Psychopharmacology (2004) 173: 434–439
DOI 10.1007/s00213-004-1791-0

ORIGINAL INVESTIGATION

K. McCardle · S. Luebbers · J. D. Carter · R. J. Croft · C. Stough

Chronic MDMA (ecstasy) use, cognition and mood

Received: 8 July 2003 / Accepted: 18 December 2003 / Published online: 16 April 2004

Abstract *Rationale:* It has been suggested that 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) causes damage to the serotonergic system, and that this damage results in cognitive and mood impairments. *Objectives:* To examine the effect of chronic MDMA usage on a wide battery of cognitive tests and psychological abilities and processes. *Methods:* In the present study, the performance of 17 participants with a history of MDMA use was compared to the performance of 15 control subjects on a battery of neuropsychological tests. This battery included tests for depression, immediate word recall, delayed recall, attention and working memory. *Results:* Results indicated that the MDMA group had significantly higher scores for depression than the control group, and displayed poorer delayed recall and verbal learning than controls after accounting statistically for the effects of cannabis and depression. *Conclusions:* These results suggest that MDMA users exhibit difficulties in coding information into long-term memory, display impaired verbal learning, are more easily distracted, and are less efficient at focusing attention on complex tasks.

Keywords Ecstasy · Cognition · Mood · MDMA

Introduction

Ecstasy, or 3,4-methylenedioxymethamphetamine (MDMA), is one of the most widely used illicit drugs (Peroutka et al. 1988; Krystal et al. 1992; Grob 2000; Schifano 2000) and its physiological and cognitive effects are the topic of much debate (Cole et al. 2002; Croft 2002; Parrott 2002). The administration of MDMA increases the overall release of the monoamine neurotransmitters, in particular serotonin (5-HT) and noradrenaline and to a lesser extent, dopamine (Harold 2001). Numerous animal studies have shown MDMA to be neurotoxic (Molliver et al. 1990; Ricaurte et al. 1992; Steele et al. 1994; Bolla et al. 1998; Grob 2000). However, the implications of these findings for humans are less clear (Ricaurte et al. 1992; Cole et al. 2002).

Brain imaging studies in humans have suggested that MDMA use may damage serotonergic neurons (McCann et al. 1998; Semple et al. 1999; Reneman et al. 2001); however, these studies have relied on brain serotonin transporter (SERT) levels as an indicator of neuronal integrity. The reliability and validity of SERT measurements as an indicator of neurotoxicity is not well established, and changes in the levels of SERT do not necessarily reflect changes in neuronal integrity (Kish 2002). Post mortem studies provide more definitive evidence of damage to nerve terminals. Kish found that the autopsied striatum of a polydrug MDMA user was low in the level of serotonin, but that the concentration of dopamine was normal. However, this single case study is the only post mortem study reported to date. In general, direct assessment of serotonergic damage in humans as a result of MDMA use is limited by a number of ethical and practical constraints.

Behavioural studies provide an alternative method by which to assess consequences of MDMA use. They provide a means by which to assess the cognitive and mood effects of MDMA consumption and from such assessments, it is possible to determine whether the effects of MDMA are consistent with the expected consequences of serotonergic damage. A number of studies have found evidence of acute cognitive deficits occurring as a result of the use of MDMA. Prior to MDMA being outlawed in the USA, Downing (1986) administered pure MDMA to subjects and reported that MDMA had no significant effects on digit repetition performance but did impair performance on tests of multiplication. Curran and Travill (1997) compared MDMA users to alcohol drinkers on a prose recall task and a serial number subtraction task and found that MDMA users scored lower on the subtraction task. Parrott and Lasky (1998) compared a group of MDMA users to drug naive control subjects and found

K. McCardle · S. Luebbers · J. D. Carter · R. J. Croft · C. Stough (✉)
Swinburne Centre for Neuropsychology, Swinburne University, PO Box 218, 3122 Hawthorn, Victoria, Australia
e-mail: cstough@groupwise.swin.edu.au

that following self-administration of MDMA, the MDMA users recalled 60–70% fewer words than controls on a memory recall task. Further, 1 and 4 days after MDMA administration, these MDMA users still displayed significantly lower scores than controls on the memory recall task.

The long-term consequences of MDMA use have been evaluated in studies that have assessed MDMA users who have been abstinent for an extended period of time (Parrot and Lasky 1988; Krystal et al. 1992; Bolla et al. 1998; Morgan 1999; Gouzoulis-Mayfrank et al. 2000). Most of these studies have found that abstinent MDMA users display significant impairments on some, but not all, cognitive tests (Krystal et al. 1992). The most pronounced cognitive deficit appears to be on verbal memory tasks, such as word recall (Krystal et al. 1992; Bolla et al. 1998; Parrot and Lasky 1998). Some of these studies have controlled for the effects of drugs other than MDMA, as MDMA users are often polydrug users, with the majority finding MDMA-related cognitive deficits. Gouzoulis-Mayfrank et al. (2000) compared a group of MDMA users, who had been abstinent for 2–8 weeks, to a group of non-MDMA users who were matched for cannabis use. The groups displayed no difference on simple tests of attention, but MDMA users displayed lower scores on verbal working memory and tests of learning, such as digit span and word recall. Gouzoulis-Mayfrank et al. concluded that typical recreational doses of MDMA may be enough to cause neurotoxicity in humans. Similarly, Morgan (1999) compared MDMA users who had been abstinent for 65 days with polydrug users who had no history of MDMA use, and found evidence of cognitive impairments in the MDMA users. These findings suggest that MDMA users display long-term cognitive deficits, over and above the deficits displayed by users of drugs other than MDMA.

McCann et al. (1999) provided evidence to suggest that the cognitive deficits displayed by MDMA users are related to lower levels of 5-HT. They measured levels of CSF 5-HIAA, which is an indirect measure of brain 5-HT, in subjects who had been heavy MDMA users but who were abstinent for 3 weeks. They found that significant decreases in CSF 5-HIAA correlated with poor memory scores on a number of cognitive tasks, suggesting that MDMA use may lead to serotonergic damage and result in impaired short-term memory, complex attention and learning, verbal reasoning and semantic recognition.

In addition to the cognitive effects of MDMA use, MDMA may also affect mood, as serotonin plays an important role in mood regulation. It has been reported that individuals on MDMA often experience feelings of euphoria but once these effects have subsided, feelings of depression predominate (Parrott and Lasky 1998). Parrott and Lasky reported that subjects who had recently consumed MDMA felt significantly more depressed than control subjects. Additionally, Peroutka et al. (1988) found that depression was the fourth highest subacute symptom in a sample of 100 MDMA users. Curran and Travill (1997) reported that 2 and 7 days after MDMA consumption, some MDMA users revealed clinically borderline levels for depression, as measured by the Beck Depression Inventory (BDI). Whereas this finding suggested that MDMA has an acute effect on mood, the findings of Krystal et al. (1992) suggested that MDMA does not have a long-term effect on mood. They examined mood in heavy MDMA users who had been abstinent for an average of 2 months and found that abstinent MDMA users did not exhibit mood deficits, as assessed by the BDI. However, the study was limited by its small sample size, its use of subjects who had a history of psychiatric disorders and the fact that subjects were administered an intravenous infusion of tryptophan (which can enhance serotonin synthesis; Young et al. 1985), 3 h prior to testing.

In summary, previous studies have suggested that MDMA use may damage the serotonergic system and that this may lead to cognitive impairments and mood fluctuations. The present study investigated the long-term effect of MDMA use on both cognitive performance and mood, by comparing abstinent MDMA users to control subjects. It was postulated that MDMA users would perform more poorly than control subjects on immediate word recall, delayed recall, attention and working memory tasks, but perform equally well on other cognitive tasks. It was also postulated that MDMA users would display higher scores for depression on the mood scales than the control subjects.

Materials and methods

Participants

Seventeen individuals with a history of MDMA use (mean age=21.06 years, SD=1.56, 13 male) and 15 controls (mean age=21.93 years, SD=1.62, 13 male) without a history of MDMA usage participated in the study. Subjects in the MDMA group reported total lifetime consumption of ecstasy tablets twice to more than 30 occasions (ranges recorded were 2–3, 4–9, 10–15, 16–20 20–30, and 30+ occasions, median=4–9). On average, MDMA subjects consumed 1.65 ecstasy tablets per occasion and had used for 2.2 years (range 1–5 years). The average time since last use of ecstasy was approximately 130 days (4.5 months) and this ranged from one week (3 participants) to more than 21 months (one participant). Controls had never used MDMA. The MDMA and control groups did not significantly differ in terms of age, gender, level of education or IQ as assessed by the vocabulary test of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS III) (Wechsler 1981). All participants were recruited by poster advertisements.

Drug history questionnaire

A modified version of Solowij et al.'s (1992) drug history survey was provided to subjects. The questionnaire consisted of two parts. The first was completed by all participants and contained items pertaining to demographic information, general tobacco consumption, general alcohol consumption and use of illicit drugs other than MDMA. The second part was completed only by subjects in the MDMA group and contained items pertaining to frequency of MDMA use, usual dosage, side effects experienced, and the co-use of other drugs with MDMA.

Neuropsychological tests

The following neuropsychological tests were administered in the order in which they are described; the Rey Auditory Verbal Learning Test (AVLT) (Rey 1964, which consists of several verbal recall trials and provides a measure of immediate memory span (trial 1), verbal learning (trials 1–5), short-term memory after interference (trial 7) and long-term memory (trial 8); the digit span (DS) subtest of the WAIS-III which consists of DS forwards, which is a measure of efficiency of attention and DS backwards which is predominantly a measure of working memory (Lezak 1995); the Trail Making Test (TMT) which measures visual processing and visual-motor tracking (Giovagnoli et al. 1996) as well as motor speed and agility (Schear and Sato 1989); the Speed of Comprehension Test (SCT), which assesses language comprehension and psychomotor speed and requires rapid decision-making and visual scanning (Baddeley et al. 1992); the Digit Symbol Substitution Test (DSST), which is a test of motor persistence, sustained attention, response speed and visuo-motor coordination (Schear and Sato 1989).

The Vocabulary subtest of the WAIS-III was also administered, in order to provide an estimate of premorbid IQ.

Mood scales

Two measures of mood were employed in order to assess differences in mood state, particularly depression. These were the Beck Depression Inventory, Second Edition (BDI-II; Beck et al. 1996) and the Profile Of Mood State (POMS; McNair et al. 1992). The BDI–II was developed to address the specific diagnostic criteria for depression, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The BDI–II is a 21-item self-report inventory with items pertaining to symptoms of depression including agitation, concentration difficulty, worthlessness, loss of energy, and changes in sleep and appetite. Subjects are required to report the severity of symptoms for the last 2 weeks. The POMS measures seven primary dimensions of mood: Depression-Dejection, Tension-Anxiety, Anger-Hostility, Vigour-Activity, Fatigue-Inertia, Confusion-Bewilderment, and Friendliness-Openness. For the purpose of the present study, the seven-factor POMS was used consisting of 65 items with 5-point rating scales. Subjects responded as to how they had been feeling during the past week.

Procedure

The study was approved by the Swinburne University Human Research Ethics Committee and informed consent was obtained from all subjects. Subjects in the MDMA group were asked to have been abstinent from MDMA for at least 1 week, although in most cases, a longer period of abstinence was reported. Test administration was divided into three parts; drug history questionnaire and the mood scales, neuropsychological testing, and the vocabulary subtest of the WAIS-III. The order of these three parts was randomised and experimenters were blind to the group status of subjects. Total duration of the testing session was approximately 1.5 h.

Results

The means and standard deviations (SDs) of self-reported drug use for the MDMA and control groups are presented in Table 1. One-way ANOVAs revealed that the two groups did not significantly differ in terms of current or prior use of: cocaine, heroin, inhalants (e.g. amyl nitrate), or other inhalants (e.g. glue, petrol). There were, however, statistically significant differences between the groups for use of cannabis, hallucinogens, amphetamines, alcohol, other opiates, tranquillisers, barbiturates and tobacco (see Table 1). Groups did not differ on WASI vocabulary scores, suggesting that premorbid IQ did not differ between the groups [$F(1,30)=0.52$, $P>0.05$].

One-way ANOVAs were performed in order to assess differences in mood and depression between the MDMA and control groups. There was a significant difference between the two groups on total BDI-II scores [$F(1,30)=6.47$, $P<0.05$]. This was due to the MDMA group scoring higher (mean=12.35, SD=9.41) than the control group (mean=5.53, SD=4.64), as shown in Table 2. No significant differences were found between the two groups for any of the seven subscales of the POMS ($Z<1.63$, $P>0.05$; Mann-Whitney U-tests were employed due to difficulties normalising the data).

A multivariate analysis of variance (MANOVA) was performed to compare the performance of the MDMA and control groups on the neuropsychological tests. BDI–II scores and cannabis use were employed as covariates as both factors significantly differed between the groups and because depression and cannabis use both may influence cognitive function. A significant difference in cognitive function was found between the groups overall

Table 1 Means and standard deviations for self-reported drug consumption

	Control group (n=15)		MDMA group (n=17)		F-value
	M	SD	M	SD	–
Cannabis	1.60	0.91	3.06	0.75	24.77**
Hallucinogens	1.20	0.56	2.29	0.69	23.99**
Amphetamine	1.20	0.56	2.35	0.93	17.38**
Alcohol[a]	3.33	0.72	4.29	0.77	13.09**
Other opiates (e.g. methadone)	1.07	0.26	1.71	0.85	7.84*
Tranquilizers	1.07	0.26	1.59	0.71	7.19*
Barbiturates	1.07	0.26	1.53	0.62	7.14*
Tobacco[b]	1.80	1.37	3.00	1.37	6.10*
Heroin	1.00	0.00	1.18	0.39	3.01
Amyl nitrate	1.07	0.26	1.35	0.61	2.88
Cocaine	1.13	0.35	1.41	0.62	2.36
Other inhalants (e.g. glue)	1.07	0.26	1.06	0.24	0.01

[a]1=Never drink alcohol, 2=No longer drink alcohol, 3=Less than once a week, 4=1–2 days a week, 5=3–4 days a week, 6=5–6 days a week, 7=Every day
[b]1=Never smoked, 2=No longer smoked, 3=Smoke occasionally, 4=1–10 cigarettes/day, 5=More than 10 cigarettes/day
For all other substances: 1=Never tried, 2=Tried/used in past, 3=Use socially/occasionally, 4=Use regularly
*$P<0.05$, **$P<0.001$

Table 2 Means and standard deviations for mood and depression rating scales

Scale	Controls		MDMA		*F*-value
	Mean	SD	Mean	SD	
Total BDI–II	5.53	4.64	12.35	9.41	6.47*
BDI cognitive-affective	2.07	2.58	5.29	5.02	5.02*
BDI somatic	3.47	2.88	7.06	4.93	6.11*
POMS friendliness	17.00	3.70	16.06	4.64	0.23
POMS confusion	9.14	4.91	7.88	6.05	0.24
POMS fatigue	8.00	3.87	6.47	6.00	0.38
POMS vigor	18.57	2.23	16.35	5.30	1.10
POMS anger-hostility	10.71	6.97	8.82	10.11	0.20
POMS depression-dejection	17.14	12.23	15.76	15.83	0.04
POMS tension	12.14	5.46	8.88	7.17	1.16

*$P<0.05$

[Wilks=0.255, $F(14,15)=3.13$, $P<0.05$]. Univariate tests revealed that after accounting for the covariates, the performance of the two groups differed significantly on four of the cognitive tests: AVLT 4 [$F(1,28)=6.00$, $P<0.05$]; AVLT 5 [$F(1,28)=4.30$, $P<0.05$]; AVLT 8, [$F(1,28)=7.90$, $P<0.01$]; DS forwards [$F(1,28)=5.51$, $P<0.05$]. Means and SDs of all cognitive tests are presented in Table 3 and indicate that compared to the MDMA users, the control group recalled more words in AVLT trials 4 and 5 (learning phase), displayed greater delayed recall in AVLT 8 and displayed more efficient attention on the DS forwards. Within the MDMA group, Spearman's measure of association failed to identify any relations between either of AVLT4, AVLT5, AVLT8 or DS forwards, and total lifetime consumption [$r(17)=0.17$, $P>0.05$; $r(17)=-0.07$, $P>0.05$; $r(17)=0.09$, $P>0.05$; $r(17)=0.16$, $P>0.05$, respectively], number of tablets per occasion [$r(17)=0.25$, $P>0.05$; $r(17)=-0.25$, $P>0.05$; $r(17)=-0.08$, $P>0.05$; $r(17)=0.42$, $P<0.10$, respectively], or time since last use [$r(17)=0.29$, $P>0.05$; $r(17)=0.48$, $P<0.10$; r(17)=0.09, $P>0.05$; $r(17)=0.37$, $P>0.05$, respectively].

Discussion

The results of the present study suggest that MDMA users display higher levels of depression and poorer cognitive functioning than controls.

MDMA users displayed significantly higher levels of depression than controls (as indexed by BDI–II ratings), with MDMA users' depression scores approaching clinical significance. This is consistent with previous findings that depression follows MDMA administration (Curran and Travill 1997; Parrott and Lasky 1998). Further, MDMA users in the present study reported being abstinent for an average of 130 days, suggesting that feelings of depression may not just result from temporary 5-HT depletion but from longer term effects on the serotonergic system, as suggested by Bolla et al. (1998).

Although, the MDMA group and control group displayed significantly different ratings of depression on the BDI–II, no significant differences were displayed on the POMS subscale of depression. This is possibly because the BDI–II contains extensive information specifically pertaining to depression in clinical populations, whereas the POMS provides a broader, less detailed profile of depression-like mood. The POMS may thus not be as sensitive to the kind of clinically relevant depressive symptoms that the MDMA participants exhibited.

As well as displaying higher levels of depression, MDMA users were found to perform worse than controls on a number of neuropsychological tests, a finding that is consistent with a number of previous studies (Krystal et al. 1992; McCann et al. 1999; Morgan 1999; Gouzoulis-Mayfrank et al. 2000).

Table 3 Means and standard deviations of cognitive measures for the control group and MDMA group. *AVLT* Rey Auditory Verbal Learning Test

Cognitive test	Control group (n=15)		MDMA group (n=17)		*F*-value
	M	SD	M	SD	–
AVLT 1 (words)	8.07	2.37	7.47	1.84	1.0
AVLT 2 (words)	10.53	2.50	9.94	2.05	2.2
AVLT 3 (words)	12.07	1.79	12.00	2.03	0.7
AVLT 4 (words)	13.40	1.30	12.76	1.89	6.0*
AVLT 5 (words)	13.40	1.55	12.41	1.97	4.3*
AVLT 7 (words)	11.93	2.46	11.65	2.42	3.7
AVLT 8 (words)	12.13	2.13	11.18	2.58	7.9**
AVLT learning rate	5.33	2.06	4.94	2.05	0.5
Trail Making A (s)	24.49	8.05	34.02	9.99	1.3
Trail Making B (s)	64.70	25.35	68.09	15.47	0.5
Digit span					
Forwards (digits)	7.07	0.96	6.41	0.87	5.5*
Backwards (digits	5.53	1.25	5.12	1.65	3.3
Speed of comprehension (% of sentences)	65.89	16.42	64.27	15.72	2.2
Digit symbol (symbols)	66.07	10.89	64.06	8.74	0.5

*$P<0.05$, **$P<0.01$

MDMA users performed significantly worse than controls on the delayed recall versions of the RAVLT, suggesting that MDMA users have a reduced capacity for verbal learning. This result is consistent with previous findings of impaired verbal learning in MDMA users (Parrot and Lasky 1988; Krystal et al. 1992; Bolla et al. 1998; McCann et al. 1999). MDMA users also performed significantly more poorly than controls on the DS forwards test, suggesting that MDMA users are more easily distracted than controls. This suggestion supports the finding that MDMA users perform poorly on complex tasks of attention (Gouzoulis-Mayfrank et al. 2000).

The cognitive impairments displayed by MDMA users are consistent with the type of impairments that result from 5-HT neurodegeneration. For example, consistent with animal research that has shown MDMA-related neurodegeneration in the hippocampus and widespread degeneration of serotoninergic axon terminals in the brain (Steele et al. 1994; Bolla et al. 1998), decreased serotonergic neurotransmission in humans has been found to impair a number of aspects of learning and memory (Altman et al. 1984; McEntee and Crook 1991), which are also thought to be related to hippocampal-limbic regions (e.g. Wood et al. 2002).

It is possible that the impairments in cognition and mood that were observed in MDMA users may have preceded MDMA exposure and that MDMA use may in fact be a form of self-medication. While this possibility cannot be discounted, it should be noted that the deficits reported here are consistent with the role of 5-HT in cognition (described above) and the findings of Croft et al. (2001a), where a relation between lifetime MDMA consumption and 5-HT dysfunction was found, independent of frequency of consumption. That is, the study of Croft et al. is consistent with the view that the observed 5-HT impairments in MDMA users may be caused by MDMA use, but difficult to reconcile with the view that MDMA is being used as a form of self-medication.

It is also possible that the impairments in cognitive functioning may be due to abuse of substances other than MDMA, as was found by others (Croft et al. 2001b). However, using a strong experimental design, Gouzoulis-Mayfrank et al. (2000) found results contrary to Croft et al. (2001b), demonstrating in a larger and better matched sample that MDMA users performed worse than controls on a range of cognitive tasks. Further, the MDMA users' poorer cognitive performance in the current study was found after covarying for (statistically removing) cannabis use, and so while the issue of polydrug contamination of MDMA research is far from resolved, there is no reason to believe that it is a problem in the present study.

Another criticism that has been leveled against MDMA research employing quasi-experimental designs is that it is not possible to accurately quantify the amount of MDMA self-administered. Commonly used ecstasy tablets may contain many other substances (Morgan 1999) and self-reports may be prone to reporter error. However, there is currently no evidence to suggest that this is more than a "hypothetical" problem.

In conclusion, the results of the present study suggest that recreational MDMA use is related to depression and poorer memory, learning and attention abilities. Of particular concern is that the feelings of depression reported by MDMA users in the present study approached clinical levels of depression. Longitudinal studies in which MDMA users are studied whilst using, and when abstinent, would provide further insight into the cognitive and mood impairments related to MDMA use and may also help to determine whether these effects are reversible.

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