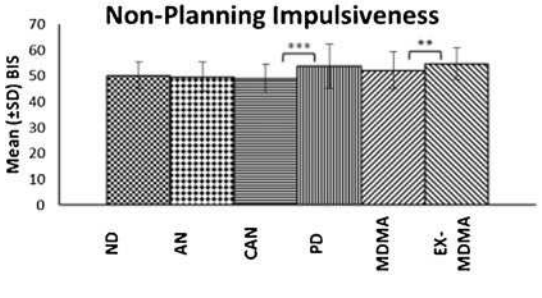

Verbal Memory
Mean (±SD) WMS-R
140
120
100
80
60
40
20
0
***
*
***
ND
AN
CAN
PD
MDMA
EX-MDMA


Attention Impulsiveness
Mean (±SD) BIS
70
60
50
40
30
20
10
0
***
***
ND
AN
CAN
PD
MDMA
EX-MDMA


Visual Memory
Mean (±SD) WMS-R
140
120
100
80
60
40
20
0
***
***
***
***
ND
AN
CAN
PD
MDMA
EX-MDMA


Motor Impulsiveness
Mean (±SD) BIS
70
60
50
40
30
20
10
0
***
**
**
ND
AN
CAN
PD
MDMA
EX-MDMA


Attention Memory
Mean (±SD) WMS-R
140
120
100
80
60
40
20
0
***
***
*
ND
AN
CAN
PD
MDMA
EX-MDMA


Non-Planning Impulsiveness
Mean (±SD) BIS
70
60
50
40
30
20
10
0
***
**
ND
AN
CAN
PD
MDMA
EX-MDMA

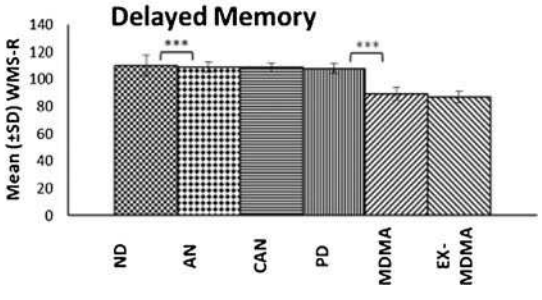

Delayed Memory
Mean (±SD) WMS-R
140
120
100
80
60
40
20
0
***
***
ND
AN
CAN
PD
MDMA
EX-MDMA

Table 4 Correlation and regression analysis of the association between lifetime exposure to ecstasy and the psychometric test scores for the Beck Depression Inventory II (BDI), Barratt Impulsiveness Scale (BIS-11), Pittsburgh Sleep Quality Index (PSQI), and Wechsler Memory Scale-revised (WMS)

Correlations with ecstasy exposure and age				Regression analysis								
Psychometric tests		*r*	*p*	Model		r^2	*F*(8, 302)	*p*	Predictors[a]	Beta	*t*	*p*
Main scales												
BDI	Global			BDI	Global	0.92	426.46	<0.001	Ecstasy	0.83	36.94	<0.001
	Ecstasy	+0.93	<0.001						Ketamine	0.15	5.30	<0.001
	Age	+0.74	<0.001						Age	0.13	4.18	<0.001
BIS-11	Global			BIS-11	Global	0.83	180.59	<0.001	Alcohol	−1.19	−5.37	<0.001
	Ecstasy	+0.84	<0.001						Cannabis	1.13	4.96	<0.001
	Age	+0.53	<0.001						Ecstasy	0.89	27.18	<0.001
									Cocaine	−0.49	−10.70	<0.001
									Ketamine	0.46	10.99	<0.001
									Amphetamine	0.13	2.56	0.011
PSQI	Global			PSQI	Global	0.94	536.17	<0.001	Ecstasy	0.75	37.13	<0.001
	Ecstasy	+0.94	<0.001						Cannabis	0.54	3.87	<0.001
	Age	+0.75	<0.001						Alcohol	−0.44	−3.20	0.002
									Age	0.11	4.04	<0.001
									Cocaine	0.11	3.98	<0.001
Subscales												
BDI	Somatic			BDI	Somatic	0.65	69.52	<0.001	Cannabis	1.65	5.08	<0.001
	Ecstasy	+0.72	<0.001						Alcohol	−1.41	−4.47	<0.001
	Age	+0.62	<0.001						Ecstasy	0.49	10.55	<0.001
BDI	Cognitive			BDI	Cognitive	0.27	14.07	<0.001	Alcohol	2.50	5.52	<0.001
	Ecstasy	+0.26	<0.001						Cannabis	−2.41	−5.16	<0.001
	Age	+0.37	<0.001						Age	0.44	4.80	<0.001
									Ketamine	−0.43	−5.02	<0.001
									Cocaine	0.29	3.11	0.002
BIS-11	Motor			BIS-11	Motor	0.89	301.50	<0.001	Alcohol	−1.15	−6.47	<0.001
	Ecstasy	+0.92	<0.001						Cannabis	1.12	6.14	<0.001
	Age	+0.58	<0.001						Ecstasy	0.94	35.60	<0.001
									Cocaine	−0.26	−7.14	<0.001
									Ketamine	0.22	6.68	<0.001
BIS-11	Nonplanning			BIS-11	Nonplanning	0.93	520.00	<0.001	Ecstasy	0.72	35.19	<0.001
	Ecstasy	+0.92	<0.001						Cocaine	0..20	6.89	<0.001
	Age	+0.79	<0.001						Age	0.15	5.21	<0.001
BIS-11	Attention			BIS-11	Attention	0.81	161.73	<0.001	Ecstasy	0.76	22.20	<0.001
	Ecstasy	+0.88	<0.001						Age	0.14	2.99	0.003
	Age	+0.69	<0.001									
Memory scales												
WMS	General			WMS	General	0.97	1,042.49	<0.001	Cannabis	−1.16	−11.34	<0.001
	Ecstasy	−0.54	<0.001						Alcohol	0.76	7.70	<0.001
	Age	−0.80	<0.001						Cocaine	−0.38	−18.81	<0.001
									Ketamine	−0.28	−14.71	<0.001
									Age	−0.06	−2.91	0.004
									Amphetamine	0.05	2.28	0.023
									Ecstasy	−0.04	−2.44	0.015
WMS	Verbal			WMS	Verbal	0.96	864.42	<0.001	Cocaine	−0.50	−22.51	<0.001
	Ecstasy	−0.41	<0.001						Cannabis	−0.44	−3.93	<0.001
	Age	−0.78	<0.001						Ketamine	−0.30	−14.59	<0.001

Table 4 (continued)

Correlations with ecstasy exposure and age				Regression analysis								
Psychometric tests		*r*	*p*	Model		r^2	$F(8, 302)$	*p*	Predictors[a]	Beta	*t*	*p*
									Age	−0.13	−5.81	<0.001
									Ecstasy	0.11	6.59	<0.001
									Amphetamine	0.07	2.94	0.004
WMS	Visual			WMS	Visual	0.95	783.98	<0.001	Cannabis	−1.44	−12.30	<0.001
	Ecstasy	−0.53	<0.001						Alcohol	1.09	9.60	<0.001
	Age	−0.78	<0.001						Cocaine	−0.49	−21.15	<0.001
									Ketamine	0.21	−9.58	<0.001
									Ecstasy	−0.04	−2.62	0.009
WMS	Attention			WMS	Attention	0.96	890.85	<0.001	Ketamine	−0.72	−35.35	<0.001
	Ecstasy	−0.44	<0.001						Alcohol	−0.54	−5.04	<0.001
	Age	−0.72	<0.001						Cannabis	0.37	3.35	0.001
									Cocaine	−0.23	−10.23	<0.001
									Ecstasy	−0.09	−5.84	<0.001
									Age	0.07	3.37	0.001
WMS	Delayed			WMS	Delayed	0.96	955.42	<0.001	Cannabis	−1.14	−10.71	<0.001
	Ecstasy	−0.53	<0.001						Alcohol	0.75	7.24	<0.001
	Age	−0.80	<0.001						Cocaine	−0.46	−21.60	<0.001
									Ketamine	−0.17	−8.64	<0.001
									Age	−0.09	−4.27	<0.001
									Amphetamine	0.06	2.38	0.018

[a] Initially, eight potential predictors were entered into the model, however, only the significant predictors are given for each measure and they are listed in descending order of their beta value ignoring sign

significant levels earlier than the same impairments would appear in the non-ecstasy population. In this regard, we should also note that, compared with past users, our present ecstasy users were younger, started consumption earlier, took larger doses, and consequently consumed more lifetime ecstasy. Thus, if the long-term effects of ecstasy are dose- and time-dependent, the prognosis for the current generation of ecstasy users is a major cause for concern. Future studies, including dose dependent studies in humans, should target this issue in an attempt to gather conclusive evidence for or against this view. Meanwhile, healthcare professionals need to be aware of the possible rise in depression, impulsiveness, sleep, and memory problems in ex-ecstasy users over the next decades and service provision should plan for an increase in ecstasy-related neuropsychological effects.

An additional health care problem may arise because increases in depression, impulsiveness, sleep disturbance, and memory impairment have all been correlated with a number of psychiatric disorders (Evenden 1999). Hence, it is plausible that ecstasy polydrug users, presenting with one psychiatric disorder, may have secondary disorders that are masked and undiagnosed.

Conclusions

Our results revealed impaired memory and clinically significant levels of depression, impulsiveness, and sleep disturbance in polydrug ecstasy users. Past ecstasy users showed few signs of recovery. In the light of these findings, the prognosis for the current generation of ecstasy users is a major cause for concern and healthcare service provision should plan for an increase in ecstasy-related neuropsychological effects over the next decades. Future research should include (1) animal studies comparing MDMA alone with MDMA in combination with other recreational drugs and (2) human studies of whether the long-term effects of ecstasy are dose and time dependent. In addition, given that disorders in 5HT-based behaviors such as those we have reported are probably the result of ecstasy-induced neurotoxicity, future research should

investigate the possible exacerbating effects of dopamine and also 5HT-related treatment options.

Acknowledgments The authors declare no conflict of interest and no sources of external funding. The study formed part of a PhD thesis submitted by LT and supervised by CC and GS.

References

Allen RP, McCann UD, Ricaurte GA (1993) Persistent effects of (+/−)3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. Sleep 16:560–564

Battaglia G, Yeh SY, De Souza EB (1988) MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacol Biochem Behav 29:269–274

Beck AT, Ward C, Mendelson M (1961) Beck Depression Inventory (BDI). Arch Gen Psychiatry 4:561–571

Bedi G, Redman J (2008) Ecstasy use and higher-level cognitive functions: weak effects of ecstasy after control for potential confounds. Psychol Med 38:1319–1330

Blagrove M, Seddon J, George S, Parrott AC, Stickgold R, Walker MP et al (2011) Procedural and declarative memory task performance, and the memory consolidation function of sleep, in recent and abstinent ecstasy/MDMA users. J Psychopharmacol 5:465–477

Bland JM, Altman DG (1997) Statistical notes: Cronbach's alpha. Br Med J 314:572

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index (PSQI): a new instrument for psychiatric research and practice. Psychiatry Res 28:193–213

Carhart-Harris RL, Nutt DJ, Munafò M, Wilson SJ (2009) Current and former ecstasy users report different sleep to matched controls: a web-based questionnaire study. J Psychopharmacol 23:249–257

Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Erlbaum, Hillsdale

Curran HV (2000) Is MDMA ('ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 42:34–41

Curran HV, Travill RA (1997) Mood and cognitive effects of +/−3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. Addiction 92:821–831

Daumann J Jr, Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E (2004) Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. Biol Psychiatry 56:349–355

De Win MM, Schilt T, Reneman L, Vervaeke H, Jager G, Dijkink S et al (2006) Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study. J Psychopharmacol 20:226–235

EMCDDA (2012) 2012 Annual Report of the State of the Drugs Problem in Europe. European Monitoring Centre for Drugs and Drug Addiction, Lisbon, November 2012. http://www.emcdda.europa.eu/publications/annual-report/2012. Accessed 18 Feb 2013

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology (Berl) 146:348–361

Falck RS, Wang J, Carlson RG (2008) Depressive symptomatology in young adults with a history of MDMA use: a longitudinal analysis. J Psychopharmacol 22:47–54

Fischer CA, Hatzidimitriou G, Wlos J, Katz JL, Ricaurte GA (1995) Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (+/−)3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). J Neurosci 15:5476–5485

Fisk JE, Montgomery C (2009) Sleep impairment in ecstasy/polydrug and cannabis-only users. Am J Addict 18:430–437

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R (1998) Serotonergic function after (+/−)3,4-methylene-dioxymethamphetamine ('ecstasy') in humans. Int Clin Psychopharmacol 13:1–9

Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J (2005) Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. Drug Alcohol Depend 78:317–323

Granado N, Ares-Santos S, Oliva I, O'Shea E, Martin ED, Colado MI et al (2011) Dopamine D2-receptor knockout mice are protected against dopaminergic neurotoxicity induced by methamphetamine or MDMA. Neurobiol Dis 42:391–403

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). Pharmacol Rev 55:463–508

Green AR, King MV, Shortall SE, Fone KCF (2012) Lost in translation: preclinical studies on 3,4-methylenedioxymethamphetamine provide information on mechanisms of action, but do not allow prediction of adverse events in humans. Br J Pharmacol 166:1523–1536

Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope HG Jr (2011) Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. Addiction 106:777–786

Hatzidimitriou G, McCann UD, Ricaurte GA (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/−)3, 4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19:5096–5107

Hernandez-Rabaza V, Navarro-Mora G, Velazquez-Sanchez C, Ferragud A, Marin MP, Garcia-Verdugo JM et al (2010) Neurotoxicity and persistent cognitive deficits induced by combined MDMA and alcohol exposure in adolescent rats. Addict Biol 15:413–423

Insel TR, Battaglia G, Johannessen JN, Marra S, De Souza EB (1989) 3, 4-Methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in rhesus monkeys. J Pharmacol Exp Ther 249:713–720

Kirilly E (2010) Long-term neuronal damage and recovery after a single dose of MDMA: expression and distribution of serotonin transporter in the rat brain. Neuropsychopharmacology (Hung) 12:413–423

Marsden J, Gossop G, Stewart D, Best D, Farrell M, Lehmann P, Edwards C, Strang J (1998) The Maudsley Addiction Profile (MAP): a brief instrument for assessing treatment outcome. Addiction 93:1857–1867

Morgan MJ (2000) Ecstasy (MDMA): a review of its possible persistent psychological effects. Psychopharmacology (Berl) 152:230–248

Parrott AC (2001) Human psychopharmacology of ecstasy (MDMA): a review of 15 years of empirical research. Hum Psychopharmacol 16: 557–577

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774

Ricaurte GA, Yuan J, McCann UD (2000) (+/−)3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy")-induced serotonin-neurotoxicity: studies in animals. Neuropsychobiology 42:5–10

Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P et al (2009) The harmful health effects of recreational ecstasy: a systematic review of observational evidence. Health Technol Assess 13:1–315, iii-iv, ix-xii

Roiser JP, Sahakian BJ (2004) Relationship between ecstasy use and depression: a study controlling for poly-drug use. Psychopharmacology (Berl) 173:411–417

Scholey AB, Owen L, Gates J, Rodgers J, Buchanan T, Ling J, Heffernan T, Swan P, Stough C, Parrott AC (2011) Hair MDMA samples are consistent with reported ecstasy use: findings from a

study investigating effects of ecstasy on mood and memory. Neuropsychobiology 63:15–21

Shen EY, Ali SF, Meyer JS (2011) Chronic administration of THC prevents the behavioural effects of intermittent adolescent MDMA administration and attenuates MDMA-induced hyperthermia and neurotoxicity in rats. Neuropharmacology 61:1183–1192

Sobell LC, Maisto SA, Sobell MB, Cooper AM (1979) Reliability of alcohol abuser's self-reports of drinking behavior. Behav Res Ther 17:157–160

Taurah LS (2011) The acute and long lasting psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): a cohort study conducted during the period 2002–2007. Ph.D. thesis. London Metropolitan University.

Verheyden SL, Henry JA, Curran V (2003) Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MAM) consumption in 430 regular users. Hum Psychopharmacol Clin Exp 18:507–517

Wechsler D (1987) Wechsler Memory Scale-Revised Manual. Psychological Corporation, San Antonio, TX