Psychopharm

Journal of Psychopharmacology
20(2) (2006) 302–311

ISSN 0269-8811
SAGE Publications Ltd,
London, Thousand Oaks,
CA and New Delhi
10.1177/0269881106059495

Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls

C. T. J. Lamers *Experimental Psychopharmacology Unit, Department of Neurocognition, Brain and Behaviour Institute, Maastricht University, Maastricht, The Netherlands.*

A. Bechara *Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, The University of Iowa College of Medicine, Iowa City, IA, USA.*

M. Rizzo *Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, The University of Iowa College of Medicine, Iowa City, IA, USA.*

J. G. Ramaekers *Experimental Psychopharmacology Unit, Department of Neurocognition, Brain and Behaviour Institute, Maastricht University, Maastricht, The Netherlands.*

Abstract

Repeated ecstasy (MDMA) use is reported to impair cognition and cause increased feelings of depression and anxiety. Yet, many relevant studies have failed to control for use of drugs other than MDMA, especially marijuana (THC). To address these confounding effects we compared behavioural performance of 11 MDMA/THC users, 15 THC users and 15 non-drug users matched for age and intellect. We tested the hypothesis that reported feelings of depression and anxiety and cognitive impairment (memory, executive function and decision making) are more severe in MDMA/THC users than in THC users.

MDMA/THC users reported more intense feelings of depression and anxiety than THC users and non-drug users. Memory function was impaired in both groups of drug users. MDMA/THC users showed slower psychomotor speed and less mental flexibility than non-drug users. THC users exhibited less mental flexibility and performed worse on the decision making task compared to non-drug users but these functions were similar to those in MDMA/THC users. It was concluded that MDMA use is associated with increased feelings of depression and anxiety compared to THC users and non-drug users. THC users were impaired in some cognitive abilities to the same degree as MDMA/THC users, suggesting that some cognitive impairment attributed to MDMA is more likely due to concurrent THC use.

Keywords

ecstasy, MDMA, marijuana, executive functions, decision making, memory

Introduction

Ecstasy mostly relies on the methamphetamine derivate 3,4-methylenedioxy-methamphetamine (MDMA) for its psychoactive action. A variety of changes in the serotonin (5HT) system, such as reduced 5HT levels, up-regulation of 5HT receptors and decreased 5-HT transporter binding densities, have been observed in abstinent MDMA polydrug users. This indicates an association between repeated MDMA use and long-lasting 5HT depletion (McCann *et al.*, 1994; McCann *et al.*, 1998; Reneman *et al.*, 2000; McCann *et al.*, 2000; Reneman *et al.*, 2002).

Normal cognitive performance is often influenced by 5HT (Meneses, 1999). Behavioural data show lower cognitive performance in repeated users of MDMA as compared to non-drug users, including impairment of memory, verbal fluency and impulse control (Curran and Travill, 1997; Schifano *et al.*, 1998; Morgan, 1998; McCann *et al.*, 1999; Morgan, 1999; Reneman *et al.*, 2000; Bhattachary and Powell, 2001). Low levels of 5HIAA (5-hydroxindole acetic acid, a serotonin metabolite) have been observed in MDMA users (Bolla *et al.*, 1998). Furthermore, researchers who observed signs of clinical depression in repeated MDMA users have speculated that low levels of 5HT may have been involved (Curran and Travill, 1997; Parrott and Lasky, 1998; Gerra *et al.*, 1998).

Yet, most MDMA users also use other drugs, mainly Δ^9-tetrahydrocannabinol (THC, marijuana) and alcohol (Schifano *et al.*, 1998; Winstock *et al.*, 2001), and cognitive impairments observed in MDMA users also affect polydrug users who do not use MDMA (Parrott *et al.*, 2001; Fox *et al.*, 2002). Impairments in

Corresponding author: Antoine Bechara, Department of Neurology, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, USA.
Email: antoine-bechara@uiowa.edu.

THC users are often subtle but include also memory, attention, timing, recognition, reproduction of designs and the processing, organization and integration of complex information (Robbe, 1994; Hall and Solowij, 1998; Solowij *et al.*, 2002). Furthermore, the severity of THC-induced impairment appears to depend on duration and frequency of THC use (Hall and Solowij, 1998; Solowij *et al.*, 2002). Measuring the effects of MDMA on reported feelings of depression and anxiety and on cognition requires controlling for these effects of THC and other concurrently used drugs. Some researchers who controlled for THC use claim that cognitive deficits are more likely to originate from THC use than from repeated use of MDMA (Croft *et al.*, 2001). Others concluded that use of drugs other than MDMA could not explain cognitive decline in MDMA polydrug users (Morgan, 1999; Verkes *et al.*, 2001).

Because most studies addressing MDMA neurotoxicity have not controlled for THC use, more studies are needed to investigate the separate effects of MDMA and THC on psychological changes and cognition. Because MDMA users often use other psychoactive substances such as marijuana and alcohol, it is almost impossible to find MDMA users who haven't at least tried other drugs. Therefore MDMA users are often compared to THC users and non-drug users. The current study was designed to assess psychological problems, defined as reported feelings of depression and anxiety, and cognitive impairments in MDMA users, controlling for effects of THC and other drugs. We hypothesized that psychological problems and impairments on cognitive tasks of memory, executive function and decision making are more severe in MDMA/THC users than in THC users.

Methods

Subjects

Forty-two subjects between 21 and 42 years old, recruited through advertisement in a local newspaper in the Iowa City area, entered the study after completing a short telephone checklist about their drug history. Subjects were excluded if they were currently diagnosed with alcohol or drug dependence, had a serious physical or mental illness (e.g. diagnosed schizophrenia, depression, antisocial behaviour), were currently using prescribed psychoactive drugs or were pregnant. According to their drug history, subjects were enrolled in the marijuana group (THC), the ecstasy and THC (MDMA/THC) group or the control group. THC users (five males, ten males) had used THC at least ten times, but with no history of MDMA use. MDMA/THC users (four females, seven males) were defined as regular users of MDMA (>10 times) and THC (>10 times). Four of the 15 control subjects (six females, nine males) had remotely tried THC (on five or fewer occasions and not within the preceding 12 months). Subjects were excluded from the study if their frequency of illicit drug use other than THC exceeded that of THC or MDMA use. Participants were asked to abstain from drug use on the day of testing. The study was approved by the IRB of the University of Iowa Hospitals and Clinics (UIHC) and was conducted according to the Declaration of Helsinki and its subsequent amendments (Edinburgh, 2000). Subjects received financial compensation for their participation.

Procedures

Total duration of testing was approximately 2–2.5 hrs. Difference in intelligence between groups was analysed using the National Adult Reading Test (NART) (Crowford *et al.*, 2001: 456). The NART consisted of a reading test of 50 words of graded difficulty and provided estimated verbal IQ (VIQ). To secure consistency and objectivity, pronunciation of the words was recorded on tape and later evaluated by one psychologist who was unaware of the drug history of the participants.

All subjects were tested for recent drug use by means of a subjective questionnaire as well as by urine drug screen (UA-Screen™ 'Dirty 5'). The test was FDA approved for medical and forensic use and tested recent use of THC, amphetamines, methamphetamine, cocaine and opiates.

Assessments

Psychological measures Symptoms of anxiety and depression were assessed by the Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988), and the Beck Depression Index (BDI-II) (Beck *et al.*, 1996), respectively. For both questionnaires, items were scored from 0 to 3, with higher scores indicating greater severity of the symptom. Total score of each questionnaire was used as dependent variable.

The Addiction Severity Index (ASI) (McLellan *et al.*, 1992) is a psychometrically sound semi-structured 30–45 minute interview that assesses problems in medical, employment, alcohol use, drug use, crime, family, social and psychiatric domains. Composite scores for recent (past 30 days) severity of problems in these domains were used as dependent variable.

Cognitive measurements The tests used assessed memory function, executive function and decision making. These measurements were selected because of their established sensitivity to cognitive impairments caused by long time drug use (Bolla *et al.*, 1998; Reneman *et al.*, 2000; Bechara *et al.*, 2001).

Memory functions The Rey Auditory Verbal Learning Test (RAVLT) assessed verbal memory and intentional learning (Bohbot *et al.*, 1998). Subjects were asked to produce a list of 15 words immediately after five individual sequencing trials and after a 30 minute delay. The latter trial assessed delayed recall. Total score of the five trials and delayed recall score were included as dependent variables.

The Rey-Osterrith Complex Figure Test (Reyo) is a standard test of visual memory. Subjects were asked to copy a figure with no overall semantic meaning and reproduce the figure after a delay of 30 minutes (Bohbot *et al.*, 1998). To secure consistency and objectivity, all drawings were scored according to the guidelines by one psychologist who was unaware of the drug history of the participants. Scores for copy and reproduction (max. 36) were used as dependent variables.

Executive function A computerized version of the Wisconsin Card Sorting Test (WCST) was used to assess executive function. The WCST measured abstract reasoning and ability to shift and maintain set (Dehaene and Changeux, 1991). For this task a set of cards had to be matched with one of four key cards according to matching principles (colour, shape etc.) that changed during the task. Dependent variables were total errors and persistent errors, defined as persisting to respond to a stimulus characteristic that is incorrect.

The Stroop colour naming task is a standard cognitive and neuropsychological measure of selective attention and cognitive flexibility, and it serves as a measure of frontal dysfunction (MacLeod, 1991). Based on the original Stroop task, we presented participants with three trial types. In the word reading trials, participants are asked to read colour words that are printed in black ink (e.g., RED, GREEN, etc.). In the colour naming trials, participants are presented with a nonword trigram (e.g., XXX) printed in various ink colours and are asked to name the ink colour that the XXX is written in. In the incongruent trial type, subjects are again asked to name ink colour, but in these trials, the colour words appear in a discrepant colour ink (e.g., RED printed in green ink; the correct response is green). A typical result from a Stroop task is that participants are slow and inaccurate when naming colours in the incongruent condition compared to the other conditions.

In a standard Stroop task, the trial types are blocked and the instruction set given in participants is applied only to that block. We also administered a modified version of the Stroop task (Carter *et al*., 2002; Cohen *et al*., 1999). In this fourth task, a block of trials was presented that intermixed trials from our Stroop task 1 and Stroop task 3. That is, subjects were presented with words printed in black ink (Stroop task 1) and with colour words printed in discrepant colours (e.g., RED written in blue ink; Stroop task 3). (The specific procedures are detailed in Golden, 1994.) Subjects were asked to read the words printed in black as quickly as they could and also to name the ink colour when words were printed in colour. This task requires subjects to remember and correctly apply the correct responses of reading word or naming ink colours and provides a measure of ability to apply and shift between instruction sets.

Each task lasted 45 seconds. Two interference scores were calculated based on published procedures (Golden, 1994) and served as dependent variables. The first interference score (1) is a measure of colour naming accuracy on standared Stroop task 3 (incongruent). It is calculated by subtracting a composite accuracy measure of colour and word naming (Stroop tasks 1 and 2) from task 3. (The composite accuracy measure of colour and word naming is $W \times C/W + C$.) The second interference score (2) also is a measure of accuracy on incongruent colour naming, but these data come from the relevant trials in our modified task 4 (colour naming accuracy on incongruent trials in task 4 minus the composite accuracy measure of colour and word naming). Thus, we can determine accuracy of colour naming is affected by asking participants to maintain additional task-relevant information in memory.

The Trail Making Test (TMT) investigated visual–conceptual and visual–motor tracking skills and involved psychomotor speed and mental flexibility (Radford *et al.*, 1978). Subjects had to connect consecutive numbers randomly arranged on a page (TMT-A) or consecutive numbers and letters in alternating order (TMT-B). Times needed to complete tests A and B (speed) were used as dependent variables. To differentiate difference in cognitive processing from impaired psychomotor speed, cognitive processing and shifting ability was defined as time to complete TMT-B minus time to complete TMT-A (TMT-BA) (Ratti *et al.*, 2002).

Decision making The Gambling Task (GT) was originally designed to study cognitive function of patients with frontal lesions who performed normally on neuropsychological tests, but often showed poor judgement in decisions and act in a generally irresponsible manner. The test is described in detail elsewhere (Bechara *et al.*, 2001). Subjects repeatedly chose a card from four decks (A', B', C' and D') that are presented on a computer screen. The computer tracks the sequence of the cards selected from the various decks. After a card is chosen, an amount of money that is won is shown on the screen, intermittently followed by a sum of money that is lost. The four decks differ in pay-off so that some decks have larger gain as well as larger penalties. The inter-trial interval between two consecutive cards was set on 1000 msec and number of cards per deck and total number of card selections (trials) was set to 60 and 100 respectively. Decks A' and B' are considered the advantageous decks (moderate gain, but smaller penalties) while C' and D' are disadvantageous decks (higher gain, but higher penalties leading to a negative balance). Net score is calculated by subtracting the total number of cards selected from advantageous decks minus disadvantageous decks $(C' + D') - (A' + B')$ and was collected for five blocks of 20 successive cards. Number of subjects per group performing advantageously, defined as total net score ≥ 10 (Bechara and Damasio, 2002), is also included as dependent variable.

Statistics

All statistical analyses were conducted using the software SPSS 11.0 for Windows. Main group differences were tested using one-way ANOVA with group (controls, THC users and MDMA/THC users) as between subject factor. For the GT ANOVA was used with Group as between factor and Block of cards as within subject factor. Planned Tukey's HSD procedure was used for in-depth analyses of differences between specific groups (control–THC, control–MDMA/THC and THC–MDMA/THC group) in case the overall group effect was significant ($p \leq 0.05$) or approached significance ($p \leq 0.06$). Tukey's HSD test uses the studentized range statistic to make all of the pair-wise comparisons between groups and sets the experiment-wise error rate at the error rate for the collection for all pair-wise comparisons. In case of the GT, *post hoc* χ^2 was conducted for analysing number of subjects performing advantageously and to compare gender ratio between groups. All tests were two-tailed and criterion for significance was set on $p < 0.05$.

Results

Table 1 presents the demographic characteristics of the three groups. History of drug use is presented in Table 2. One THC user

Table 1 Mean (SD) characteristics of the three groups. Overall group effect is analysed using one-way ANOVA (F-value). Group comparisons were analysed by means of *post hoc* Tukey's HSD test

Variable	Mean (SD)			ANOVA F(2,39)
	Controls N=15	THC users N=15	MDMA/THC users N=11	Group effect
Age (yrs)	23.9 (3.2)	24.3 (5.3)	22.9 (2.4)	0.422
Education (yrs)	16.5 (1.2)	15.3 (1.4)	15.6 (0.5)	4.206*
Verbal IQ (NART)	109.1 (4.5)	108.8 (4.7)	104.3 (6.8)	3.055

* $p<0.05$.

Table 2 Mean (SD)[N] frequency of lifetime use of illicit drugs in the control group, the THC users and the MDMA/THC users. Alcohol and drug use are described as lifetime use (days). Group comparisons were analysed by means of *post hoc* Tukey's HSD test (reported as ns if $p>0.06$)

Variable	Mean (SD)			ANOVA F(2,39)	Group comparison Tukey *post hoc* test Significance (p)		
	Controls	THC users	MDMA/THC users	Group effect	Control THC	Control MDMA/THC	MDMA/THC THC
Alcohol	317.5 (332.5) [15]	779.6 (471.6) [15]	880.7 (530.0) [11]	6.331**	0.019	0.008	ns
THC	1.2 (2.1) [4]	1581.6 (1432.5) [15]	932.4 (873.0) [11]	9.875**	0.000	0.055	ns
THC abstinence (days)	1232.8 (1376.9) [4]	15.2 (46.8) [15]	15.5 (36.0) [11]	12.103**	0.000	0.000	ns
MDMA	0.0 (0.0) [0]	0.0 (0.0) [0]	37.6 (33.6) [11]	19.107**	ns	0.000	0.000
MDMA abstinence (days)			228.1 (140.3) [11]				
Cocaine	0.0 (0.0) [0]	4.5 (10.5) [5]	15.4 (22.6) [8]	4.406*	ns	0.015	ns
psilocybin	0.0 (0.0) [0]	5.3 (12.7) [7]	8.1 (6.8) [10]	3.137#	ns	0.054	ns
LSD	0.0 (0.0) [0]	4.8 (12.8) [5]	2.3 (5.3) [4]	1.269			
Opium	0.0 (0.0) [0]	3.3 (12.9) [1]	0.0 (0.0) [0]	0.861			
Methamphetamines	0.0 (0.0) [0]	0.0 (0.0) [0]	0.1 (0.3)	1.390			
Sedatives	0.0 (0.0) [0]	0.1 (0.5)	[1]	0.0 (0.0) [0]	0.861		
Nitrous gas	0.0 (0.0) [0]	0.3 (1.0) [1]	0.0 (0.0) [0]	0.861			

** $p<0.01$
* $p<0.05$
# $p<0.06$

did not perform the GT correctly and his GT data were not included in the analyses.

Analyses showed that frequency of alcohol use was significantly lower in non-drug users than in THC and MDMA/THC users. Furthermore, 19 of the 26 drug users tested positive for THC on the day of testing (see Subjects section). Therefore, additional analyses were conducted to investigate a possible influence of these three factors on task performance finding. All analyses were repeated twice: once with all subjects with lifetime alcohol use and THC use as covariates and once with THC and MDMA/THC users with days of THC abstinence as covariate. The results are reported at the end of the result section.

Subjects

Fifteen non-drug using controls, 15 regular THC users and 11 MDMA/THC users completed the study. One subject did not complete cognitive testing due to personal reasons and was excluded from further analyses. Absolute number of females differed between the three study groups, but there was no significant difference in gender between the groups ($\chi^2=0.144$, $p=$ns). While all controls produced negative drug screens, seven MDMA users (64%) and 12 THC users (80%) produced positive urine drug screens for THC (level of detection $\geq$50 ng/ml). At this level, THC can be detected for 1–30 days, depending on level of use, potency of the drug etc. In the current study no participant tested positive for THC

use when reported THC use was more than 7 days ago. Reported mean days of abstinence of THC did not differ between groups of drug users (see Table 1). With the exception of one male non-drug user and one female THC user who were 33 and 42, respectively, all subjects were between 21 and 28 years of age. Groups did not differ in age, and mean age of males and females did not differ between groups F[2.35]=1.058, p=ns. THC users had fewer years of education relative to controls (Tukey's HSD: p=0.03). This difference in education was marginal, however, (1.2 years) and since VIQ did not differ significantly between groups, may be considered clinically irrelevant. Years of education, VIQ, frequency of alcohol and illicit drugs use, other than MDMA, did not differ significantly between the two groups of drug users (see Table 2). In regard to most other studies that have investigated MDMA users, participants in the current study can be regarded as mild to moderate users (Gerra *et al.*, 1998; McCann *et al.*, 1998; Semple *et al.*, 1999; Reneman *et al.*, 2000; Reneman *et al.*, 2001).

Psychological measures (BDI-II, BAI and ASI)

Relative to non-drug users, MDMA/THC users' score on BAI was higher, and their BDI-II score was higher than both non-drug users and THC users (Table 3). BDI-II and BAI scores did not differ between non-drug users and THC users. ASI scores showed similar alcohol and other drug use profiles in the MDMA/THC and THC users. Both drug groups reported greater alcohol use

Table 3 Mean (SD) reported depression (BDI-II) and anxiety (BAI), findings on the Addiction Severity Index (ASI) and cognitive task performance. Group comparisons are only reported when overall group effect (ANOVA) showed at least trend significance (p<0.06). *P*-values are reported as ns if p>0.06.

Variable	Mean (SD) Controls N=15	THC users N=15	MDMA/ THC users N=11	ANOVA F(2.38) Group effect	Tukey's Post-hoc test Significance (p) Control THC	Control MDMA/ THC	MDMA/ THC THC
Psychological measures							
BDI-II	2.47 (2.2)	4.40 (3.9)	9.82 (12.0)	3.955*	ns	0.024	ns
BAI	4.0 (4.3)	2.9 (1.9)	10.3 (10.4)	5.263**	ns	0.034	0.010
ASI-alcohol	0.08 (0.05)	0.19 (0.13)	0.23 (0.09)	8.810**	0.008	0.001	ns
ASI-drug	0.00 (0.00)	0.07 (0.05)	0.06 (0.05)	10.732**	0.000	0.002	ns
ASI-medical	0.06 (0.17)	0.11 (0.17)	0.03 (0.08)	0.912			
ASI-psychiatric	0.05 (0.07)	0.02 (0.07)	0.16 (0.20)	4.664*	ns	0.059	0.015
ASI-employment	0.31 (0.20)	0.32 (0.17)	0.28 (0.17)	0.125			
ASI-social	0.03 (0.07)	0.04 (0.05)	0.07 (0.09)	1.247			
ASI-legal	0.00 (0.00)	0.05 (0.10)	0.05 (0.10)	2.069			
Memory							
Rey O' figure Copy (score)	35.1 (1.1)	33.4 (4.3)	34.4 (1.7)	1.340			
Rey O' figure Recall (score)	23.7 (4.2)	22.3 (6.8)	20.6 (7.6)	0.784			
RAVLT recall (total words)	60.0 (5.3)	52.3 (7.1)	51.5 (7.6)	7.067**	0.008	0.007	ns
RAVLT delayed recall	13.1 (1.5)	10.7 (3.5)	11.6 (2.8)	2.825#	0.060	ns	ns
Executive functions							
Trail A (sec)	19.0 (5.7)	22.3 (8.5)	26.8 (9.7)	3.051#	ns	0.047	ns
Trail B (sec)	38.1 (9.3)	45.0 (13.3)	51.0 (17.7)	3.013#	ns	0.051	ns
Trail BA (sec)	19.1 (6.4)	22.7 (2.5)	24.2 (3.8)	1.005			
Stroop I1	10.6 (5.4)	10.6 (9.8)	16.3 (17.4)	1.015			
Stroop I2	48.2 (9.9)	39.5 (9.1)	40.5 (9.0)	3.703*	0.040	ns	ns
WCST total error	11.3 (6.4)	12.9 (7.3)	11.5 (7.8)	0.235			
WCST perseverative error	6.7 (4.0)	7.6 (5.1)	6.0 (3.5)	0.417			

* p<0.01
** p<0.05
\# p<0.06

than non-drug users (see Table 3). MDMA/THC users showed greater psychiatric problems than non-drug users and THC users, although the latter comparison reached only a tendency for significance. There was no difference in psychiatric problems between THC users and non-drug users. Effect sizes of significant group differences on psychological measures were generally low and ranged from 0.179 to 0.239. Problems in the medical, employment, social or legal field did not differ in severity between groups.

Memory functions (RAVLT and CFT)

Immediate recall did not differ between MDMA/THC and THC users but was impaired in both these groups as compared to non-drug users (see Fig. 1). After 30 minutes THC users tended to recall fewer words as compared to non-drug users, but this effect was not significant. Delayed recall in MDMA/THC users did not differ from THC users or non-drug users. Groups did not differ in total score of the copy and reproduction trial of the CFT.

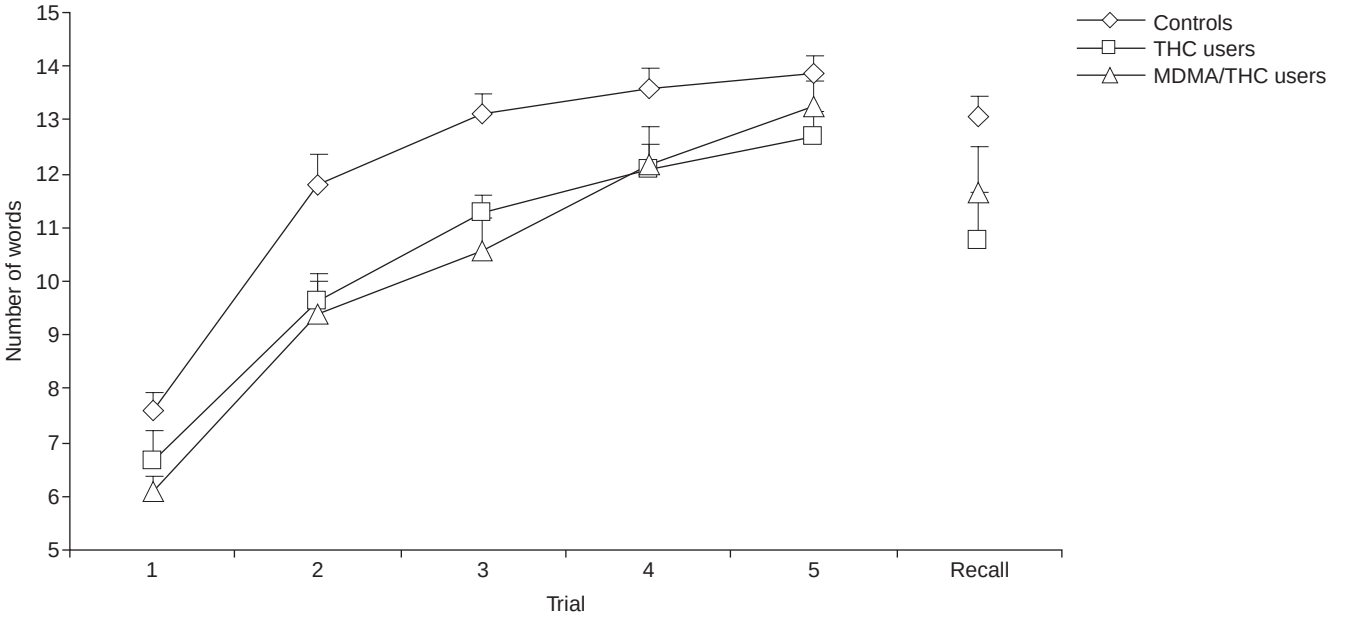

Figure 1 Mean (+SEM) word score per trial in the Rey Auditory Verbal Learning Task as a function of group.

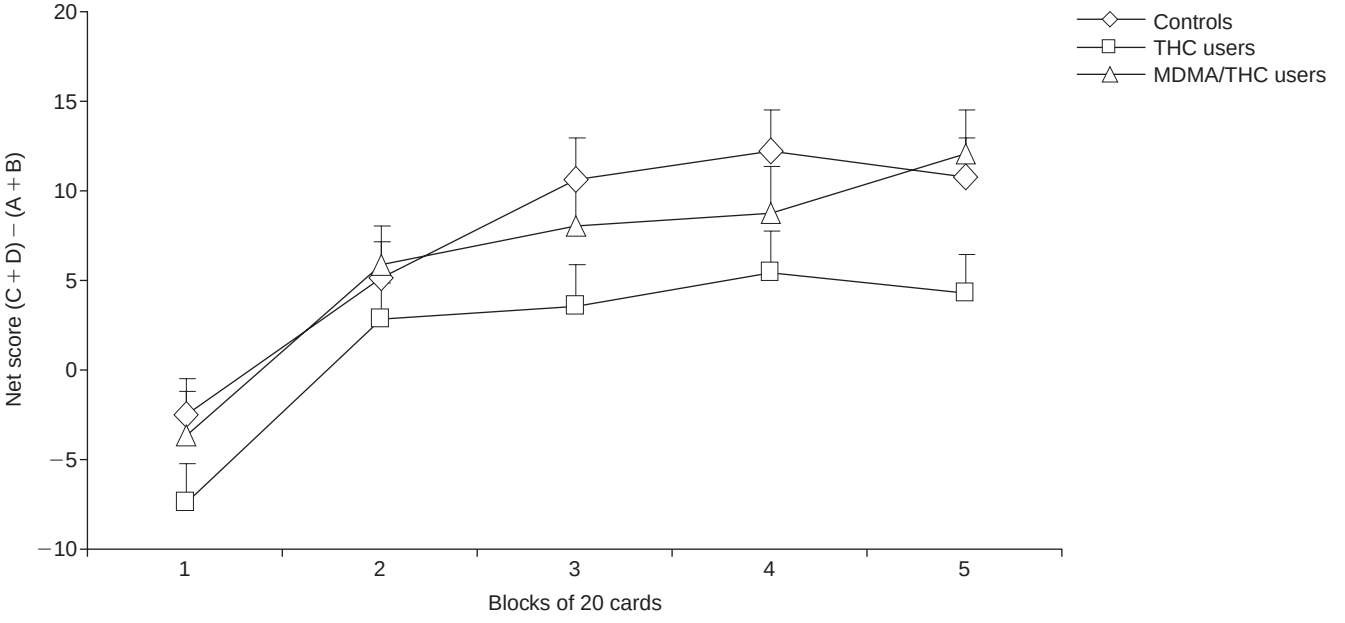

Figure 2 Mean performance (+SEM) on the GT as a function of group and decks of 20 cards.

Executive function (WCST, Stroop and TMT)

On the WCST, the groups did not differ in number of total errors and perseverative errors. On the Stroop test, the groups did not differ on the I-1 score. The I-2 score was significantly lower in THC users than in non-drug users, but MDMA/THC users did not differ significantly from non-drug users or THC users. MDMA/THC users, but not THC users, needed more time to complete TMT-A and TMT-B than non-drug users; the time needed measure did not differ between the drug user groups. Calculated TMT-BA did not differ between groups.

Decision making (GT)

Fig. 2 presents mean performances of the three study groups on the decision making task per block of 20 cards. An overall group effect on the net score of the GT was observed ($F[2,37]=4.026$, $p=0.026$). A main effect was found for within subject-factor Block of cards ($F[4,34]=14.009$, $p<0.01$), but no significant interaction was observed between Block of cards and Group ($F[8,70]=0.598$, p=ns). This indicates that performance of subjects, regardless of group, learned to select good cards over bad cards as the test progressed. Analyses of the effect of Group using Tukey's HSD procedure showed that performance of MDMA/THC users did not differ from that of non-drug users (p=0.124) and THC users ($p=0.869$). THC users performed worse than non-drug users ($p=0.026$). *Post hoc* analyses showed a trend towards more controls performing advantageously than THC users ($\chi^2=2.727$, $p=0.099$). No other group differences in advantageous performance were detected ($\chi^2 \leq 1.896$, $p=$ns).

Effect sizes of significant group differences in cognitive task performance as described above were generally low and ranged from 0.137 to 0.271.

Covariates

Variables are only reported if their significance changed after implementing the covariates lifetime alcohol or THC use and THC abstinence. Changes are discussed per covariate.

Lifetime alcohol use Feelings of depression did not differ significantly between the two drug groups, but when frequency of alcohol use was included as a covariate, significance increased indicating higher levels of feelings of depression in MDMA/THC users compared to THC users ($p=0.039$). Also, the trend significance indicating impaired delayed memory (RAVLT) in THC users compared to non-drug users became significant after lifetime alcohol use was controlled for ($p=0.017$).

Lifetime THC use For difference in feelings of anxiety, significance increased when we controlled for lifetime THC use, indicating increased anxiety in MDMA/THC users as compared to THC users ($p=0.041$). Impaired performance in the GT was observed between THC users relative to non-drug users only but when frequency of THC use was included as a covariate, performance between THC users and MDMA/THC users became significantly different as well ($p=0.039$).

MDMA/THC users needed more time to complete both subtasks of the TMT. After including frequency of THC use as a covariate, MDMA/THC's speed in Trail B no longer differed significantly from that of non-drug users, although a trend was still detected ($p=0.065$).

THC abstinence Number of days that THC and MDMA/THC users reported to be abstinent from THC did not affect task performance observed in the current study suggesting that results were not influenced by residual effects of recent THC use.

Discussion

The current study assessed differences in feelings of depression and anxiety and cognitive functioning between MDMA/THC users, non-drug users and THC users.

Psychological measures

We found that MDMA/THC users reported more symptoms of anxiety than non-drug users and THC users. A similar finding was observed for feelings of depression when we controlled for frequency of alcohol and THC use, suggesting that increased feelings of depression related to use of MDMA, rather than use of alcohol or THC. Increased feelings of depression have been observed previously on days directly following MDMA use (Curran and Travill, 1997; Peroutka *et al.*, 1988) and after longer periods of abstinence (Gerra *et al.*, 1998; Gamma *et al.*, 2000; Morgan, 2000; Gamma *et al.*, 2001), presumably due to effects on serotoninergic systems. MDMA, but not THC, may cause long term 5HT depletion in abstinent users (Kish *et al.*, 2000; Reneman *et al.*, 2002). Feelings of anxiety were significantly higher in MDMA/THC users compared to THC users, even after we corrected for frequency of alcohol use and THC use. These findings support the suggestion that MDMA, rather than THC, may be involved in increased feelings of depression in MDMA/THC users.

Memory functions

In this study MDMA/THC users and THC users exhibited problems acquiring new verbal information and needed more trials to adequately store the information. Their retrieval of words 30 minutes after presentation was not significantly impaired, although there was a trend for impaired delayed recall in THC users relative to non-drug users. When frequency of alcohol use was introduced as a covariate, this impairment in delayed recall in THC users became significant, suggesting that THC use may also affect retrieval from memory. Visual memory assessed by reproduction of a complex figure copied 30 minutes earlier was not affected. Along similar lines, Croft *et al.* (2001) found that memory functions of MDMA/THC users resembled that of THC users as in the current study, indicating that observed deficits in memory function in the former group may be attributed to repeated use of THC, rather than MDMA.

Other studies using similar study designs have shown memory

impairments in MDMA/THC users as compared to THC users and non-users controls (Morgan, 1999; Gouzoulis-Mayfrank *et al.*, 2000; Verkes *et al.*, 2001). Possibly, the groups investigated in these studies were better matched for lifetime use of THC and/or consisted of heavy users of MDMA as compared to the MDMA group in the current study. An association between MDMA use and memory impairment was shown by Bolla *et al.* (1998). It has been suggested by Fox *et al.* (2002) that any reduction in the learning curve observed in ecstasy polydrug users reflects difficulties in storage and/or retrieval of information. So, although the current findings indicate that THC use may be responsible for memory impairment in MDMA/THC users, these findings do not conclusively rule out an additive role of MDMA in the observed impairment. Furthermore, it can not be excluded that other specific memory functions may be more sensitive to possible additive effects of MDMA in MDMA polydrug users than measured with the tests included in this study.

Executive function

Several aspects of executive functions were assessed in the current study. Performance on the WCST was not impaired in MDMA/THC users and THC users indicating that abstract reasoning was not affected.

Performance on the original versions of the Stroop test was not affected in MDMA/THC users and THC users. These findings are in line with most research (reviewed by Parrott, 2000), although some researchers report impaired performance on the Stroop test in abstinent MDMA users (Croft *et al.*, 2001). In the current study, a new subtask was added to the Stroop test in which subjects had to read colour names printed in black and identify the colour of words printed in blue, red or yellow. This subtask adds an extra dimension to the test. Not only are subjects required to suppress irrelevant information, but they additionally have to shift between applying rules. It has been suggested that THC users are vulnerable to increasing task complexity creating more sources of interference (Solowij *et al.*, 2002). The present impairment in Stroop performance in THC users may indicate problems with mental shifting and motor inhibition in more complex situations.

Performance on the Trail Making Task requires mental flexibility and explores visual–conceptual and visual–motor tracking skills, which are based on psychomotor speed, divided attention, mental flexibility and the ability to shift (Townsend *et al.*, 2001; Ratti *et al.*, 2002). Performance on the TMT was not significantly affected in THC users but MDMA/THC users exhibited impaired performance as compared to non-drug users. MDMA/THC users needed more time for TMT-A, reflecting psychomotor speed, and for TMT-B, considered a measure of shifting ability and cognitive processing speed. This effect on TMT-B in MDMA/THC users changed to trend significance when we corrected for lifetime THC use, suggesting that frequency of THC use might have been associated with slower speed on this subtask. Furthermore, once we corrected performance on TMT-B for impaired psychomotor speed on TMT-A, the performance difference between groups was no longer significant. This may indicate that performance on this task by MDMA/THC users may rely on impaired psychomotor speed rather than impaired cognitive processing speed.

In summary, users of MDMA/THC and THC users displayed some specific deficits in executive function. Since performance did not differ between these groups of drug users, impairment can not exclusively attributed to use of MDMA. Drug users in the current study may exhibit problems with psychomotor speed, concept shifting and response inhibition in complex situations while abstract reasoning is not affected.

Decision making

The GT assesses the ability to balance immediate rewards against long term negative consequences. According to Grant *et al.* (2000) the task has strong validity for evaluating a cognitive deficit that may contribute to drug use. Poor decision making has been observed in polydrug users in prior studies (Rogers *et al.*, 1999; Grant *et al.*, 2000; Bechara and Damasio, 2002). This is in line with findings of the current study where users of THC performed more disadvantageously as compared to non-drug user. There was no significant difference between MDMA/THC users and controls. Once we controlled for frequency of THC use, performance of THC users became significantly worse than that of MDMA/THC users, suggesting that frequency of THC use might be associated with poor performance on the GT. Furthermore, the percentage of subjects performing disadvantageously was lower in controls than in THC users and MDMA/THC users although only the difference between controls and THC users reached trend significance (respectively 13%, 40% and 36% of the total subjects per group). The latter suggests that even relatively mild drug use may be associated with poor decision making. The ventromedial region may function as a link between certain categories of events stored in memory records and the activation of these events in working memory during decision making processing (Bechara, 2002). When memory function is impaired, as in drug users in the current study, decision making may be compromised. At least a subgroup of drug users displayed poor performance on decision making. Poor decision making in drug users makes it more likely that they maintain their current drug use and have more problems discontinuing drug use because they tend to choose immediate reward (desired effects of a drug) over future consequences (financial and social problems etc.).

Limitations

Some potential limitations of the current study need to be addressed. First, because substance abuse often co-exists with psychopathology and cognitive impairment (Lin *et al.*, 1998), we cannot exclude whether psychopathology antedated drug use in some participants, e.g., attempted self-medication in subjects with cognitive distress. Second, some of the observed cognitive deficits might reflect effects of recent THC use in certain individuals. This is because eight THC users and four MDMA/THC users reported THC use the day before assessment and two THC users and two MDMA/THC users used THC 2–3 days before assessment. Results from the drug screen were consistent with subjective reports of recent drug use by participants. Residual effects on cognitive functioning existing a day after THC use often prove to be subtle, inconsistent and of little clinical importance (Chait, 1990;

Chait and Perry, 1994; Fant *et al.*, 1998; Pope *et al.*, 2001). Of note, mean time of THC abstinence (15 days) did not differ between MDMA/THC users and THC users. Furthermore, results did not change when number of days since last THC use was included as a covariate in the statistical analyses. Group differences observed in the present study are, therefore, most likely not affected by residual effects of recent THC use. Third, mean frequency of MDMA use was relatively low compared to that in other studies of long term effects of MDMA. Compared to other studies investigating effects of MDMA and THC in abstinent drug users, participants in the current study can be regarded as mild to moderate recreational users. Greater frequency and number of MDMA pills used are associated with greater task performance impairments (Bolla *et al.*, 1998; Bhattachary and Powell, 2001). Therefore, the current study may have underestimated cognitive impairment and feelings of depression and anxiety in drug users who used MDMA more frequently. Fourth, the sample size of the current study was relatively small. It can not be excluded that tests on which performance is apparently unimpaired in THC or MDMA/THC users in the current study may have been not sensitive enough to pick up subtle impairment due to a type 2 error. The latter may also explain the discrepancy with literature indicating memory impairment in MDMA as well as cannabis users. Fifth, it is sometimes suggested that an amotivational syndrome might be responsible for impairment in users of THC, rather than cognitive deterioration. The amotivational syndrome is associated with marijuana use and includes apathy, loss of effectiveness and decreased willingness to carry out complex long term plans (McGlothlin and West, 1968). Prior studies have shown that the syndrome is observed only in heavy marijuana users (use more than four to six times a week for an average of 6 years) who recently suffered from depression (Musty and Kaback, 1995). In comparison, use of marijuana in participants of the present study was mild and none of them was diagnosed with depression in the last year. Furthermore, if drug using subjects in the current study were not motivated to perform well on tests during the experiment, we would have observed impaired performance on all the tests that were assessed. On a personal note, many drug users in the present study expressed that one of the reasons for their participation was to prove that drug use had not impaired their cognitive performance. It is therefore unlikely that current findings result from unmotivated participants, rather than from other variables, such as drug use.

In conclusion, we observed that increments in anxiety and depression may be specific to MDMA users since none of those were observed in the group of THC users or non-drug controls. Cognitive impairments were evident in both the MDMA/THC group and the THC group. Memory disturbances were similar in both groups of drug users and impaired in regard to controls. Some impairments, i.e. poor decision making and mental flexibility, appeared specific to the THC group alone while impaired motor responses were more prevalent in MDMA/THC users.

Acknowledgements

The authors would like to thank Nicole Skaar, Cynthia Cutshal, Jennifer Smothers, Matt Wilson and Carol Devore for their help during the project.

Declaration of interest

This project was supported by NIDA grants DA11779, DA12487 and DA17341, by the National Institute of Aging, grants NIA AG 17177 and NIA AG 1507 and the Foundation De Drie Lichten.

References

Bechara A (2002) The neurology of social cognition. Brain *125*: 1673–1675

Bechara A, Damasio H (2002) Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia *40*: 1675–1689

Bechara A, Dolan S, Denburg N, Hindes A, Anderson S W, Nathan P E (2001) Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia *39*: 376–389

Beck A T, Epstein N, Brown G, Steer R A (1988) An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol *56*: 893–897

Beck A T, Steer R A, Ball R, Ranieri W (1996) Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess *67*: 588–597

Bhattachary S, Powell J H (2001) Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': evidence for cognitive impairment. Psychol Med *31*: 647–658

Bohbot V D, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L (1998) Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia *36*: 1217–1238

Bolla K I, McCann U D, Ricaurte G A (1998) Memory impairment in abstinent MDMA ('ecstasy') users. Neurology *51*: 1532–1537

Carter C S, Macdonald A M, Botvinick M, Ross L L, Stenger V A, Noll D, Cohen J D (2000) Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc Natl Acad Sci USA *97*: 1944–1948

Chait L D (1990) Subjective and behavioral effects of marijuana the morning after smoking. Psychopharmacology *100*: 328–333

Chait L D, Perry J L (1994) Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. Psychopharmacology *115*: 340–349

Cohen J D, Barch D M, Carter C, Servan-Schreiber D (1999) Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. Journal of Abnormal Psychology *108*(1): 120–133

Croft R J, Mackay A J, Mills A T, Gruzelier J G (2001) The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology *153*: 373–379

Crowford J R, Deary I J, Starr J, Whalley L J (2001) The NART as an index of prior intellectual functioning: a retrospective validity study covering a 66-year interval. Psychol Med *31* (3): 451–458

Curran H V, Travill R A (1997) Mood and cognitive effects of (±)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. Addiction *92*: 821–831

Dehaene S, Changeux J P (1991) The Wisconsin Card Sorting Test: theoretical analysis and modeling in a neuronal network. Cereb Cortex *1*: 62–79

Fant R V, Heishman S J, Bunker E B, Pickworth W B (1998) Acute and residual effects of marijuana in humans. Pharmacol Biochem Behav *60*: 777–784

Fox H C, McLean A, Turner J J, Parrott A C, Rogers R, Sahakian B J (2002) Neuropsychological evidence of a relatively selective profile of

temporal dysfunction in drug-free MDMA ('ecstasy') polydrug users. Psychopharmacology *162*: 203–214

Gamma A, Buck A, Berthold T, Vollenweider F X (2001) No difference in brain activation during cognitive performance between ecstasy (3,4-methylenedioxymethamphetamine) users and control subjects: a [H2(15)O]-positron emission tomography study. J Clin Psychopharmacol *21*: 66–71

Gamma A, Frei E, Lehmann D, Pascual Marqui R D, Hell D, Vollenweider F X (2000) Mood state and brain electric activity in ecstasy users. Neuroreport *11*: 157–162

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R (1998) Serotonergic function after (±)3,4-methylenedioxymethamphetamine ('Ecstasy') in humans. Int Clin Psychopharmacol *13*: 1–9

Golden C (1994) The Stroop Color and Word Test. Stoelting, Wood Dale, IL

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert H J, Fimm B, Sass H (2000) Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry *68*: 719–725

Grant S, Contoreggi C, London E D (2000) Drug abusers show impaired performance in a laboratory test of decision making. Neuropsychologia *38*: 1180–1187

Hall W, Solowij N (1998) Adverse effects of cannabis. Lancet *352*: 1611–1166

Kish S J, Furukawa Y, Ang L, Vorce S P, Kalasinsky K S (2000) Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user. Neurology *55*: 294–296

Lin C C, Bai Y M, Hu P G, Yeh H S (1998) Substance use disorders among inpatients with bipolar disorder and major depressive disorder in a general hospital. Gen Hosp Psychiatry *20*: 98–101

MacLeod C M (1991) Psychol Bull *109*: 163–203

McCann U D, Eligulashvili V, Ricaurte G A (2000) (±)3,4-methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. Neuropsychobiology *42*: 11–16

McCann U D, Mertl M, Eligulashvili V, Ricaurte G A (1999) Cognitive performance in (±)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users: a controlled study. Psychopharmacology *143*: 417–425

McCann U D, Ridenour A, Shaham Y, Ricaurte G A (1994) Serotonin neurotoxicity after (±)3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'): a controlled study in humans. Neuropsychopharmacology *10*: 129–138

McCann U D, Szabo Z, Scheffel U, Dannals R F, Ricaurte G A (1998) Positron emission tomographic evidence of toxic effect of MDMA ('Ecstasy') on brain serotonin neurons in human beings. Lancet *352*: 1433–1437

McGlothlin W H, West L J (1968) The marihuana problem: an overview. Am J Psych *125*: 126–134

McLellan A T, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M (1992) The Fifth Edition of the Addiction Severity Index. J Subst Abuse Treat *9*: 199–213

Meneses A (1999) 5-HT system and cognition. Neurosci Biobehav Rev *23*: 1111–1125

Morgan M J (1998) Recreational use of 'ecstasy' (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology *19*: 252–264

Morgan M J (1999) Ecstasy (MDMA): a review of its possible persistent psychological effects. Psychopharmacology *141*: 30–36

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

Musty R E, Kaback L (1995) Relationships between motivation and depression in chronic marijuana users. Life Sci *56*: 2151–2158

Parrott A C (2000) Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. Neuropsychobiology *42*: 17–24

Parrott A C, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology *139*: 261–268

Parrott A C, Milani R M, Parmar R, Turner J D (2001) Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. Psychopharmacology *159*: 77–82

Peroutka S J, Newman H, Harris H (1988) Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. Neuropsychopharmacology *1*: 273–277

Pope H G Jr, Gruber A J, Yurgelun-Todd D (2001) Residual neuropsychologic effects of cannabis. Curr Psychiatry Rep *3*: 507–512

Radford L M, Chaney E F, O'Leary M R, O'Leary D E (1978) Screening for cognitive impairment among inpatients. J Clin Psychiatry *39*: 712–715

Ratti M T, Bo P, Giardini A, Soragna D (2002) Chronic alcoholism and the frontal lobe: which executive functions are impaired? Acta Neurol Scand *105*: 276–281

Reneman L, Booij J, Schmand B, van den Brink W, Gunning B (2000) Memory disturbances in 'Ecstasy' users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology *148*: 322–324

Reneman L, Endert E, de Bruin K, Lavalaye J, Feenstra M G, de Wolff F A, Booij J (2002) The acute and chronic effects of MDMA ('ecstasy') on cortical 5-HT2A receptors in rat and human brain. Neuropsychopharmacology *26*: 387–396

Reneman L, Lavalaye J, Schmand,B, de Wolff F A, van den Brink W, den Heeten G J, Booij J (2001) Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'): preliminary findings. Arch Gen Psychiatry *58*: 901–906

Robbe H W J (1994) Influence of Marijuana on Driving. University of Maastricht, Maastricht

Rogers R D, Everitt B J, Baldacchino A, Blackshaw A J, Swainson R, Wynne K, Baker N B, Hunter J, Carthy T, Booker E, London M, Deakin J F, Sahakian B J, Robbins T W (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology *20*: 322–339

Schifano F, Di Furia L, Forza G, Minicuci N, Bricolo R (1998) MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. Drug Alcohol Depend *52*: 85–90

Semple D M, Ebmeier K P, Glabus M F, O'Carroll R E, Johnstone E C (1999) Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. Br J Psychiatry *175*: 63–69

Solowij N, Stephens R S, Roffman R A, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA *287*: 1123–1131

Townsend L A, Malla A K, Norman R M (2001) Cognitive functioning in stablilized first-episode psychosis patients. Psychiatry Res *104*: 119–131

Verkes R J, Gijsman H J, Pieters M S, Schoemaker R C, de Visser S, Kuijpers M, Pennings E J, de Bruin D, Van de Wijngaart G, Van Gerven J M, Cohen A F (2001) Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology *153*: 196–202

Winstock A R, Griffiths P, Stewart D (2001) Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. Drug Alcohol Depend *64*: 9–17