Psychopharmacology (2007) 189: 505–516
DOI 10.1007/s00213-005-0101-9

ORIGINAL INVESTIGATION

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Neuropsychological function in ecstasy users: a study controlling for polydrug use

Received: 3 June 2005 / Accepted: 3 June 2005 / Published online: 15 September 2005
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Abstract *Rationale:* A number of studies have compared ecstasy users to control groups on various measures of neuropsychological function in order to determine whether ecstasy use results in lasting cognitive deficits. However, few of those studies controlled adequately for non-ecstasy illicit drug use. *Objective:* The aim of this study was to investigate neuropsychological function in chronic ecstasy users while controlling for polydrug use. *Methods:* Neuropsychological function was assessed in four groups—30 current 3,4-methylenedioxymethamphetamine (MDMA) users with a little history of illicit drug use other than ecstasy and cannabis, 30 polydrug controls, 30 drug-naïve controls and 20 ex-MDMA users—using a battery of well-validated, computerized neuropsychological tests. The battery focused on memory, executive function, impulsivity and risk-taking. *Results:* Few differences were apparent between the groups, and on no measure were the current MDMA users impaired significantly relative to the polydrug controls. However, within the current MDMA users, questionnaire-measured impulsivity correlated with performance on a number of tests—a relationship that was not apparent in the controls. *Conclusions:* These data highlight the complexity in understanding the current ecstasy literature and suggest that some individuals may be particularly vulnerable to cognitive impairment following chronic use. Although no differences were identified between the current MDMA users and the controls, trait impulsiveness was significantly correlated with impairment on a number of neuropsychological outcome measures in the MDMA users, but not in the controls. These data suggest that impulsive individuals may be those most at risk for the development of cognitive impairment following chronic ecstasy use.

Keywords 3,4-Methylenedioxymethamphetamine (MDMA) · Ecstasy · Neuropsychology · Polydrug use · Executive function · Memory · Decision-making · Risk-taking · Impulsivity

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA or 'ecstasy') is a ring-substituted amphetamine derivative, whose use as a drug of abuse has increased steadily over the last 15 years. MDMA has a half-life of approximately 9 h in humans, and users report heightened mood, increased extroversion, derealization and mild perceptual alterations, with peak effects occurring approximately 2–4 h after ingestion (Gamma et al. 2000). MDMA, unlike other stimulant drugs, does not commonly produce a dependence syndrome, but rather is used recreationally at rave parties, especially in large dance clubs. Typically, users take at least one ecstasy tablet, containing anywhere from 0 to 150 mg of MDMA, although this is often mixed with other substances (Cole et al. 2002). Recent estimates have concluded that, in England, between 500,000 and 2,000,000 ecstasy tablets are taken each week (United Nations Office for Drug Control and Crime Prevention 2003).

There is good evidence that chronic MDMA administration causes long-term depletions of serotonin (5-HT) and its metabolite 5-hydroxyindole acetic acid (5-HIAA) in rats (Battaglia et al. 1991; McKenna and Peroutka 1990; O'Shea et al. 1998). A number of studies have also shown long-term depletions of 5-HT following MDMA administration in non-human primates (Ricaurte et al. 1992; Scheffel et al. 1998), in one case 7 years following initial administration (Hatzidimitriou et al. 1999).

Although no study has yet examined indices of 5-HT function before and after chronic ecstasy use in humans, a number of studies have compared ecstasy users to controls on various indices of 5-HT function. It has been reported that ecstasy users show reduced cerebrospinal fluid 5-HIAA concentration (Bolla et al. 1998; McCann et al. 1994; Ricaurte et al. 1990), blunted cortisol and prolactin response to fenfluramine challenge (Gerra et al. 2000; Verkes et al. 2001) and blunted response to the 5-HT_2 agonist *m*-chlorophenylpiperazine (McCann et al. 1999). In addition, ligand-binding studies employing positron emission tomography and single photon emission computed tomography have reported lower specific binding potentials to the 5-HT transporter in ecstasy users compared to controls (Buchert et al. 2004; McCann et al. 1998; Reneman et al. 2001; Semple et al. 1999; Thomasius et al. 2003). However, one of these studies found a degree of recovery in 5-HT transporter levels following a period of abstinence (Thomasius et al. 2003).

Several studies have reported that ecstasy users perform significantly worse on cognitive tests than controls. The most commonly reported deficit is in memory performance (see Morgan 2000 for a review), especially on tests of verbal recall, including the Rivermead Behavioural Memory Test (Morgan 1999) and the Wechsler Logical Memory Test (Rodgers 2000). However, results are equivocal, with some studies reporting no differences between ecstasy users and controls, especially if control groups and ecstasy using groups are matched for cannabis use (Croft et al. 2001; Dafters et al. 1999, 2003; Gouzoulis-Mayfrank et al. 2000). Measures of executive function, such as planning, task switching and working memory, are less commonly affected in ecstasy users (Fox et al. 2002; Gouzoulis-Mayfrank et al. 2003), although verbal fluency, considered to be a measure of 'cognitive flexibility', has frequently been reported to be impaired (Bhattachary and Powell 2001; Fox et al. 2002; Heffernan et al. 2001).

Data comparing ecstasy users to controls on questionnaire-based impulsiveness measures, such as the Impulsiveness, Venturesomeness and Empathy Questionnaire (IVE; Eysenck and Eysenck 1991) and the Barratt Impulsiveness Scale (Patton et al. 1995), have not been consistent, with some studies reporting elevated scores (Morgan et al. 2002; Parrott et al. 2000; Verheyden et al. 2002) and some reporting lower scores in ecstasy users relative to controls (McCann et al. 1994), but with others reporting no difference (Gouzoulis-Mayfrank et al. 2003; Morgan 1998). The few studies that have assessed decision-making behaviours in ecstasy users report conflicting findings (Butler and Montgomery 2004; Fox et al. 2002).

The aim of the present study was to evaluate neuropsychological performance in ecstasy users while controlling for non-ecstasy drug use. We aimed to test performance in four domains of function: episodic memory, executive function, decision-making and impulsivity. Based on previous findings, we predicted that the ecstasy users would differ from the drug-naïve controls on tests tapping episodic memory, decision-making and impulsivity, but not on those tapping executive function. We further predicted that no differences would be apparent between the ecstasy users and the polydrug controls on any measure of cognitive function.

Methods

Participants and experimental design

A cross-sectional design was employed to investigate neuropsychological function in four groups: current MDMA users, ex-MDMA users, polydrug controls with no history of ecstasy use and drug-naïve controls. The participants were recruited as described in Roiser and Sahakian (2004): 30 current MDMA users, 30 polydrug controls, 30 drug-naïve controls and 20 ex-MDMA users. Demographic and drug use statistics are provided in Tables 1, 2 and 3.

Procedure

Participants were tested at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital (Cambridge, UK). All participants provided informed consent, and the study was approved by the Cambridge Local Research Ethics Committee (LREC number 02/076). A 10-ml blood sample was taken, which was used to screen for the recent use of stimulants (performed by Tricho Tech; http://www.trichotech.co.uk) and to extract deoxyribonucleic acid as part of a related investigation. Verbal intelligence quotient (IQ) was estimated using the National Adult Reading Test (NART; Nelson 1982). Participants also completed a drug use questionnaire and the IVE (Eysenck and Eysenck

Table 1 Demographic characteristics

Variables	Current MDMA (mean (SD))	Polydrug control (mean (SD))	Drug-naïve control (mean (SD))	Ex-MDMA (mean (SD))	Significant difference
N (M:F)	30 (15:15)	30 (15:15)	30 (15:15)	20 (10:10)	–
Age (years)	22.4 (6.05)	25.7 (8.87)	24.0 (3.55)	27.5 (6.32)	EM>CM
NART IQ	114.4 (8.35)	111.7 (8.83)	113.9 (5.79)	111.9 (8.21)	–
Alcohol (units last month)	67.5 (48.41)	41.4 (37.33)	32.6 (28.58)	43.2 (57.9)	CM>NC and EM
Cigarettes (last month)	198 (189)	173 (252)	–	186 (223)	–

Table 2 Self-reported use of ecstasy

Variables	Current MDMA (mean (SD))	Ex-MDMA (mean (SD))	Significant difference (*p*)
Lifetime exposure (tablets)	274.6 (410.4)	792.6 (1,525.8)	–
Highest average regular dose (tablets)	4.0 (2.9)	4.0 (2.6)	–
Highest regular frequency (times per month)	4.8 (3.5)	9.9 (7.2)	0.005
Highest amount in a 12-h period (peak; tablets)	7.3 (4.3)	5.2 (2.6)	0.03
Time since last taken (days)	75 (79)	1,021 (1,018)	<0.001

1991). Following completion of the questionnaire measures, participants were administered a battery of neuropsychological tests focusing on memory, executive function and decision-making.

Psychological rating scales and neuropsychological assessment

All participants were assessed on the same battery of rating scales and neuropsychological tests as detailed below. Other than the Tile Manipulation test, all tests used in this study have been described elsewhere, so only a brief description is provided of each. All participants sat approximately 60 cm from a touch-sensitive computer screen controlled by an Advantech Pentium personal computer (Model PPC-120T-RT) and carried out the tests in the same order as described below.

IVE questionnaire

The IVE is a personality questionnaire that consists of 42 yes/no items that factor onto three personality domains: impulsiveness (self-control), venturesomeness (risk-taking) and empathy (identification with the emotional state of

Table 3 Self-reported use of illicit drug use other than ecstasy

Variables	Current MDMA (mean (SD))	Polydrug control (mean (SD))	Ex-MDMA (mean (SD))	Significant comparisons
Cannabis (*n*)	30	30	20	
Joints last month	36.5 (63.5)	53.0 (87.0)	41.1 (104.0)	–
Joints in lifetime	4,254.6 (8,775.0)	5,621.8 (11,704.9)	5,748.1 (11,890.0)	–
Psilocybin (*n*)	26	6	14	
Times in lifetime	5.1 (6.9)	4.9 (3.3)	14.3 (21.9)	–
LSD (*n*)	17	5	15	
Trips in lifetime	9.4 (9.5)	4.8 (5.8)	44.8 (99.1)	–
Amphetamine (*n*)	26	10	17	
Grams in lifetime	21.5 (32.9)	86.1 (148.0)	231.0 (330.9)	EM>CM
Amyl nitrate (*n*)	21	4	13	
Times in lifetime	11.4 (12.0)	57.3 (67.9)	9.7 (8.6)	–
Ketamine (*n*)	14	0	5	
Grams in lifetime	6.7 (7.0)	–	6.2 (6.9)	–
Cocaine (*n*)	25	8	19	
Grams in lifetime	11.8 (14.6)	6.4 (8.3)	161.0 (591.3)	EM>PC
Opiates (*n*)	5	0	9	
Grams in lifetime	0.2 (0.1)	–	68.2 (83.6)	EM>CM

Reported statistics include only those subjects reporting the use of substance.

another). Impulsiveness and empathy scores range from 0 to 19, while venturesomeness scores range from 0 to 16; in each case, high scores are indicative of high levels of these personality traits.

Tile Manipulation test

The Tile Manipulation test is a computerized version of the Block Design subtest of the Wechsler Adult Intelligence Scale and indexes spatial working memory and planning (Haaxma et al. 1993). Participants are required to recreate a two-dimensional pattern made up of four smaller blocks, picking from four correct blocks and four incorrect distractors. Participants carry out the test by touching the screen and moving each block to its correct position. Participants are encouraged to plan their answer before making their first response. In the first stage ('Copy'), participants simply have to identify and move a perfect match of each of the smaller blocks. In the second stage ('Mirror'), the smaller target blocks are the mirror image of those in the two-dimensional pattern. In the third stage ('Mental Rotation'), the smaller target blocks are the 180° rotation of those in the two-dimensional pattern. If participants make five consecutive errors, a grid is added to the two-dimensional pattern to aid the visualization of the smaller blocks. Four further errors are permitted before a participant is considered to have failed that problem. Measures arising from this test are the number of problems completed perfectly, the number of moves per problem and thinking time and a measure of latency unconfounded by impulsive responding. The 'Copy' stage of this test assesses spatial abilities, while the 'Mirror' and 'Mental Rotation' stages additionally assess working memory and planning.

Mental Rotation test

Working memory test is based on an original investigation by Shepard and Metzler (1971). Participants are required to decide if a letter, either an 'R' or an 'F', is presented as usually seen or in the mirror image. Letters are presented at various degrees of rotation (from 0° to 360° in 30° intervals) such that participants are required to mentally rotate the image before pressing the appropriate button on a response box. Stimuli are presented at a fixed interval of 2 s, with a failure to respond considered as an error. Measures arising from this task are the number of errors and the latency at each degree of rotation.

Decision-making task

The task used has been described previously (Rogers et al. 2003, 2004a,b). On each trial, participants are asked to choose between playing one of two simultaneously presented gambles (see Fig. 1). Each gamble is represented visually by a histogram, the height of which indicates the probability of winning a number of experimenter-defined points. Potential gains are indicated in green text above the histogram, while potential losses are indicated in red text underneath (note: all text in white in Fig. 1). One of the gambles (left in Fig. 1) is a 'control' gamble, consisting of a 0.5 probability of winning 10 points and a 0.5 probability of losing 10 points. The alternative 'experimental' gamble (right in Fig. 1) varies in the probability of winning (which can be either high or low; 0.75 vs 0.25), potential gains (which can be either large or small; 80 vs 20 points) and potential losses (which can be either large or small; 80 vs 20 points). An orthogonal combination of these three factors produces eight trial types.

The 'control' and 'experimental' gambles appear randomly on the left or right of the display. The participant presses the '1' or '2' key on the computer keyboard to indicate the choice of the gamble presented on the left or right. Measures arising from this task are the proportion of choices of the 'experimental' gamble over the 'control' gamble as a function of its probability of winning, the size of potential gains and losses ('proportionate choice') and the mean deliberation time for these choices.

As previously described (Rogers et al. 2003), we included two extra trial types that represented choices between gambles known to be subjected to the non-normative biases of risk-averting and risk-seeking behaviours (the 'reflection effect'; see Kahneman and Tversky 1979). The first of such type is a 'gains-only' trial in which volunteers are presented simultaneously with a guaranteed win of 40 points vs a 0.5 chance of winning 80 points and a 0.5 chance of losing 0 points. Neither option involves any losses. In contrast, on the 'losses-only' trials, the volunteers are presented simultaneously with a guaranteed loss of 40 points vs a 0.5 chance of losing 80 points and a 0.5 chance of losing 0 points. Neither option offers any gains. For both the 'gains-only' and 'losses-only' trials, measures arising are the proportion of trials on which the volunteers choose the guaranteed option and the mean deliberation time associated with these choices.

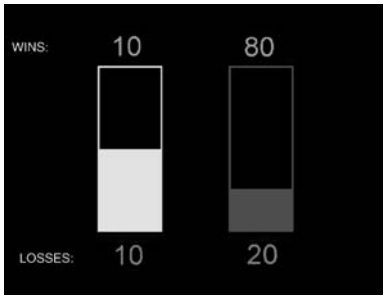

Fig. 1 Screenshot of the decision-making task. In this example, the participant has a choice between a gamble involving a 50% chance of winning 10 points and a 50% chance of losing 10 points, and a gamble involving a 25% chance of winning 80 points and a 75% chance of losing 20 points (Rogers et al. 2003)

Pattern Recognition Memory

In this episodic memory test, participants are shown a series of 12 abstract patterns and are instructed to remember them. Following a 5-s delay, each pattern, paired with a novel pattern, is then shown again to the participant in reverse order. Participants are required to make a forced-choice discrimination by touching the pattern they have seen previously. Feedback is provided to the participant by way of green ticks and red crosses. This procedure is then repeated with a further 12 patterns. Following a delay of approximately 20 min, the recognition phase of the task is repeated with the same forced-choice trials. Measures arising from this test are percent correct and latency.

Delayed Match to Sample

In this test of working memory, participants are presented with a complex abstract pattern, which they are required to remember. Following a variable delay of either 0, 4 or 12 s, four patterns are presented, one of which is identical to the pattern previously displayed. Participants are instructed to touch the pattern that they have seen before. As a control for motor speed, simultaneous match-to-sample trials are also included, where the complex abstract pattern does not disappear. Measures arising from this test are percent correct and latency.

Statistical analysis

Data were analysed using SPSS 10 (SPSS Inc., Chicago, IL, USA). Group differences, including all four groups (current MDMA, polydrug control, drug-naïve control and ex-MDMA) were analysed using analysis of variance (ANOVA) where test assumptions were met. When variances were significantly different between groups, Welch's F statistic was used in place of the standard ANOVA. Where appropriate, data were transformed prior to analysis to reduce skewness and stabilize variances. Proportionate choice data were arcsine-transformed, as is appropriate whenever the variance of a measure is proportional to its mean (Howell 2002); however, all of the data reported in the text and figures described untransformed values. Post-hoc comparisons were conducted using the Tukey Honest Significant Difference test if variances were equivalent, or Tamhane T^2 test if variances were significantly different. Of the drug use variables, only alcohol, tobacco, cannabis in the last month and ecstasy use variables (other than days since last use) were normally distributed following transformation. For other drug use variables, the non-parametric Kruskal–Wallis test was used, and post-hoc comparisons were conducted using the Mann–Whitney U test. For tests where more than one condition or set of conditions was present, repeated-measures ANOVA was employed. In cases where there was a departure from the assumption of homogeneity of covariance in the repeated-measures ANOVA, an epsilon (ε) factor was calculated and used to adjust degrees of freedom accordingly. The Greenhouse–Geisser procedure for adjusting the degrees of freedom was used, unless the value calculated was near or above 0.75, in which case the Huynh–Felt procedure was used (Howell 2002). Proportionate choice and mean deliberation times on the decision-making task were analysed using repeated-measures ANOVA with the between-subject factor 'group' and the within-subject factors 'probability of winning' (high vs low), 'size of potential gains' (large vs small) and 'size of potential losses' (large vs small). The proportionate choices and mean deliberation times for the 'gains-only' and 'losses-only' trials were analysed with 'group' as the between-subject factor and 'trial type' as the within-subject factor. For each of the above tests, a significance level of α=0.05 was adopted. Each variable in the study was additionally submitted to a correlational analysis against each of the drug variables. As a large number of correlations were carried out, a conservative significance level of α=0.005 was used to avoid type I errors.

Results

Demographic variables

The current MDMA users did not differ from the polydrug controls on any demographic or drug use variable. Both the current MDMA users and polydrug controls had relatively low use of illicit drugs other than cannabis and ecstasy. No participant showed a positive plasma screen for stimulant drugs. The groups differed in terms of monthly alcohol consumption; the current MDMA users had drunk more alcohol in the last month than the drug-naïve controls and the ex-MDMA users ($F_{3,106}$=3.6, p=0.016; post-hoc, p=0.008 and p=0.023, respectively). The ex-MDMA users were significantly older than the current MDMA users ($F_{3,106}$=2.9, p=0.038; post-hoc, p=0.039).

The ex-MDMA users had taken more ecstasy tablets than the current MDMA users (t_{48}=2.0, p=0.050), had taken ecstasy more frequently than the current MDMA users ($t_{29.6}$=3.4, p=0.002) and, as expected, had a longer abstinence period than the current MDMA users (Z=5.8, p<0.001). The ex-MDMA users had a greater lifetime exposure to amphetamine and opiates than the current MDMA users (Z=3.6, p<0.001 and Z=2.5, p=0.012, respectively) and also had a greater lifetime exposure to cocaine than the polydrug controls (Z=2.2, p=0.025).

Questionnaire measures

Table 4 lists all results from questionnaire and neuropsychological measures in this study. A number of behavioural measures correlated with the extent of previous drug use; any association reaching the α=0.005 significance level is

Table 4 Questionnaire and neuropsychological test data

Test/stage of test	Measure	Current MDMA	Polydrug control	Drug-naïve control	Ex-MDMA user	Significant comparisons
IVE						
	Impulsiveness	8.4 (4.4)	8.6 (3.5)	6.8 (4.5)	10.5 (5.3)	EM>NC
	Venturesomeness	10.5 (2.5)	10.1 (3.5)	10.7 (3.0)	9.6 (4.0)	–
	Empathy	12.7 (3.1)	13.2 (3.0)	12.3 (2.7)	13.8 (3.7)	–
Tile Manipulation						
Copy	Moves per problem	4.2 (0.34)	4.3 (0.38)	4.1 (0.22)	4.4 (0.33)	EM>NC
	Number completed perfectly	4.1 (1.1)	3.9 (1.1)	4.5 (0.90)	3.8 (0.95)	–
	Thinking time	1,499.8 (590.8)	1,927.5 (1,181.7)	1,912.3 (1,191.1)	2,049.7 (897.7)	–
Mirror	Moves per problem	4.5 (0.56)	4.8 (0.79)	4.4 (0.36)	4.9 (0.85)	–
	Number completed perfectly	2.6 (1.2)	2.2 (1.4)	2.6 (1.1)	2 (1.5)	–
	Thinking time	2,416.1 (1,004.3)	2,979.1 (1,684)	3,556.4 (2,604.6)	2,932.3 (1,438.4)	–
Mental Rotation	Moves per problem	4.8 (0.76)	4.8 (0.69)	4.6 (0.61)	4.7 (0.68)	–
	Number completed perfectly	2.4 (1.2)	2.1 (1.3)	2.6 (1.3)	2.2 (1.1)	–
	Thinking time	2,387.0 (1,175.6)	2,983.2 (1,691.5)	3,750.7 (2,527.7)	2,489.1 (923.4)	CM<NC[a]
Mental Rotation						
Standard	Latency	694.2 (105.7)	732.8 (135.7)	702.2 (90.6)	693.6 (106.5)	–
	Errors	5.2 (4.4)	6.4 (6.4)	4.7 (5.1)	6.4 (4.9)	–
Mirror	Latency	796.8 (95.4)	839.7 (154.8)	815.6 (111.5)	824.2 (105.6)	–
	Errors	5.5 (5.0)	5.6 (6.5)	4.6 (3.3)	7.4 (6.9)	–
Decision-Making						
High probability	Proportion choices	0.77 (0.19)	0.75 (0.17)	0.76 (0.16)	0.78 (0.15)	–
	Latency	2,376.2 (751.1)	2,190.6 (648.8)	2,291.8 (956.5)	2,363.3 (1,000.6)	–
Low probability	Proportion choices	0.27 (0.21)	0.29 (0.20)	0.20 (0.17)	0.24 (0.18)	–
	Latency	2,724.0 (991.3)	2,491.4 (909.4)	2,422.3 (935.5)	2,449.4 (957.0)	–
High win	Proportion choices	0.62 (0.14)	0.62 (0.17)	0.56 (0.12)	0.62 (0.13)	–
	Latency	2,434.8 (829.8)	2,365.5 (852.1)	2,387.2 (892.2)	2,430.8 (1,022.7)	–
Low win	Proportion choices	0.42 (0.13)	0.42 (0.13)	0.41 (0.11)	0.40 (0.12)	–
	Latency	2,665.4 (871.8)	2,316.6 (774.4)	2,326.9 (1,012)	2,382.0 (934.2)	–
High loss	Proportion choices	0.41 (0.17)	0.41 (0.19)	0.36 (0.18)	0.41 (0.12)	–
	Latency	2,632.3 (683.7)	2,344.8 (732.7)	2,431.0 (1,017.4)	2,564.4 (1,055.9)	–
Low loss	Proportion choices	0.64 (0.11)	0.62 (0.11)	0.61 (0.12)	0.61 (0.13)	–
	Latency	2,467.9 (1,010.0)	2,337.2 (747.1)	2,283.0 (858.6)	2,248.3 (871.0)	–
Gains only	Proportion choices	0.80 (0.27)	0.73 (0.32)	0.81 (0.24)	0.76 (0.32)	–
	Latency	2,219.5 (1,317.6)	2,006.1 (776.3)	2,353.0 (1,583.8)	2,279.5 (1,198.9)	–
Losses only	Proportion choices	0.27 (0.32)	0.37 (0.30)	0.40 (0.36)	0.42 (0.29)	–
	Latency	3,834.2 (1,770.5)	3,579.0 (1,691.4)	3,565.6 (1,927.8)	3,728.1 (1,704.2)	–
PRM						
Immediate	Percent correct	88.9 (15.1)	91.4 (10.7)	92.2 (7.3)	86.2 (14.9)	–
	Latency	1,753.2 (372.4)	1,672.5 (383.3)	1,713.1 (356.9)	1,729.5 (504.3)	–
Delayed	Percent correct	88.3 (8.4)	87.9 (12.4)	89.0 (9.4)	83.8 (16.5)	–
	Latency	1,701.7 (346.7)	1,748.7 (472.9)	1,678.3 (392.9)	1,849.9 (591.8)	–
DMTS						
Simultaneous	Percent correct	96.7 (6.1)	95.0 (7.3)	94.7 (7.3)	94.5 (8.9)	–
	Latency	3,019.6 (818.8)	3,244.4 (648.4)	3,120.8 (628.9)	3,164.8 (1,225.8)	–
0-s delay	Percent correct	90.3 (8.1)	89.0 (14.5)	89.3 (9.8)	88.0 (10.6)	–
4-s delay	Percent correct	88.7 (14.6)	86.7 (13.2)	89.0 (11.2)	87.5 (15.2)	–
12-s delay	Percent correct	80.3 (16.5)	77.3 (15.1)	77.7 (16.3)	76.5 (19.0)	–
	Latency	2,418.0 (488.0)	2,815.3 (842.6)	2,608.9 (610.3)	2,608.6 (604)	–

Numbers represent the mean (SD)
IVE Impulsiveness, Venturesomeness and Empathy Questionnaire, *PRM* Pattern Recognition Memory, *DMTS* Delayed Match to Sample
[a]The comparison no longer reached significance following statistical control for alcohol use

reported following the analyses of group differences for each test.

IVE questionnaire

The groups differed on impulsiveness ($F_{3,106}$=2.9, p=0.039), but not on venturesomeness or empathy. Post-hoc analyses revealed that the ex-MDMA users were significantly more impulsive than the drug-naïve controls (p=0.022) (see Fig. 2). Impulsiveness correlated with monthly tobacco use (r=0.46, p<0.0001), lifetime cannabis use (ρ=0.34, p<0.001), lifetime ecstasy use (r=0.59, p<0.0001), frequency of ecstasy use (r=0.46, p<0.001) and lifetime amphetamine use (ρ=0.44, p<0.001). Empathy correlated with lifetime amphetamine use (ρ=0.40, p=0.003).

Neuropsychological assessment

Tile Manipulation test

Data from one participant (a polydrug control) were not collected due to equipment failure. Therefore, the following analyses are based on data from 109 participants:

Copy stage

The ex-MDMA users made significantly more moves per problem than the drug-naïve controls ($F_{3,105}$=2.8, p=0.041; post-hoc, p=0.046) (see Fig. 3). The groups did not differ in terms of thinking time. 'Copy' stage thinking time correlated with lifetime amphetamine use (ρ=0.39, p=0.004).

Mirror stage

The groups differed on moves per problem (Welch's $F_{3,105}$=3.0, p=0.037). However, post-hoc analyses could not differentiate between the groups (p>0.1 for all comparisons). The groups did not differ in terms of thinking time. 'Mirror' stage thinking time correlated negatively with monthly alcohol use (r=−0.34, p<0.001) and positively with lifetime cocaine use (ρ=0.53, p<0.001).

Mental Rotation stage

The groups did not differ on moves per problem. However, the groups did differ in terms of thinking time ($F_{3,105}$=2.8, p=0.043). Post-hoc analyses revealed that the current MDMA users required less thinking time than the drug-naïve controls (p=0.037). However, monthly alcohol use showed a strong trend towards correlating with thinking time (r=−0.26, p=0.006), and when alcohol use was included as a covariate, this comparison no longer reached statistical significance ($F_{3,104}$=1.9, p=0.13). Lifetime cannabis use correlated positively with 'Mental Rotation' stage moves per problem and negatively with number completed perfectly (ρ=0.34, p=0.002 and ρ=−0.31, p=0.005). 'Mental Rotation' stage thinking time correlated with lifetime cocaine use (ρ=0.41, p=0.003).

Mental Rotation test

Data from one participant (an ex-MDMA user) were not collected due to equipment failure. Therefore, the following analyses are based on data from 109 participants. As not all participants made at least one correct response at every angle in both reflection conditions, the analyses of latency are based on data from 99 participants.

Participants were slower ($F_{1,95}$=204.6, p<0.001) when the letters were in the mirror image, were slower ($F_{3.1,296.7}$=342.8, p<0.001, ε=0.52) and less accurate ($F_{3.8,400.2}$=75.3, p<0.001, ε=0.64) at higher degrees of rotation and were particularly slow ($F_{3.4,320.5}$=14.0, p<0.001, ε=0.56) and inaccurate ($F_{3.7,386.7}$=11.0, p<0.001, ε=0.61) at higher degrees of rotation when the letters were in the mirror image. The main effects of group and all interactions with group were non-significant. There was a marginal reflection × angle × group interaction ($F_{11.1,386.7}$=1.8, p=0.053, ε=0.61). However, since this interaction did not reach the α=0.05 level of significance, it was not analysed further.

Decision-making

Proportionate choice

As expected, participants chose the 'experimental' gamble over the 'control' gamble more often when the probability of winning was high ($F_{1,106}$=314.8, p<0.001), when potential gains were high ($F_{1,106}$=190.3, p<0.001) and when potential losses were low ($F_{1,106}$=152.1, p<0.001). However, neither the main effect of group nor any interactions with group approached significance.

Deliberation times

Participants were quicker when the probability of winning was high ($F_{1,106}$=13.7, p<0.001) and when potential losses were low ($F_{1,106}$=12.0, p<0.001), but potential gains did not affect latency ($F_{1,106}$<1). However, neither the main effect of group nor any interactions with group approached significance.

'Gains-only'/'losses-only' trials: proportionate choice

All participants showed the usual reflection effect ($F_{1,106}$=64.8, p<0.001). However, the reflection effect did not differ between the groups ($F_{3,106}$<1).

'Gains-only'/'losses-only' trials: deliberation times

Participants made their choices more quickly on 'gains-only' trials than on 'losses-only' trials ($F_{1,106}$=103.0, p<0.001). However, this increase in deliberation time did not differ between the groups ($F_{3,106}$<1).

Pattern Recognition Memory

Participants were more accurate at the immediate stage of the Pattern Recognition Memory (PRM) ($F_{1,106}$=7.0,

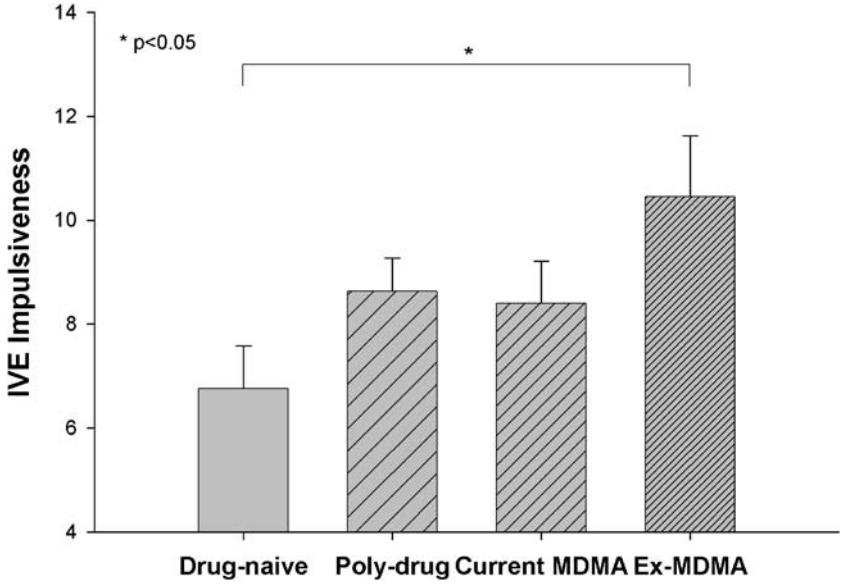

Fig. 2 IVE impulsiveness scores. Bars represent the mean; error bars represent one standard error of the mean (SEM)

p=0.009). The main effects of group and group × delay interaction were non-significant for both accuracy and latency. Delayed PRM latency correlated with total ecstasy use (r=0.40, p=0.004), lifetime amphetamine use (ρ=0.45, p=0.001) and lifetime cocaine use (ρ=0.40, p=0.004).

Delayed Match to Sample

Participants were more accurate ($F_{3,318}$=44.4, p<0.001) and quicker ($F_{1,106}$=72.2, p<0.001) in matching with the sample at shorter delays. The main effects of group and group × delay interaction were non-significant for both accuracy and latency.

Correlations with IVE impulsiveness

Since the sample of ecstasy users in the present study did not score higher on the impulsiveness subscale of the IVE than either control group, and since it has recently been reported that cognitive impairment following acute tryptophan depletion was related to trait impulsiveness (Cools et al. 2005), we sought to determine whether our failure to identify differences between current MDMA users and controls might be related to the relatively low levels of impulsiveness in the MDMA users.

In the MDMA users (current users and ex-users combined; N=50), greater impulsiveness was associated with latency at the delayed stage of the PRM test (r=0.33, p=0.029) and negatively with percent correct at the 12-s

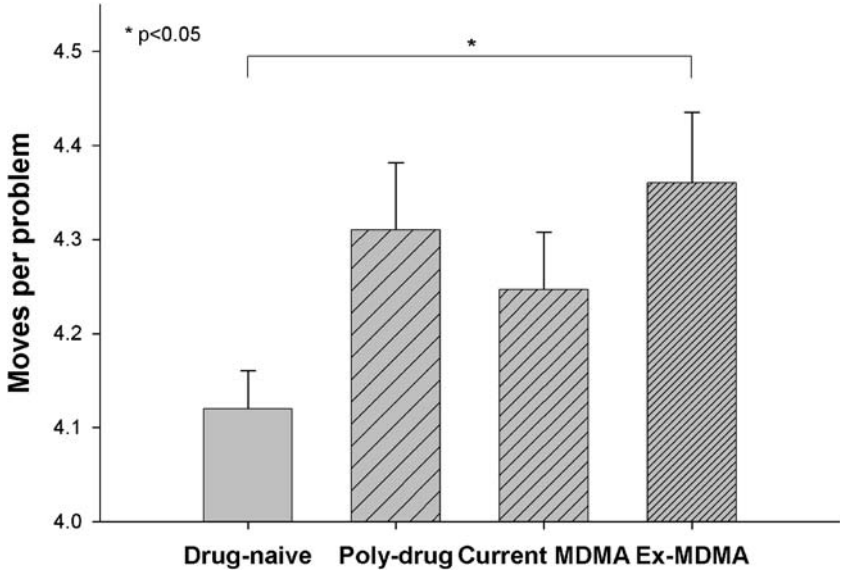

Fig. 3 Moves per problem at the 'Copy' stage of the Tile Manipulation test. Bars represent the mean; error bars represent 1 SEM

(most difficult) stage of the Delayed Match to Sample (DMTS) test (r=−0.44, p=0.001). In addition, impulsiveness correlated with the Tile Manipulation test 'Copy' stage thinking time (r=0.33, p=0.021), 'Mirror' stage moves per problem (r=0.39, p=0.005) and the number completed perfectly (r=−0.36, p=0.011). However, 'Copy' stage thinking time and impulsiveness were both also correlated with lifetime amphetamine use, and when amphetamine use was controlled for statistically, the relationship between these two variables only showed a trend towards significance (r=0.273, p=0.058). In the current MDMA users (N=30), impulsiveness correlated negatively with discrimination between high and low potential gains on the decision-making task (r=−0.41, p=0.024).

In the controls (N=60), impulsiveness correlated positively with accuracy at the simultaneous stage of the DMTS (r=0.30, p=0.018).

Discussion

This study used a cross-sectional design to investigate neuropsychological function in regular ecstasy users. The results in each of the domains of function assessed will be discussed in turn and compared to previous studies examining cognitive function in ecstasy users.

Executive function

On the 'Mental Rotation' test, the Tile Manipulation test and the DMTS, the current MDMA users did not differ from either control group. The ex-MDMA users made more moves per problem than the drug-naïve controls at the 'Copy' stage of the Tile Manipulation test, but not at the 'Mirror' or 'Mental Rotation' stage. This finding is more suggestive of a parietal impairment in the ex-MDMA users than a frontal impairment, since the groups differed only at the 'Copy' stage, a purer measure of spatial ability, and did not differ at the high working memory stages of the test.

Accuracy on the Tile Manipulation test at the 'Mirror' stage was associated with impulsiveness in the ecstasy users. An association between thinking time at the 'Copy' stage and impulsiveness in ecstasy users was unclear and at least partially confounded by amphetamine use. Impaired accuracy at the most difficult stage of DMTS was correlated with impulsiveness. In the controls, increased impulsiveness was related to a better performance on the DMTS.

A number of studies have examined other tests of executive function in ecstasy users, with some reporting impairments (Alting Von Geusau et al. 2004; Fox et al. 2001; Wareing et al. 2000, 2004; Zakzanis and Young 2001) and others reporting no impairments (Gouzoulis-Mayfrank et al. 2003) on various measures of executive function. However, none of these studies controlled adequately for other non-ecstasy illicit drug use or measured impulsivity. In particular, Wareing et al. (2004) reported that when cannabis use was controlled for statistically, the impairment in the ecstasy users no longer reached statistical significance.

Episodic memory

On the PRM, the current MDMA users did not differ from either control group. However, latency at the delayed stage of PRM correlated with trait impulsiveness in the ecstasy users but not the controls. The finding that, overall, the ecstasy users did not score worse than controls on this visual episodic memory test was in disagreement with previous findings that visual memory was impaired in ecstasy users (Fox et al. 2002; Verkes et al. 2001), but was in agreement with other reports finding no impairment (Bhattachary and Powell 2001; Rodgers 2000). However, none of these studies measured impulsivity and also did not control fully for non-ecstasy drug use, making comparison with the present study difficult.

Impulsivity and decision-making

The ex-MDMA users scored higher on IVE impulsiveness than the drug-naïve controls. The ex-MDMA users, current MDMA users and polydrug controls did not differ. Previous research on questionnaire-measured impulsivity in ecstasy users has provided conflicting results (Butler and Montgomery 2004; McCann et al. 1994; Morgan 1998). However, in the current study, since IVE impulsiveness was correlated not only with ecstasy use but also with other indices of drug use, such as cannabis and amphetamine, it is possible that such elevated impulsiveness scores are not caused by ecstasy use per se but may instead reflect the personalities of those individuals who choose to abuse illegal drugs. As discussed above, the most impulsive ecstasy users were also those most impaired on tests of visual episodic and working memory.

The decision-making task failed to differentiate the groups in this study. This finding was somewhat surprising since Rogers et al. (2003) reported that tryptophan depletion resulted in reduced discrimination between potential gains on the same task in healthy volunteers, although it was in agreement with Fox et al. (2002), who reported that ecstasy users were not impaired on another decision-making task (Rogers et al. 1999).

However, a contemporaneous study using an amended version of the decision-making task used in the present study has found significant deficits in ecstasy users (Morgan, Impallomeni, Pirona and Rogers, unpublished). These authors compared the decision-making of a sample of recreational ecstasy users (who reported a modest use of illicit drugs other than cannabis), a sample of polydrug controls (ecstasy-naïve illicit drug users) and a sample of drug-naïve controls—finding that the ecstasy users showed reduced discrimination between potential gains and losses when making choices compared to the two control groups. Discrimination between the probabilities of different outcomes was not affected.

There are several possible factors that might account for the discrepancy between these results and the results of the present study, including the use of a task with a slightly reduced variability in the probability of winning and losing (0.66 vs 0.33 compared to 0.75 vs 0.25 as used here). However, in contrast to the current MDMA users who participated in our study, the ecstasy users studied by Morgan et al. were significantly more impulsive than both the polydrug controls and the drug-naïve controls, as measured by the Matching Familiar Figures Test (Cairns and Cammock 1978). Notably, the discrimination between high-potential and low-potential wins was significantly correlated with IVE impulsiveness in our current MDMA user group. In the study of Morgan et al., the changes on the part of the ecstasy users were associated with higher impulsivity scores on the Matching Familiar Figures Test, highlighting the possibility that impulsivity mediates cognitive impairments in ecstasy users and suggesting that it is associated with a failure to attend to reinforcement signals in the context of risky choice. This result is also consistent with a recent report showing that impulsive healthy volunteers were those most affected by acute tryptophan depletion, a dietary manipulation resulting in reduced 5-HT synthesis, on a test of cued-reinforcement operant responding (Cools et al. 2005).

A recent study employing a novel risk-taking measure, the Bets16, reported that 'high-ecstasy users', although not 'low-ecstasy users', displayed greater risk-taking behaviours (Butler and Montgomery 2004). However, the 'high-ecstasy' and 'low-ecstasy' users in that study differed from controls in terms of ecstasy use, use of other illicit drugs and impulsiveness, making this result difficult to interpret. Previous studies examining the effects of chronic drug use on risk-taking behaviour have found specific effects depending on the drug abused (Rogers et al. 1999). Future studies examining decision-making in ecstasy users should therefore attempt to match ecstasy users and comparison subjects on measures of non-ecstasy illicit drug use.

Study limitations and potential improvements

The aim of this study was to assess cognitive function in ecstasy users while controlling for polydrug use. Although this was achieved for the current MDMA users, who did not differ from the polydrug controls on any measure of illicit drug use, the ex-MDMA users had significantly greater past cocaine use than the polydrug controls, which may have contributed to some of the impairment seen in this group. The ideal control group with which to compare the ex-MDMA users recruited in the present study would consist of individuals who had past regular cannabis, cocaine and amphetamine use and with no exposure to ecstasy, but were now leading relatively drug-free lives. However, recruitment of such individuals in sufficient numbers for a meaningful comparison would be very difficult.

In this study, few differences were identified between the groups and none between the polydrug controls and the current MDMA users. This could be due to the matching of the groups, but might also be a result of low statistical power. Although larger than most studies in the literature, with N=30 in the largest groups, this study had 80% power to identify an effect size of 0.72 at α=0.05. The value 0.72 is in the range of a large effect size (Cohen 1988), and it is therefore likely that a difference of medium effect size (e.g. 0.5) might have been missed. It is also conceivable that the tests used in this study were not sensitive to 5-HT disturbance. However, some of the tests used have been employed to demonstrate cognitive changes following acute tryptophan depletion (Rogers et al. 2003; Rubinsztein et al. 2001); therefore, this explanation seems unlikely.

Finally, the MDMA users selected in this sample may not provide a true reflection of the general MDMA user population. The current MDMA users were selected based on a low use of other illegal substances, although their ecstasy use was relatively high compared to those included other studies. However, this recruitment strategy may have resulted in an unusual sample of MDMA users—in particular, the MDMA users studied here were not significantly more impulsive than the drug-naïve controls. Notably, the most impulsive MDMA users were those most impaired on tests of visual episodic and working memory, and also showed reduced discrimination between potential wins on the decision-making task—correlations that were not present in the controls.

These data are consistent with previous studies suggesting that impulsive individuals or those with a family history of disorders relating to impulse control are most vulnerable to cognitive impairment following acute tryptophan depletion (Cools et al. 2005; LeMarquand et al. 1999; Sobczak et al. 2002). Since impulsive individuals are more likely to use illegal substances (Moeller et al. 2001), these data suggest that those most likely to use ecstasy may also be those most likely to suffer from long-term cognitive problems following chronic use. However, it is acknowledged that this supposition is based only on post-hoc correlational analyses and that the causality of this relationship would be better ascertained by a longitudinal study.

In contrast to most other studies, the current MDMA users in this sample also reported levels of depressive symptomatology to equivalent to those of controls (Roiser and Sahakian 2004). Since depression is associated with impaired cognitive function (Tavares et al. 2003), the relatively low levels of depression might also have contributed to the lack of cognitive impairment seen in this sample of ecstasy users.

Summary

This study compared current MDMA users, polydrug controls, drug-naïve controls and ex-MDMA users on a battery of tests measuring episodic memory, executive

function, decision-making and impulsivity. Significant differences were found between the ex-MDMA users and the drug-naïve controls on the impulsiveness scale of the IVE and the 'Copy' stage of the Tile Manipulation test. Within the ecstasy users, but not the controls, poorer performance on a number of tests was related to questionnaire impulsiveness. These data highlight the complexities in interpreting cross-sectional studies of ecstasy users and controls. Longitudinal studies are needed to unambiguously determine whether chronic ecstasy use leads to long-term cognitive impairment and whether particular groups or individuals are more vulnerable to its effects than others.

Acknowledgements This study was funded by a Wellcome Trust Program Grant (number 019407) to Trevor Robbins, Barbara Sahakian, Barry Everitt and Angela Roberts, and was completed within the MRC Centre for Behavioural and Clinical Neuroscience. J.P.R. was funded by a Medical Research Council Studentship. Many thanks to Caroline Humphries and all the staff at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital, for their help and support. We would also like to thank Professor Trevor Robbins and Dr. Andrew Blackwell for a valuable discussion of the manuscript, and the Cambridge Evening News for their support in recruiting the participants. Barbara Sahakian is a consultant for Cambridge Cognition.

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