Journal of Psychopharmacology 15(4) (2001) 273–281

SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269–8811[200112]15:4; 273–281; 019600

Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug

H. C. Fox, A. C. Parrott and J. J. D. Turner

Department of Psychology, University of East London, London, UK.

Previous research has shown drug-free Ecstasy users to demonstrate selective cognitive impairment. However, there seems to be a degree of individual variation in the occurrence of such deficits. The present study aimed to assess whether these cognitive deficits are related to an awareness of problematic Ecstasy use, or to past drug dosage. Twenty regular Ecstasy users who reported experiencing Ecstasy-related problems were compared with 20 Ecstasy users who had not reported any previous problems. The two groups displayed similar past histories in relation to a range of illicit drugs, and were divided into low, medium and high users. The controls comprised 20 illicit recreational drug users who had never taken Ecstasy. Executive task measures comprised the Tower of London (TOL), the Wisconsin Card Sorting Task (WCST) and spatial working memory. Immediate and delayed word recall, matched verbal recognition and recall and simple reaction time were also included. Both Ecstasy groups performed significantly worse than controls on two executive measures: TOL planning time and spatial working memory score. There were no differences in cognitive impairment between the Ecstasy users who complained of problems and those who did not. In both groups, decrement on executive tasks was demonstrated as a function of previous drug dose. The study confirms that heavy Ecstasy polydrug use may culminate in selective executive deficits. It also demonstrates that two differently self-perceived Ecstasy groups showed similar cognitive impairment, despite only one group complaining of problems. Because all Ecstasy participants also consumed a range of other illicit drugs, the results are reflective of Ecstasy polydrug use in individuals who use Ecstasy as a drug of preference.

Key words: drug use problems; executive; neurotoxicity; MDMA; memory; serotonin

Introduction

Recreational Ecstasy users have been shown to display selective cognitive deficits. Memory problems were first described in a clinical report of nine former heavy users, five of whom demonstrated mild to moderate impairment, while four did not; performance on an extensive battery of other neuropsychological measures remained similar to normative data (Krystal *et al.*, 1992). A later comparison of Ecstasy users versus non-user controls again found immediate and delayed verbal recall to be significantly impaired, whilst performance on other basic cognitive functions was similar between groups (Parrott *et al.*, 1998). More recently, memory deficits have been confirmed within various other research paradigms. Whilst under the influence of Ecstasy, marked deficits in both auditory recall and visual search were apparent whereas, at the drug-free sessions, visual search scores were normal, but memory abilities remained significantly impaired (Parrott and Laskey, 1998). Subsequent studies employing polydrug controls have also confirmed that Ecstasy users display moderate cognitive problems when drug free (Bolla *et al.*, 1998; Morgan, 1999; Fox *et al.*, 2000; Gouzoulis-Mayfrank, 2000; Rodgers, 2000; Verkes *et al.*, 2001) and that executive decrements may be associated with heavier use of the drug (Wareing *et al.*, 2000; Morgan, 2000).

It may be the case that these cognitive deficits reflect neurodegeneration of central serotonergic functioning. In non-human primates, depletions in anterograde transport to the frontal cortex and a loss of 5-HT markers, including striatal type 2 vescular monoamine (VMAT2) transporters, have been shown in doses similar to those used recreationally in humans (Ricaurte *et al.*, 2000). In humans, indices of Ecstasy-related serotonin toxicity have included global depletions of the 5-HT transporter protein (McCann *et al.*, 1998), reduced neuroendocrine functioning (Gerra *et al.*, 2000) and decreased levels of the serotonin metabolite (5-HIAA) in cerebrospinal fluid (McCann *et al.*, 1999).

The psychological sequelae of these chemical disruptions have often been associated with a host of mental, emotional and behavioural problems including depression, anxiety, impulsivity, aggression and eating disorders (Wurtman, 1988; Linnoila *et al.*, 1992; Risch *et al.*, 1992). Furthermore, research examining

cognitive decline following problems such as depression (Beck, 1976; Elliot *et al.*, 1997), anxiety (Luu *et al.*, 1998), weight loss (Mathias and Kent, 1998) and sleep disruption (Randazzo *et al.*, 1998), serves to emphasize the fact that emotional and biological states are integral to an individual's cognitive appraisal of a situation or task (Lazarus, 1982). It may therefore be the case that Ecstasy users are at risk from cognitive impairment, either as a direct result of the drug's primary neurotoxic effects or as a consequence of secondary affective problems, or both.

These findings raise a number of important questions. Do cognitive deficits occur in all recreational Ecstasy users, or just particular individuals? Are certain aspects of drug consumption important for inducing cognitive and psychological problems, or are differences regarding individual susceptibility more likely to heighten the risk of suffering such adverse consequences? A large survey conducted in the UK and Italy found that certain participants attributed both cognitive and affective problems to repeated use of the drug, whilst others stated that they had experienced no problems (Milani *et al.*, 2000).

The aim of the current study was to investigate this issue more systematically in relation to both dose and problem use of the drug. As such, the working hypothesis was as follows: individuals who reported experiencing Ecstasy-related problems would be more sensitive to the neurocognitive effects of the drug, whereas those who reported no problems would be more robust. The interaction of dosage variables was examined by placing the Ecstasy groups into low, medium and high users.

The current study therefore compared young recreational users who complained of Ecstasy-induced problems with those who stated that they remained unimpaired. The cognitive test battery was selected to cover a range of cognitive skills and abilities. A measure of daily uplifts, stresses, hassles and cognitive failures was also used to further assess the frequency of these occurrences over the preceding month. In order to clarify potential differences in susceptibility, other premorbid and self-rating variables were also collated as part of a qualitative assessment, which is presented elsewhere (Fox *et al.*, in preparation).

Methods

Participants

Three groups of 20 participants were used in the study. These included two groups of Ecstasy polydrug users; one group that had complained of Ecstasy-related problems and another group that had not complained of problems related to the drug. A third control group was also used comprising individuals who had taken a range of illicit and legal drugs, but who had never used Ecstasy. All 60 participants were recruited through advertisements placed in magazines serving the London area or via the 'snowball' technique (Solowij *et al.*, 1992). Participants were requested to tick one of three statements prior to testing. These were: (i) I have never used the drug Ecstasy; (ii) I have used the drug Ecstasy and experienced no problems as a result of taking the drug; and (iii) I have used the drug Ecstasy and experienced problems attributable to the use of the drug. Participants in the latter category were asked to specify the nature of these problems.

All three groups of participants were required to give details of past drug history. Both problem and non-problem Ecstasy groups were also compared with regard to duration of Ecstasy use,

Table 1 Participant characteristics and pattern of drug use (means ± SD)

	Control (n = 20)	Non-problem (n = 20)	Problem (n = 20)
Personal characteristics			
Age	23.3 ± 6.5	26.2 ± 5.0	27.4 ± 4.5
Gender	6M/14F	9M/11F	12M/8F
Premorbid verbal IQ (NART)	108.7 ± 6.2	111.6 ± 6.3	107.9 ± 4.6
Years in education after the age of 11	9.4 ± 2.0	8.0 ± 2.7	7.7 ± 2.8
Pattern of Ecstasy use			
No. of tablets taken	–	356.9 ± 339.8	372.3 ± 663.3
Last taken (months)	–	2.5 ± 5.4	7.8 ± 11.5
Duration of use (months)	–	65.2 ± 28.1	62.6 ± 33.8
No. of tablets usually taken	–	2.9 ± 3.2	1.9 ± 0.7
Largest no. of tablets ever taken	–	7.8 ± 7.3	4.7 ± 2.6

	Control (n = 20)	Low (n = 14)	Medium (n = 14)	High (n = 11)	p	Duncan's range
Personal characteristics						
Age	23.3 ± 6.5	25.7 ± 4.5	26.9 ± 4.8	28.0 ± 5.3		
Gender	6M/14F	5M/9F	9M/5F	6M/5F		
Pre-morbid verbal IQ (NART)	108.7 ± 6.2	109.7 ± 5.5	109.9 ± 4.5	109.3 ± 7.9		
Years in education after the age of 11	9.4 ± 2.0	8.3 ± 2.3	7.9 ± 2.6	6.6 ± 3.3	*	(H,M&L) vs. (M,L&C)
Pattern of Ecstasy use						
Last taken (months)	–	5.6 ± 12.0	5.5 ± 7.3	2.8 ± 5.9		
Duration of use (months)	–	46.4 ± 24.1	80.9 ± 32.6	64.5 ± 25.1	**	(H&L) vs. (M&H)
No. of tablets usually taken	–	1.8 ± 0.9	2.2 ± 1.1	3.7 ± 3.8		
Largest no. of tablets ever taken	–	3.6 ± 1.5	5.1 ± 2.0	10.9 ± 8.7	**	(L&M) vs. (H)

*p < 0.05, **p < 0.001. The number of low, medium and high users total 39 because one participant failed to complete drug use forms.

Table 2 Drug use (means ± SD)

Drug use (% of users in each group)	Control (n = 20)	Non-problem (n = 19)†	Problem (n = 20)	p	Kruskall-Wallace C/NP	C/P	NP/P
Ecstasy	–	100	100	$p < 0.001$	*	*	
Cannabis	100	100	100	NS			
Amphetamine	55	95	100	$p < 0.001$	*	*	
Cocaine	25	89	90	$p < 0.001$	*	*	
LSD	20	89	95	$p < 0.001$	*	*	
Barbiturates	15	26	35	NS			
Opiates	10	42	50	NS			
Psilocybin mushrooms	20	63	85	$p < 0.001$	*	*	
Solvents	0	16	40	$p < 0.01$	*	*	
Nicotine	60	79	65	NS			
Alcohol	95	74	80	NS			

Drug use (% of users in each group)	Control (n = 20)	Low (n = 14)	Medium (n = 14)	High (n = 11)	p	Kruskall-Wallace C/L	C/M	C/H	L/M	L/H	M/H
Ecstasy	–	100	100	100	$p < 0.001$						
Cannabis	100	100	100	100	$p < 0.01$			*		*	
Amphetamine	55	93	100	100	$p < 0.001$	*	*	*	*	*	
Cocaine	25	71	93	100	$p < 0.001$	*	*	*			
LSD	20	86	93	100	$p < 0.001$	*	*	*	*	*	
Barbiturates	15	0	57	36	NS						
Opiates	10	14	64	64	$p = 0.001$		*	*	*	*	
Psilocybin mushrooms	20	50	86	91	$p < 0.001$		*	*	*	*	
Solvents	0	14	50	18	NS						
Nicotine	60	71	64	82	NS						
Alcohol	95	79	79	73	NS						

†One participant failed to complete drug use forms.

duration of time since Ecstasy was last taken, the number of tablets usually consumed on any one occasion and the largest number of tablets ever consumed on any one occasion. Both Ecstasy groups were also placed into low, medium and high user categories. The low user group comprised 14 participants who had consumed between 0 and 100 tablets. The medium user group comprised 14 participants who had consumed between 100 and 500 Ecstasy tablets, and the high user group comprised 11 participants who had consumed 500+ tablets. All participant characteristics and drug profiles are shown in Tables 1 and 2.

All participants were requested not to consume any illicit drugs for 2 weeks prior to testing. All participants gave their written informed consent and the University of East London Ethics Committee approved the study.

Task measures

Tasks were administered in the order of presentation below.

Uplifts, Hassels, Stresses and Cognitive Failures questionnaire (Parrott and Kaye, 1999)

Each subscale comprised items with a 4-point response scale ranging from 'never' to 'often'.

Immediate and Delayed Prose Recall (Gudjonsson, 1984)

The prose was adapted from the Logical Memory (LM-O) component of the Weschler Memory scale. It was redeveloped for 'healthy' volunteers and parsed into 40 'ideas' rather than the 23 in the original. Immediately following the tape-recording of a short story, participants were requested to recall as much of the passage as they could remember (immediate condition). They were then requested to repeat the task a second time, following an interval of 1 h 30 min (delayed condition). Participants were not informed of the delay part of the task. One point was given for each correct 'idea' recalled, and half a point for synonym substitutes that did not alter the actual concept.

Reaction time

Fifty crosses appeared on a computer screen at random intervals. Mean response latency was recorded.

Spatial working memory

A spatial working memory task designed at the University of East London was employed, whereby a sketched outline of a house appeared in the centre of a computer screen for 3 s. The house comprised 12 windows, five of which were 'lit up' (highlighted) and participants were instructed to remember the five 'lit' windows. Once the house was removed from the screen, a 7-s delay followed, after which a second house appeared; again with 12 windows, five 'lit'. Participants had to recall which two 'lit' windows were common to both houses. Participants were given 10 s to respond by ticking two 'windows' on the sketch of a house placed in front of them. The task comprised 16 trials in total (32 houses) and one mark was given for each 'window' correctly recalled.

Wisconsin Card Sorting Task (WCST)

The Heaton (1992) computerized 'version-2' of the WCST was employed in order to assess ability to shift attention. The task is explained in detail in Heaton *et al.* (1993). Participants must learn a rule in order to establish which one of three 'dimensions' a pack of 128 cards were being filed under (i.e. colour, shape or number). Once 10 consecutive cards were placed successfully into the correct pile, the rule was changed. There were six trials, whereby

relevant dimensions were changed from colour to shape to number, and then repeated. The task was terminated if a trial was not completed within 50 attempts. Participants were scored for: number of trials correctly completed, number of trials taken to complete the first category, percentage number of perseverative and non-perseverative errors and failure to maintain set.

Matched verbal recall/recognition task

Both auditory tasks were matched for difficulty and are described in Calev (1984). The recall list comprised 24 words that were semantically categorized and ordered into six categories including types of drink, trees, alcohol, clothing, measurements and fuel. Each participant received one point for a correctly recalled word, any 'intrusions' were subtracted from the total score. The recognition list comprised 40 unrelated words and was made more difficult by employing 40 'distractor' words that were either semantically linked to or rhymed with the 'target' items. Points were also allocated to 24 specific 'target' words only. Any 'false-alarms' were subtracted from the total score.

Tower of London (TOL)

A manual version of the Shallice (1982) planning task was employed; all rules were identical to those used in the original version. Participants were instructed to arrange three coloured balls (blue, red and green) on an abacus from a starting position to a 'goal' position (demonstrated on a second abacus) in a specified minimal number of moves. Twelve trials had to be completed: two 2-move trials, two 3-move trials, four 4-move trials and four 5-move trials. All trials were tape-recorded in order for 'planning times' and 'solution times' to be calculated later using a stopwatch. Planning time represented the interval between the last verbalization of the investigator to the first 'click' of the apparatus. Solution time represented the duration of moves (clicks) until completion of that particular problem. Solutions were terminated if problem solving exceeded 1 min. Participants were also scored for mean total number of errors made, as well as total number of trials completed. Planning and solution times were all averaged across trials.

Statistical analysis

All data analysis was processed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA), version 8.0 for Windows. Two analyses were performed on the data. The first assessed differences between the controls group and problem/non-problem Ecstasy users and the second analysis examined task data in relation to drug dosage. In order to protect the error rate, an alpha level of 0.01 was used.

Task data

One-way analysis of variance (ANOVA) tests were performed for all tasks apart from immediate and delayed verbal recall where a repeated measures ANOVA with two levels (immediate and delayed) was employed. Latency data from the TOL task was $\log_{10}$ transformed, in order to prevent skewness (Howell, 1997). Post-hoc analysis comprised paired comparisons between groups using the Duncan's range statistic.

Participant characteristics and drug use

Drug consumption data did not satisfy parametric requirements. As such, Kruskall-Wallace comparisons were employed in order to analyse all differences in drug use. One-way ANOVA was used to determine any differences in pattern of Ecstasy use and demographics. Chi-squared was used in order to test for any significant differences in participant distribution across both dosage and problem categories.

Results

Task data

All task data are displayed in Tables 3 and 4.

Problem users scored significantly higher on the Cognitive

Table 3 Task results for dosage groups (means ± SD)

Tasks	Control (n = 20)	Non-problem group (n = 20)	Problem group (n = 20)	p	Duncan's range
Simple reaction time (s)	277.9 ± 25.4	290.1 ± 28.5	302.1 ± 34.7	*	(C + NP) *vs.* (NP + P)
Spatial recall					
(no. of windows recalled)	28.3 ± 2.9	25.5 ± 3.3	25.8 ± 3.3	*	(NP + P) *vs.* (C)
Tower of London					
Planning time (s)	6.5 ± 2.9	13.3 ± 9.9	9.4 ± 5.0	**	(C + P) *vs.* (P + NP)
Solution time (s)	5.8 ± 1.4	6.4 ± 1.5	6.6 ± 1.7		
No. of errors	3.8 ± 2.7	3.9 ± 2.6	5.2 ± 3.1		
No. of trials completed	11.8 ± 0.6	11.6 ± 0.8	11.7 ± 0.5		
Immediate/delayed recall					
Immediate recall	19.8 ± 4.6	20.9 ± 5.4	17.7 ± 6.6		
Delayed recall	18.2 ± 4.0	19.5 ± 6.1	16.9 ± 5.8		
Matched recall/recognition					
Recognition (hits, false alarms)	16.3 ± 5.2	14.7 ± 5.6	12.2 ± 5.8		
Recall (hits, intrusions)	14.5 ± 5.3	15.5 ± 6.2	15.2 ± 4.9		
Wisconsin Card Sorting Task					
% Perseverative errors	12.6 ± 7.3	14.4 ± 9.8	12.1 ± 4.4		
% Non perseverative errors	13.7 ± 10.5	16.6 ± 13.4	13.4 ± 6.5		
Categories completed	11.7 ± 8.4	14.9 ± 9.3	16.0 ± 13.4		
Trials to first category	14.1 ± 6.2	18.0 ± 21.9	20.1 ± 27.4		
Failure to maintain set	0.6 ± 1.2	0.7 ± 1.0	1.1 ± 1.1		

*$p < 0.05$, **$p < 0.01$.

Table 4 Task results for dosage groups (means and standard deviations shown)

Tasks	Control (n = 20)	Low (n = 14)	Medium (n = 14)	High (n = 11)	p	Duncan's range	Linear contrasts
Simple reaction time (s)	277.85 ± 25.4	292.2 ± 33.5	301.0 ± 28.2	291.2 ± 35.4			
Spatial recall							
(no. of windows recalled)	28.3 ± 2.9	26.9 ± 2.9	25.4 ± 3.1	24.5 ± 3.7	**	(H&M) *vs.* (M,L&C)	***
Tower of London							
Planning time (s)	6.5 ± 2.9	8.9 ± 4.7	9.8 ± 5.4	15.3 ± 11.6	**	(H,M&L) *vs.* (L&C)	***
Solution time (s)	5.8 ± 1.3	6.8 ± 1.5	6.5 ± 1.5	6.2 ± 1.8			
No. of errors	3.8 ± 2.7	4.1 ± 2.2	5.1 ± 3.0	4.6 ± 3.8			
No. of trials completed	11.8 ± 0.6	11.6 ± 0.5	11.6 ± 0.5	11.8 ± 0.4			
Immediate/delayed recall							
Immediate recall	19.8 ± 4.6	21.4 ± 4.4	17.7 ± 5.9	19.5 ± 7.8			
Delayed recall	18.2 ± 4.0	20.0 ± 4.3	15.8 ± 6.6	19.8 + 6.1			
Matched recall/recognition							
Recognition (hits, false alarms)	16.3 ± 5.2	14.9 ± 5.4	13.1 ± 5.4	11.9 ± 6.8			*
Recall (hits, intrusions)	14.5 ± 5.3	15.4 ± 4.3	14.9 ± 5.6	15.8 ± 7.2			
Wisconsin Card Sorting Task							
% Perseverative errors	12.6 ± 7.3	11.4 ± 6.0	15.8 ± 10.2	11.8 + 5.3			
% Non perseverative errors	11.7 + 8.4	14.6 + 10.3	15.9 + 14.4	14.1 + 7.5			
Categories completed	5.3 ± 1.3	5.3 ± 1.8	4.6 ± 2.1	5.5 ± 0.7			
Trials to first category	14.1 ± 6.2	13.6 ± 3.2	27.6 ± 40.8	15.0 ± 9.8			
Failure to maintain set	0.6 ± 1.2	0.9 ± 1.2	0.8 ± 0.8	0.9 ± 1.3			

*p < 0.05, **p < 0.01, ***p < 0.001.

Failures subscale of the Uplifts, Hassles, Stresses and Cognitive Failures questionniare compared with non-problem users [F(2,57) = 5.59, p = 0.006]. No group differences were established in relation to dosage [F(3,55) = 1.33, p = 0.27].

Problem Ecstasy users demonstrated significantly slower reaction times compared with controls [F(2,57) = 3.3, p = 0.04] and non-problem users demonstrated significantly increased planning times on the TOL compared to both problem users and controls [F(2,56) = 5.2, p = 0.003] (Figure 1). Both Ecstasy groups made significantly more errors on the spatial working memory task compared to controls [F(2,56) = 4.4, p = 0.02] (Figure 2). However, they performed similarly to controls on all other task measures.

With regard to Ecstasy dosage, the high user group demonstrated significantly increased planning times compared to low users and controls [F(3,57) = 4.7, p = 0.007] (Figure 3). Increases in errors on the spatial working memory task were also shown as a function of dosage, with high and medium users making significantly more errors compared to controls [F(3,57) = 4.1, p = 0.01] (Figure 4). No significant differences in dosage were established on any other task.

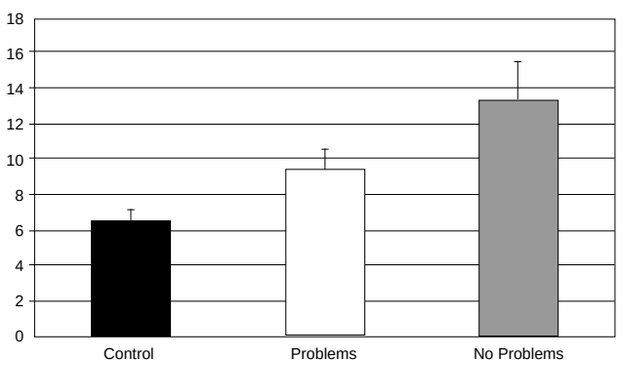

Figure 1 Mean TOL planning times (s) for control, problem and non-problem Ecstasy groups

Personal characteristics and drug data

There were no differences between the problem and non-problem Ecstasy users with regard to either personal characteristics or

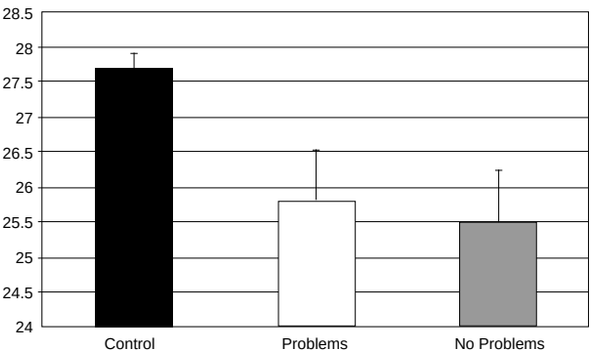

Figure 2 Mean number of 'windows' correctly recalled on the spatial working memory task for control, problem and non-problem Ecstasy groups

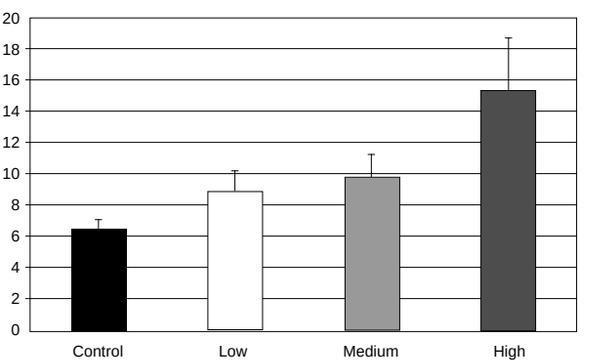

Figure 3 Mean TOL planning times (s) as a function of Ecstasy dose

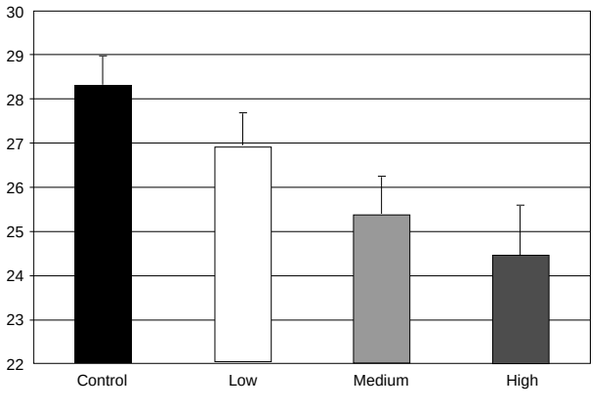

Figure 4 Mean number of 'windows' correctly recalled on the spatial working memory task as a function of Ecstasy dose

pattern of Ecstasy use (Table 1). There were also no significant group differences between the two Ecstasy groups regarding the quantity of any drug consumed, including Ecstasy. Both groups, however, had consumed significantly more amphetamine, cocaine, LSD, mushrooms and solvents compared to controls (Table 2).

There were no significant group differences between controls, low, medium and high Ecstasy users with regard to age, gender or IQ. However, the controls had spent significantly longer in education than the high Ecstasy users. Low Ecstasy users had consumed a mean (SD) of 58.3 ± 32.1 tablets, medium users a mean (SD) of 236.4 ± 116.5 tablets and high users a mean (SD) of 918.2 ± 730.5 tablets. The medium user group had taken Ecstasy for a significantly longer duration than the low user group [$F(2,36) = 5.4$, $p = 0.009$] and the high user group had consumed a significantly greater number of tablets on one specific occasion than both other groups [$F(2,36) = 7.5$, $p = 0.002$]. No significant group differences were shown in relation to the last time Ecstasy had been consumed [$F(2,36) = 0.38$, $p = 0.67$] and the number of tablets usually taken on any one occasion [$F(2,36) = 2.5$, $p = 0.10$] (Table 1). The controls had consumed similar amounts of all drugs compared to the low user group, except for amphetamine, cocaine and LSD. However, they had consumed significantly less of all other drugs compared to the higher user groups. The medium and high user groups consumed a similar quantity of all drugs, with the exception of Ecstasy. The low user group also consumed similar amounts of cocaine, barbiturates, solvents, nicotine and alcohol, but significantly less cannabis, amphetamine, LSD, mushrooms and opiates than both the medium and high users (Table 2).

Table 5 Ecstasy-related problems experienced by the problem group ($n = 20$)

Problems experienced	No. of participants
Psychological problems	
Confidence loss	2
Less sociable	1
Mood swings	3
Aggression	1
Depression	7
Anxiety	7
Paranoia	4
Morbid/obsessive thoughts	2
Hallucinations/flashbacks	2
Somatic problems	
Backache	1
Breathlessness	1
General illness	1
Weight loss	2
Sleep problems	2
Tremors	1
Cognitive problems	
Memory loss	8
Concentration loss	2
Loss of organizational skills	2
Motivational problems	1

Chi-squared analysis indicated that there was no significant difference in the distribution of participants across both categories (chi-squared = 1.94, d.f. = 2, $p = 0.38$). The low user category comprised seven problem and non-problem users. The medium user category comprised nine problem users and five non-problem users and the higher user category comprised seven non-problem users and four problem users.

Ecstasy-related problems described by the problem group were classified into three main categories on the basis of participants' responses: psychological, somatic and cognitive. Informal consultation with an external investigator clarified the appropriateness of each category. The results are displayed in Table 5.

Discussion

The present study confirms previous findings showing that recreational Ecstasy users demonstrate selective cognitive impairment (Bolla *et al.*, 1998; Parrott *et al.*, 1998). It is also consistent with research that has shown heavy users to be impaired on tasks that measure executive function or working memory (Milani, 1997; Fox *et al.*, 2000; Wareing *et al.*, 2000).

The main findings concern the fact that both Ecstasy groups demonstrated task impairment, despite only one group complaining of problems and despite problem users scoring significantly higher than non-problem users on a cognitive failures subscale. Both Ecstasy groups made a significantly greater number of errors on the spatial working memory task compared to controls (Figure 3) and the self-reported non-problem users demonstrated significantly increased planning times compared to controls on the TOL task (Figure 1). Most importantly, both Ecstasy groups were impaired only as a function of drug dosage and not as a function of the extent of problematic use of the drug. On the TOL task, heavy users took significantly longer to plan compared with the low users and controls (Figure 2). On the spatial working memory task, the high and medium user groups made a significantly greater number of errors compared to controls (Figure 4). In both cases, means revealed a highly significant polynomial linear function (Table 1). Previous data has also associated increased total consumption of Ecstasy use with cognitive problems (Bolla *et al.*, 1998; Parrott and Laskey, 1998), whilst other studies have related impaired performance with the amount of Ecstasy consumed per session and duration of use (Morgan, 1999).

Despite the problem group demonstrating increased psychomotor slowing compared to controls, they performed no differently to the non-problem group. Furthermore, not only did both problem and non-problem users demonstrate similar cognitive impairments, they also showed relatively similar drug consumption profiles. The problem users showed no difference in the duration or

pattern of Ecstasy use, or the total life consumption of Ecstasy (or that of any other drug) compared to non-problem users (Table 1).

The results from the current study indicate that an individual's self-perception of problematic drug use may not necessarily be dose-related. With regard to cognitive problems in particular, there were no significant group differences between low, medium and high users on the cognitive failures subscale. As such, individuals who are heavier polydrug Ecstasy users may not be aware of potential problems. This is of particular concern if cognitive decrements are dose related.

Deficits on both the TOL and spatial working memory tasks indicate that control of strategy function may be problematic for heavier Ecstasy users. The spatial working memory task employed in the present study required participants to hold spatial information 'on line' and 'manipulate' the information in order to match two stimuli. Importantly, these processes represent similar strategies to those identified and imaged in the TOL task (Baker *et al.*, 1996). Potential decrements in strategy implementation may also be consistent with deficits shown in retrieval strategies on both verbal fluency tasks (Fox *et al.*, 2000) and random letter generation tasks (Wareing *et al.*, 2000).

As demonstrated in previous research, cognitive impairment in both problem and non-problem Ecstasy groups was not global. However, a lack of impairment on verbal recall and immediate and delayed prose recall is in marked contrast to several studies (Bolla *et al.*, 1998; Parrott *et al.*, 1998; Morgan, 1999; Rodgers, 2000). A possible explanation for these inconsistencies may be related to the fact that the verbal recall list comprised semantically ordered words, eliminating the requirement for organizational strategies. If working memory functions represent a potential problem for Ecstasy users, this may explain why deficits in unstructured free recall tasks have been shown in other studies, but not in the current study. Conceptual priming may also have had a marked effect on the results of the task. In relation to immediate and delayed prose recall, subtleties in task variation may have produced conflicting data. The current study employed a prose passage double the length of that used in previous studies. As such, greater emphasis may have been placed on verbal learning processes and concept formation, and less on short-term span and verbatim recall.

Although heavy Ecstasy polydrug use may be associated with a disruption of efficient strategy application, other executive functions may be relatively spared in the early stages of use. Low, medium and high Ecstasy users all failed to show impairments regarding attentional shifting paradigms on the WCST. This is also consistent with previous research. Fox *et al.* (2000) found drug-free Ecstasy users to be unimpaired on the shift components of the analogous 3-D Intra Dimensional/Extra Dimensional task, and Turner *et al.* (1999) found drug-free users unimpaired on an identical computerized version of the WSCT. One possibility may relate to the fact that inhibitory processes required to effect successful attentional shifting (Robbins *et al.*, 1996) are essentially dissociable from mnemonic processes and occur at a later stage in any degenerative process (Cohen *et al.*, 1998). This is a pattern of degeneration that has also been shown in normal human functioning (Roberts *et al.*, 1994), schizophrenia (Cohen *et al.*, 1998) and animal research (Roberts *et al.*, 1994). Furthermore, Ornstein *et al.* (2000) found impaired set-shifting in a group of chronic amphetamine users who had been using the drug for 14 years. Ecstasy users in the current study had only been taking the drug for approximately five years. Because Ecstasy is an Amphetamine-derivative, future research may be more likely to find problems associated with attentional shifting at a later stage of usage.

Executive performance deficits that have been shown in the current study may reflect a reduction of central serotonergic functioning within the frontal cortex of heavy Ecstasy users. Forebrain regions such as the frontal cortex and the hippocampal areas are richly innervated with 5-HT neurones (Brodkin *et al.*, 1993) and have been widely implicated in the neurodegenerative processes of Ecstasy. Moreover, interconnectivity with areas of the frontal cortex is integral to the neural circuitry of working memory (Goldman-Rakic and Friedman, 1991) and includes behaviour such as goal formulation and planning, sustained attention and prospective memory (Rabbitt, 1997).

Despite these assumptions, it is important to acknowledge that this study, and Ecstasy research in general, is often associated with problems regarding the monitoring and profiling of participant drug use. Drug use data in this study was reliant only upon self-reported estimates, and there was no biological monitoring of abstinence from illicit drugs. Data should also be interpreted with caution due to the fact that post-hoc analysis of Ecstasy use resulted in small participant samples. With regard to assessing the effects of Ecstasy use alone, the controls had consumed significantly less of certain illicit drugs compared to the two Ecstasy groups. Furthermore, the low Ecstasy users had also consumed lower quantities of other illicit drugs compared to the high Ecstasy users. Such methodological issues are, however, difficult to overcome as alternatives also present problems. Studying individuals who only consume Ecstasy may be considered unrepresentative or atypical of the majority of Ecstasy users, who are (in most cases) polydrug users (Schifano *et al.*, 1998; Milani *et al.*, 2000). This also means that the use of regression models in drug research is often inappropriate, as many of the drugs consumed are too highly correlated with each other to produce meaningful analysis.

Rather than representing a fundamentally unique type of drug user, individuals who take Ecstasy would appear to be polydrug users whose Ecstasy consumption is relatively indicative of other illicit drug use (Milani *et al.*, 2000). Therefore, the cognitive profiles demonstrated in the present study should be viewed as a reflection of Ecstasy polydrug use in individuals who have consumed Ecstasy as a drug of preference. As such, results from the present study may be largely reflective of serotonin depletion. However, the effects of other monoaminergic systems cannot be discounted due to heavier use of other methamphetamine derivatives. Whilst Ecstasy use may culminate in cognitive impairments, issues of causality remain complex and should also be viewed in terms of quantity and pattern of other drug use. Despite these methodological difficulties, this study does show two very different self-perceived Ecstasy groups who demonstrated similar drug use and cognitive profiles. Equally, both the medium and high Ecstasy users had consumed comparable amounts of other illicit and legal drugs.

This is the first study to examine the interaction between dose and self-reported problematic drug use in relation to cognitive impairment in recreational Ecstasy users. The conclusions emphasize dose-related working memory problems in heavy Ecstasy polydrug users that may be independent of the 'affective'

and 'somatic' complications associated with problem use. Our findings also indicate that perceived problems are not dose-related and future research should be encouraged within the area of problem awareness. As the use of Ecstasy and related substances has increased two-fold within the younger population, in the years between 1990 and 1998 (Schuster *et al.*, 1998), harm reduction programmes should be mindful of the fact that many of these young people may not be aware of underlying cognitive problems.

Acknowledgements

The authors wish to acknowledge Margherita Milani for her helpful comments on the manuscript and Time Out magazine for providing advertising space.

Address for correspondence

Helen Fox
Department of Psychology
University of East London
Romford Road
London E15 4LZ
UK
Email: h.c.fox@uel.ac.uk

References

Baker S C, Rogers R D, Owen A M, Frith C D, Dolan R J, Frackowiak R S J, Robbins T W (1996) Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia *34*: 515–526

Beck A T (1976) Cognitive theory and emotional disorders. International University Press, New York

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

Brodkin J, Malyala A, Nash F (1993) Effect of acute monoamine depletion on 3,4-methylenedioxymethamphetamine-induced neurotoxicity. Pharmacol Biochem Behav *45*: 647–653

Calev A (1984) Recall and recognition in mildly disturbed schizophrenics: the use of matched tasks. Psychol Med *14*: 425–429

Cohen J D, Braver T S, O'Reilly R C (1998) Computational approach to prefrontal cortex, cognitive control and schizophremia: recent developments and current challenges. In Roberts A C, Robbins T W, Weiskrantz L (eds), The prefrontal cortex executive and cognitive functions. Oxford University Press, Oxford

Elliott R, Baker S C, Rogers R D, O'Leary D A, Paykel E S, Frith C D, Dolan R J, Sahakian B J (1997) Prefrontal dysfunction in depressed pateints performing a complex planning task. A study using positron essimion tomography. Psychol Med *27*: 931–942

Fox H C, McLean A, Turner J J D, Parrott A C, Rogers R D, Sahakian B J (2000) Heavy MDMA ('Ecstasy') users: selective performance deficits on the Cambridge Neuropsychological Test Automated Battery (CANTAB). Int J Neuropsychopharmacol *3* (Suppl. 1): 14.27

Fox H C, Milani R M, Parrott A C, Turner J J D (2001) Differences in premorbid adjustment between problematic and non-problematic Ecstasy users (abstract). Proceedings of the 24th Annual Meeting of the Canadian College of Neuropsychopharmacology joint with the British Association for Psychopharmacology and the Japanese Society of Neuropsychopharmacology

Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, Marczocchi G F, Delsignore R, Brambilla F (2000) Long-lasting effects of (+/–) 3,4-methylenedioxymethamphetamine (ecstasy) on serotonin system function in humans. Biol Psychiatry *47*: 127–136

Goldman-Rakic P S, Friedman H R (1991) The circuitry of working memory revealed by anatomy and metabolic imaging. In Levin H S, Eisenberg H M, Benton A L (eds), Frontal lobe function and dysfunction, pp. 72–89. Oxford University Press, Oxford

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

Gudjonsson G H (1984) The Gudjonsson Suggestibility Scales. Psychology Press, Hove, East Sussex

Heaton R K (1992) Wisconsin Card Sorting Test (version 2) (computer software). Psychological Assessment Resources, Inc., Odessa, FL

Heaton R K, Chelune, G J, Talley J L, Kay G G, Curtiss G (1993) Wisconsin Card Sorting Test manual: revised and expanded. Psychological Assessment Resources, Inc., Odessa, FL

Howel D C (1997) Statistical methods for psychology. Duxbury Press, California

Krystal J H, Price L H, Opsahl C, Ricaurte G A, Heninger G R (1992) Chronic 3,4-methylenedioxymethamphetamine (mdma) use – effects on mood and neuropsychological function. Am J Drug Alcohol Abuse *18*: 331–341

Lazarus R S (1982) Thoughts on the relation between emotion and cognition. Am Psychol *37*: 1019–1024

Linnoila V, Verkkunen M (1992) Aggression, suicidality and serotonin. J Clin Psychiatry *53*: 46–51

Luu P, Tucker D M, Derryberry D (1998) Anxiety and the motivational basis of working memory. Cognit Ther Res *22*: 577–594

Mathias J L, Kent P S (1998) Neuropsychological consequences of extreme weight loss and dietry restriction in patients with anorexia nervosa. J Clin Exp Neuropsychol *20*: 548–564

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

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

Milani R (1997) Disturbi neuropsicologici associati all'uso di Ecstasy. doctoral dissertation. Universita' degli Studi di Padova, Italy

Milani R, Turner J J D, Parrott A C (2000) Recreational drug use and pasychobiological problems. Collaborative UK/Italy Study (5): Ecstasy (MDMA) polydrug user findings. J Psychopharmacol *14* (Suppl. 3): PA22

Morgan M J (1999) Memory deficits associated with recreational use of 'ecstasy' (MDMA). Psychopharmacology *141*: 30–36

Morgan M J (2000) Memory deficits persist for at least 6 months after abstinence from Ecstasy (MDMA). J Psychopharmacol *14* (Suppl. 3): PA15

Ornstein T S, Iddon J L, Baldacchino A M, Sahakian B J, London M, Everitt B J, Robbins T W (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology *23*: 113–123

Parrott A C, Kaye F (1999) Uplifts, hassels, stresses and cognitive failures, in cigarette smokers and non smokers. Behav Pharmacol *10*: 639–646

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, Lees A, Garnham N J, Jones M, Wesnes K (1998) Cognitive performance in recreational users of MDMA or ecstasy: evidence for memory deficits. J Psychopharmacol *12*: 79–83

Rabbitt P (1997) Methodologies and models in the study of executive function. In Rabbitt P (ed), Methodology of frontal and executive functioning, pp. 1–35. Psychology Press Ltd, Hove, East Sussex

Randazzo A C, Muehlbach M J, Schweitzer P K, Walsh J K (1998) Cognitive function following acute sleep restriction in children ages 10–14. Sleep *21*: 861–868

Ricaurte G A, Yuan J, McCann U D (2000) (+/–) 3,4-methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology *42*: 5–10

Risch S, Nemeroff C (1992) Neurochemical alterations of serotonergic neuronal systems in depression. J Clin Psychiatry *53* 3–7

Robbins T W, Weinberger D R, Frith C D, Weiskrantz L (1996) Prefrontal dysfunction in neuropsychiatric disorders – general discussion. Philosophical transactions of the Royal Society of London Series B. Biol Sci *351*: 1513–1514

Roberts A C, De Salvia M A, Wilkinson L S, Collins P, Muir J, L., Everitt B J, Robbins T W (1994) 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analogue of the Wisconsin Card Sorting test: possible interactions with subcortical dopamine. J Neurosci *14*: 2531–2544

Rodgers J (2000) Cognitive performance amongst recreational users of 'ecstasy'. Psychopharmacology *151*: 19–24

Schifano F, DiFuria L, Forza C, 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

Schuster P, Lieb R, Lamertz C, Wittchen H U (1998) Is the use of Ecstasy and hallucinogens increasing? Results from a community study. Eur Addict Res *4*: 75–82

Shallice T (1982) Specific impairments in planning. Philos Trans R Soc B *298*: 199–209

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of ecstasy users and their experiences with the drug. Br J Addict *87*: 1161–1172

Turner J J D, Godolphin M, Parrott A C (1999) Cognitive task performance profiles of current 'Ecstasy' (MDMA) users. J Psychopharmacol *13*: (abstract)

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

Wareing M, Fisk M, Murphy J E (2000) Working memory deficits in current and previous users of MDMA ('Ecstasy'). Br J Psychol *91*: 181–188

Wurtman J (1988) Carbohydrate craving, mood changes and obesity. J Clin Psychiatry *49*: 37–39