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Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': evidence for cognitive impairment

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ABSTRACT

Background. It has recently been shown that 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy' causes long-lasting alterations to brain structure and function in animals, and there is mounting evidence that recreational users of the drug show impairments in some aspects of cognitive functioning including memory for verbal information. The present study investigates possible effects on other cognitive functions and explores the temporal course of development and resolution of these impairments by comparing novice, regular and abstaining users with a matched group of non-users.

Methods. Eighty participants categorized as non-users, novice users, regular users or currently abstinent users of MDMA were assessed on tests of verbal IQ, reversed digit span, immediate and delayed recall of a prose passage and of a complex geometric figure and verbal fluency.

Results. The four groups were well-matched for verbal IQ and on demographic variables. They differed in frequency of cannabis use over the last month, but this did not correlate with any cognitive test scores. All three groups of MDMA users showed significantly poorer verbal fluency and immediate and delayed prose recall than non-users. Days since last use and total lifetime consumption of MDMA made separate contributions to the variance in recall scores, accounting jointly for almost half of the variance in delayed recall. By contrast, the groups did not differ on either visual recall or reversed digit span.

Conclusions. The observed deficits provide further evidence of impairments of verbal but not visual memory in MDMA users, and indicate that the deficits are not attributable either to differences in general reasoning ability or to impairment of working memory. The data further suggest that the observed impairments may be attributable to a combination of reversible acute effects of MDMA resolving over a period of 2–3 weeks and more long-term changes associated with extent of lifetime consumption.

INTRODUCTION

The compound 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy', is a synthetic amphetamine derivative with mixed stimulant and hallucinogenic properties (Shulgin, 1986). Evidence has been accumulating since the early 1980s that MDMA and its de-methylated metabolite, 3,4-methylenedioxyamphetamine (MDA), have enduring neurotoxic effects; thus, animals show long-term depletions of brain levels of 5-HT (serotonin) and of its uptake sites, and there are degenerative changes to 5-HT axons and terminals (e.g. Frederick & Paule, 1997). Fischer *et al.* (1995) reported that in primates, damage to nerve terminals was still apparent in some brain regions 12 months after drug administration and that where reinnervation had occurred it was abnormal. Such research leads to a concern that similar physio-

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logical changes may occur in humans and that recreational use of the drug may cause either transient or permanent alterations in brain structure and function. Indeed, a recent review by Ricaurte *et al*. (2000) concludes that the dosages of MDMA that have been shown to be toxic in animals are equivalent to those typically used recreationally, while in a neuro-imaging study using positron emission tomography (PET), McCann *et al*. (1998) found that 14 MDMA users showed dose-related reductions in the level of a 5-HT transporter. McCann *et al*. (2000) summarize a growing body of additional evidence for abnormal serotonergic activity in the central nervous systems of human MDMA users (e.g. low levels of serotonergic metabolites in cerebrospinal fluid; decreased serotonergic transporter receptor sites; blunted neuroendocrine responses to pharmacological challenges).

However, despite its widespread use as an illicit recreational drug, and its well-documented physiological and subjective mood effects (e.g. Petrouka, *et al*. 1988; Davison & Parrott, 1997; Parrott & Stuart, 1997), there is a distinct paucity of research on its cognitive effects. Rigorously controlled laboratory studies of MDMA are rarely practicable because of its illegal status and consequently the majority of published studies have documented the effects of the drug in open trials, or in 'field' experiments with recreational users.

Krystal *et al*. (1992) assessed nine longstanding MDMA users, who had been abstinent for a mean of 66 days, on a battery of neuropsychological tests and found them to perform significantly below age-related norms on immediate and delayed recall of prose passages. However, interpretation of these data is difficult, since seven of the participants had psychiatric histories and all were injected with tryptophan, a precursor of 5-HT, prior to testing. Subsequently, Curran & Travill (1997) evaluated the acute and residual effects of self-administration of MDMA in 12 users by comparison with the performance of 12 participants who had consumed only alcohol. Participants' mood state and cognitive function were assessed during the evening of drug use (Day 1), the following day (Day 2) and 4 days later (Day 5). By comparison with the alcohol-only group, the MDMA group showed significant impairments on a task of prose recall; however, both groups had improved by the Day 5. The MDMA group was also impaired on a task tapping concentration and working memory (Serial 7s), most markedly on Day 2.

Parrott *et al*. (1998) compared 10 'regular' MDMA users, who had taken the drug more than 10 times, with 10 'novice' users, who had taken it between one and nine times, and with a control group of non-users of MDMA. Again, by comparison with non-users, both regular and novice users of MDMA showed significantly impaired immediate and delayed recall of verbal information. Parrott & Lasky (1998) additionally found that 15 regular ecstasy users showed deficits on a short-term verbal memory test not only shortly after taking the drug but also following a subsequent 7 day abstinent period. Extending these findings, Bolla *et al*. (1998) found not only that 24 abstinent MDMA users showed a verbal memory deficit compared with 25 non-users, but that within the MDMA users there was an inverse correlation between average monthly MDMA consumption and memory performance. Most recently, Morgan (1999) compared 25 polydrug users with a history of MDMA use against 22 polydrug users without a history of MDMA use and 19 non-drug users. The MDMA/polydrug group showed significant impairment of both immediate and delayed recall relative to both comparison groups.

Parrott *et al*. (1998) considered a range of explanations for the memory deficits observed in MDMA users, including the possibility that they reflect a subtle change in cognitive strategy: 'MDMA users often state that their phenomenological experience becomes more immediate and less verbal whilst on drug. They become more concerned with direct perception, and do not feel the necessity for labelling thoughts and feelings'. They hypothesize that if this change towards a more visual and less verbal cognitive style persisted, it might explain residual verbal memory deficits. As yet no studies have tested this hypothesis, from which it would follow that MDMA users should show less impairment of visual than of verbal memory.

The purpose of the current study was to investigate further the cognitive consequences of recreational MDMA use, with particular emphasis on memory function, comparing regular users, novice users and 'currently abstinent'

users with non-users. Based on the preceding review, it was hypothesized first that novice, regular and abstaining MDMA users would show poorer immediate and delayed recall of verbal information than non-users; and secondly, that MDMA users would perform at least as well as non-users on immediate and delayed recall of visual information. In addition to tests of verbal and visual recall, participants were also assessed on brief tests of working memory and executive function. Relationships of test performance to self-reported recency and lifetime extent of MDMA use were further explored via correlational analysis within the three groups of MDMA users. The study controlled for possible differences in general reasoning ability and for frequency of the use of other drugs.

METHOD

Design

A between-groups design was employed. Eighty participants were categorized into four groups based on their responses to a questionnaire concerning their use of MDMA over their lifetime and during the previous 30 days: 'Non-users' ($N = 20$), had never taken MDMA; 'Novice users' ($N = 18$), had taken MDMA between one and five times in total; never more frequently than once in a month; and at least once within the 21 days; 'Regular users' ($N = 26$), had taken MDMA at least five times; and at least twice during the previous 21 days; and, 'Currently abstinent users' ($N = 16$), had in the past been regular users of MDMA, but had not taken any for at least 30 days prior to participation in the present study. None, however, had been abstinent for more than 120 days.

All participants were tested on a battery of cognitive tests. The experimenter remained blind to participants' self-reported drug-using status until testing had been completed.

Participants

A total of 94 participants were tested. Five withdrew before testing was complete, and nine were excluded because of incomplete questionnaire data. Of the remaining 80 participants, 54 were undergraduates; the other 26 were all in full-time employment and had been educated to at least degree level.

Participants were not paid, and all reported having used no drugs in the 24 h before testing.

Assessment measures

Drug history

This was ascertained via a self-completed questionnaire on which participants specified their frequency of use of all the major classes of recreational drugs (including alcohol) in the past 24 h and in the 30-day period prior to testing. They also estimated the number of days that had elapsed since the last occasion that they had used MDMA. Finally, they were asked to categorize their total lifetime use of MDMA as follows: 1 = 1–5 tablets/doses; 2 = 6–15 tablets/doses; 3 = 16–30 tablets/doses; 4 = 31–50 tablets/doses; 5 = $\geqslant$ 51 tablets/doses.

Cognitive tests

Verbal IQ

This was assessed using the Quick Test (Ammons & Ammons, 1962). This is a forced choice task in which participants examine four line drawings of action scenes and decide which is the most appropriate referent for a particular word. A series of words of increasing abstractness and rarity in the English language is presented. Thus, the test taps both crystallized intelligence (insofar as it requires knowledge of word meaning) and fluid intelligence (in abstracting and comparing the meanings of the four pictures).

Verbal memory

This was assessed using a prose recall test (Powell *et al.* 1993) in which a short story containing 24 'ideas', initially read aloud by the experimenter, has to be recalled in as much detail as possible (*a*) immediately and (*b*) after a delay of 30 min. One point is given for each 'idea' recalled perfectly and half a point for each idea recalled partially.

Visuospatial memory

This was assessed using the Rey–Osterrieth test (Rey, 1941; Osterrieth, 1944). Forty minutes after copying a complex geometric figure, participants were, without warning, asked to reproduce it from memory. The 'copy' score provides an index of visual-constructional ability, and the

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'recall' score of retention. Scoring followed Lezak's (1995) guidelines, yielding a maximum score of 36 for both copy and recall accuracy.

Working memory

This was briefly assessed via reversed digit span. Participants repeated, in reverse order, sequences of digits presented orally by the experimenter. The sequences increased in length from two to seven. Participants were credited with one point for each digit in the longest sequence accurately recalled.

Executive function

This was assessed using the Controlled Oral Word Association or 'Verbal Fluency' test (Benton & Hamsher, 1976). Participants had to generate as many words as possible (excluding proper nouns) beginning with the letters 'F', 'A' and 'S' in 1 min for each letter. The score was the sum of all admissible words for the three letters.

Statistical analysis

For each cognitive variable, a one-way ANOVA was conducted with user-defined *a priori* contrasts: (*a*) to compare each of the MDMA groups separately with the non-users; and (*b*) to compare abstaining users with regular users, in order to determine whether there was evidence of recovery of function over a period of abstinence. Where the groups differed in their use of another substance over the previous 30 days, the relationships between this substance use and cognitive test performance were first explored correlationally. If significant associations were found, this other substance use was controlled for within the ANOVAs described above.

The possibility that recent use of MDMA might produce transient effects on cognitive functioning was explored correlationally within: the combined drug-using groups, i.e. novice, regular, and abstaining users; and, the current drug-using groups, i.e. novice and regular users. The hypothesis that longer-term use results in progressive cognitive impairment was also addressed by correlating test scores with the 'lifetime MDMA consumption' variable for the combined drug-using groups (novice, regular and abstaining). Finally, for those cognitive variables which correlated with both recency of use and lifetime consumption, stepwise regression was used to determine the extent to which their contributions were independent of each other, of IQ, and of any other drug use which was also associated with test performance.

RESULTS

Demographics

Mean ages were 22·1($\pm$2·8) for the 11 male and nine female non-users; 23·6($\pm$3·0) for the nine male and nine female novice users; 23·8 ($\pm$3·4) for the 16 male and 10 female regular users; and 24·6 ($\pm$3·4) for the 10 male and six female currently abstinent users. The groups did not differ in either age ($F_{3,76} = 2{\cdot}0$, NS) or gender ratio ($\chi^2 < 1$, NS).

Drug use

The frequencies with which each class of drugs were reported to have been used in the last 30 days by each group are shown in Table 1. Cocaine and amphetamine use were each reported by $< 16\%$ of participants in any group, and LSD had been used by only one participant. There were no main effects of Group for any of these drugs ($F_{3,76} < 1$, NS in each case). Although alcohol was taken once or twice a week on average, the groups did not differ in this respect either ($F_{3,76} < 1$, NS).

There were, however, main effects of Group for use of both MDMA ($F_{3,76} = 90{\cdot}2$, $P < 0{\cdot}001$) and cannabis ($F_{3,76} = 3{\cdot}24$, $P < 0{\cdot}05$). For MDMA, this reflected the basis of group categorization, with non-users and currently abstinent users both reporting zero use, and the regular users reporting more frequent use than the novice users. For cannabis, non-users all reported zero consumption, while by contrast average use over the past month in the other three groups was twice or more; at least some cannabis use was reported by 11 (61%) of the novice MDMA users, 12 (46%) of the regular users and 8 (50%) of the currently abstinent users. Pairwise comparisons revealed cannabis use to differ significantly between non-MDMA users and novice MDMA users ($t_{76} = 2{\cdot}6$, $P < 0{\cdot}05$) and between non-users and currently abstinent users ($t_{76} = 3{\cdot}0$, $P < 0{\cdot}005$); the difference between non-users and regular users was just short of significance ($t_{76} = 1{\cdot}8$, $P =$

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Table 1. *Self-reported frequency of drug use during previous 30 days*

	Non-users Mean (S.D.)	Novice users Mean (S.D.)	Regular users Mean (S.D.)	Abstaining users Mean (S.D.)	ANOVA: main effect of group
MDMA	0·00 (0·00)	1·0 (0·0)	2·65 (1·09)	0·00 (0·00)	***
Alcohol	5·35 (4·75)	7·56 (5·81)	6·62 (6·19)	5·88 (5·34)	NS
Cannabis	0·00 (0·00)	2·83 (3·45)	2·38 (3·46)	4·44 (7·91)	*
Amphetamines	0·00 (0·00)	0·11 (0·32)	0·42 (1·06)	0·13 (0·50)	NS
LSD	0·00 (0·00)	0·00 (0·00)	0·03 (0·20)	0·00 (0·00)	NS
Cocaine	0·00 (0·00)	0·11 (0·47)	0·46 (1·21)	0·25 (0·77)	NS

Two-tailed probability levels compared the groups: * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

0·07). When the cannabis use of the three MDMA groups was compared in an ANOVA which excluded the non-users, there was no overall main effect of Group ($F_{2,57} < 1$, NS).

No participant reported using any substance (even alcohol) in the 24 h prior to testing. Days since last use of MDMA was reported as 8·56 (S.D. 6·44, range 2–21) by novice users; 7·42 (S.D. 6·34, range 2–21) by regular users; and 46·25 (S.D. 25·15, range 30–120) by currently abstaining users, with all but three of this group reporting their last use between 30 and 45 days previously. Across the three groups combined, the distribution was strongly skewed to the left (i.e. towards recent use) with a mean of $18{\cdot}1 \pm 22{\cdot}0$ days. Given this distribution, Spearman's rho has been used in correlational analyses involving this variable.

Life-time frequency (doses) of MDMA use was reported to be zero by all non-users and 1–5 by all novice users. All regular and currently abstinent users reported having used MDMA at least 16 times; the modal response in both groups was $\geqslant 51$. Of the regular users, three reported using 16–30 times, ten 31–50 times, and thirteen $\geqslant 51$ times; of the currently abstinent users, two reported 16–30 times, five 31–50 times, and nine $\geqslant 51$. Since this distribution is non-normal, and in view of the ordinal coding system used, Spearman's rho was used in correlational analyses.

Cognitive tests

Table 2 presents the scores on the various cognitive tests by Group; Table 3 shows correlations of test scores with days since last MDMA use and with lifetime consumption of MDMA both for current users (novice and regular) and for all users (novice, regular and currently abstinent).

Quick Test

Cannabis use over the last 30 days showed no relationship to scores on the Quick Test, either within the whole sample ($N = 80$, $r = -0{\cdot}08$, NS) or within the three drug-using groups ($N = 60$, $r = -0{\cdot}10$, NS). There was consequently no need to control for it within the ANOVA. This revealed no main effect of Group ($F_{3,76} < 1$, NS), and none of the *a priori* contrasts between groups reached significance ($t < 1$, NS, in all cases). Neither recency of MDMA use nor lifetime consumption predicted IQ scores in either the combined users (novice, regular and currently abstaining) or the current users (novice and regular).

Verbal memory

Both immediate and delayed recall were uncorrelated with cannabis use both within the whole sample ($N = 80$, $r = -0{\cdot}16$ and $-0{\cdot}11$, NS) and within the three drug-using groups ($N = 60$, $r = 0{\cdot}02$ and $0{\cdot}08$, NS); possible confounding effects of differential cannabis use are thus not considered further.

ANOVA revealed a main effect of Group for immediate recall ($F_{3,76} = 39{\cdot}8$, $P < 0{\cdot}001$), with non-users showing significantly better memory than novice users ($t_{76} = 2{\cdot}3$, $P < 0{\cdot}03$), regular users ($t_{76} = 9{\cdot}5$, $P < 0{\cdot}001$), and abstaining users ($t_{76} = 7{\cdot}6$, $P < 0{\cdot}001$). Regular and abstaining users did not differ ($t_{76} < 1{\cdot}0$, NS).

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Table 2. *Scores on cognitive tests, by group, with results for between groups contrasts in ANOVA (with cannabis use as a covariate)*

	Non-users (NU)	Novice users (N)	Regular users (R)	Currently abstaining users (A)	Comparison of pairs of groups within ANOVA			
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	NU *v.* N	NU *v.* R	NU *v.* A	R *v.* A
Quick Test	96·60 (4·16)	96·33 (3·09)	97·77 (4·88)	95·75 (3·49)	NS	NS	NS	NS
Prose recall								
Immediate	15·80 (1·55)	14·44 (1·97)	10·58 (1·93)	11·09 (1·86)	*	***	***	NS
Delayed	14·33 (2·01)	13·31 (1·98)	8·94 (1·76)	10·38 (1·66)	NS	***	***	*
Percentage retained	90·67 (8·46)	92·22 (6·84)	84·96 (10·59)	93·89 (6·83)	NS	*	NS	**
Rey–Osterreith Recall	23·38 (3·44)	24·11 (2·80)	24·92 (3·38)	23·28 (2·91)	NS	NS	NS	NS
Verbal fluency	44·50 (4·58)	43·67 (3·85)	38·00 (3·98)	38·56 (2·83)	NS	***	***	NS
Reversed digit span	5·85 (1·04)	5·56 (1·09)	5·50 (0·99)	5·44 (0·96)	NS	NS	NS	NS

Probability levels: $*P < 0{\cdot}05$; $**P < 0{\cdot}01$; *** $P < 0{\cdot}005$.

Table 3. *Correlations of cognitive test scores with recency of MDMA use and lifetime consumption in*: (a) *combined MDMA users* (*novice, regular and abstaining*); (b) *current* (*novice and regular*) *groups*

		Days since last MDMA use (Pearson's *r*)	Lifetime consumption (Spearman's rho)
Prose recall (immediate)	Combined group ($N = 60$)	0·06	−0·48***
	Current users ($N = 44$)	0·39**	−0·64***
Prose recall (delayed)	Combined group ($N = 60$)	0·12	−0·51***
	Current users ($N = 44$)	0·43**	−0·70***
… with immediate recall partialled out	Combined group ($N = 60$)	0·16	−0·23†
	Current users ($N = 44$)	0·17	−0·37†**
Rey–Osterreith (delayed)	Combined group ($N = 60$)	−0·25*	0·02
	Current users ($N = 44$)	−0·04	0·14
Reversed digit span	Combined group ($N = 60$)	−0·09	0·03
	Current users ($N = 44$)	−0·01	0·01
Verbal fluency	Combined group ($N = 60$)	−0·10	−0·48***
	Current users ($N = 44$)	0·06	−0·57***
Quick Test	Combined group ($N = 60$)	−0·17	0·04
	Current users ($N = 44$)	−0·07	0·11

One-tailed tests: * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.
† Pearson's *r*.

For delayed recall, there was again a main effect of Group ($F_{3,76} = 39{\cdot}5$, $P < 0{\cdot}001$); again, non-users outperformed regular users ($t_{76} = 9{\cdot}7$, $P < 0{\cdot}001$) and abstaining users ($t_{76} = 6{\cdot}3$, $P < 0{\cdot}001$), though they did not differ from novice users ($t_{76} = 1{\cdot}7$, $P < 0{\cdot}10$). Abstaining users showed better recall than regular users ($t_{76} = 2{\cdot}4$, $P < 0{\cdot}02$). Unsurprisingly, delayed recall was highly correlated with immediate recall ($r = 0{\cdot}92$, $P < 0{\cdot}001$); however, even with immediate recall entered as a covariate there was a significant effect of Group ($F_{3,75} = 3{\cdot}9$, $P = 0{\cdot}01$). This reflected a significant superiority of non-users compared with regular users ($t_{75} = 2{\cdot}3$, $P < 0{\cdot}02$) but not with either novice users ($t_{75} < 1$, NS, in both cases).

As shown in Table 3, lifetime consumption of MDMA correlated strongly with both immedi-

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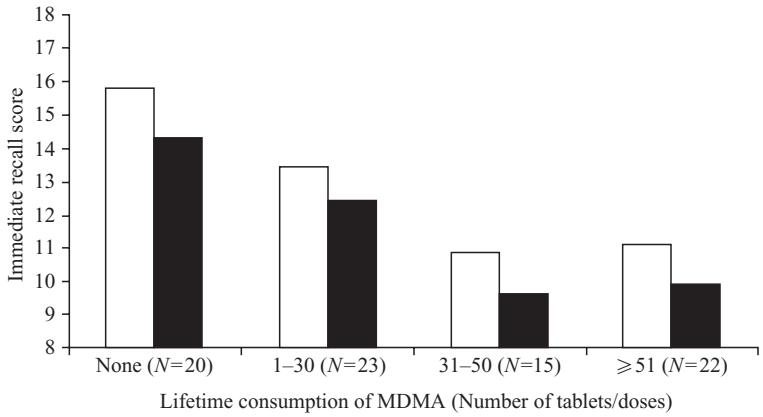

FIG. 1. Immediate (□) and delayed (■) verbal recall scores for participants with differing levels of lifetime consumption of MDMA.

ate and delayed recall, heavier use predicting poorer scores. This relationship was slightly stronger when currently abstinent participants were excluded but nevertheless remained highly significant. Fig. 1 shows the mean immediate and delayed recall scores for participants separated into four levels of lifetime MDMA consumption. ANOVA confirmed a significant main effect of consumption level for immediate recall ($F_{3,76} = 24{\cdot}1$, $P < 0{\cdot}001$). *Post hoc* contrasts comparing each level of use with the preceding level revealed significant decrements from 'no use' to '1–30 doses' ($t_{76} = 3{\cdot}7$, $P < 0{\cdot}001$), and from '1–30' to '31–50 doses' ($t_{76} = 3{\cdot}7$, $P < 0{\cdot}001$), but no difference between '31–50' and '$\geqslant 51$' doses ($t_{76} < 1{\cdot}0$, NS). Although a similar main effect of Group was seen for delayed recall ($F_{3,76} = 21{\cdot}3$, $P < 0{\cdot}001$), this no longer reached significance once immediate recall was covaried out.

Number of days since last use showed a complex relationship with recall. Specifically, in the current (i.e. novice and regular) users, there was a significant positive correlation with both immediate and delayed recall (though the latter was not significant when immediate recall was partialled out; $r = 0{\cdot}16$, NS). By contrast, when currently abstaining users were also included the correlations with days since last use fell well short of significance. This suggests a curvilinear relationship, and the immediate recall data were therefore examined visually (Fig. 2).

With all participants included, neither quadratic nor cubic functions described the data well (F_{56} and $F_{57} < 1{\cdot}2$, NS). However, when three outliers who had abstained for more than 60 days were excluded from the analysis, both cubic and quadratic functions provided good models ($F_{53} = 6{\cdot}4$, $P < 0{\cdot}001$ and $F_{54} = 8{\cdot}0$, $P < 0{\cdot}001$, respectively). Thus, in the present sample, while increasing duration of abstinence was associated with higher recall scores up to about 15 days, participants who had abstained for longer than this scored less well. Further scrutiny of the raw data suggested that this reflected an interaction between prior history of MDMA use and time since last use: thus, the longest abstinence periods were (by definition) reported by the currently abstaining users, who also reported relatively high levels of prior MDMA use (median $\geqslant 51$ doses). Within the current users (novice and regular) there was no relationship between lifetime consumption and time since last use (novice and regular; $r = -0{\cdot}1$, NS).

Stepwise regression was therefore conducted in the combined users (i.e. regular, novice and currently abstinent) to determine whether time since last use and lifetime use of MDMA made separate contributions to the variance in immediate recall. Cannabis use and IQ were included as additional predictors. Lifetime use emerged as the strongest predictor, yielding an adjusted R^2 of 0·34 ($F_{1,58} = 30{\cdot}8$, $P < 0{\cdot}001$), with days since last MDMA use emerging as a second significant predictor which increased the adjusted R^2 to 0·39 ($F_{2,57} = 20{\cdot}1$, $P < 0{\cdot}001$). No additional contribution was made by either

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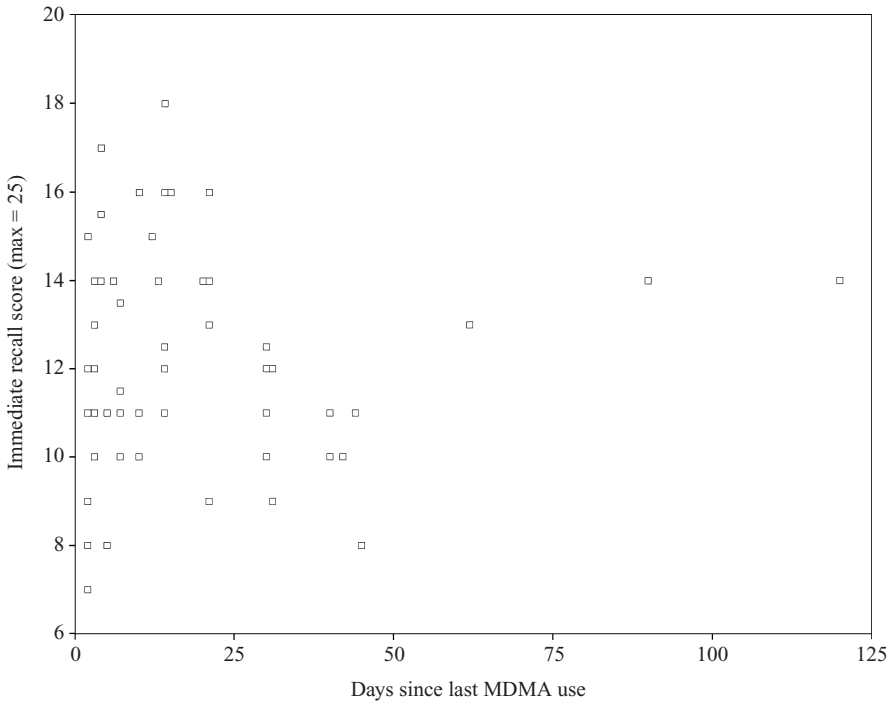

FIG. 2. Scatterplot showing relationship between days since last MDMA use and immediate verbal recall scores.

frequency of cannabis use in last 30 days or IQ. The same pattern emerged for delayed recall: lifetime consumption was again the strongest predictor, yielding an adjusted R^2 of 0·36 ($F_{1,58} = 34{\cdot}6$, $P < 0{\cdot}001$), which increased to 0·46 ($F_{2,57} = 26{\cdot}7$, $P < 0{\cdot}001$) when days since last use was entered. Again, neither cannabis use nor IQ made any additional significant contribution.

Visuospatial memory

Cannabis use over the last 30 days showed no relationship to recall scores on the Rey–Osterreith, either within the whole sample ($N = 80$, $r = -0{\cdot}15$, NS) or within the three drug-using groups ($N = 60$, $r = -0{\cdot}23$, NS). It was consequently not controlled for within group comparisons.

All 80 participants scored the maximum 36 points for the 'copy' phase. For delayed recall, there was no main effect of Group ($F_{3,76} = 1{\cdot}3$, NS) and neither did any of the *a priori* contrasts between pairs of groups reach significance ($t < 1$, NS, in each case). There were no correlations with either recency of MDMA use or lifetime consumption.

Working memory

Again, cannabis use over the last 30 days showed no relationship to scores on reversed digit span, either within the whole sample ($N = 80$, $r = -0{\cdot}15$, NS) or within the three drug-using groups ($N = 60$, $r = -0{\cdot}13$, NS).

There was no main effect of Group ($F_{3,76} < 1$, NS) or any significant pairwise contrasts between groups ($t_{75} < 1$, NS, for each *a priori* contrast); neither did recency of MDMA use or lifetime consumption correlate with performance on this task.

Verbal fluency

Scores on this test were, like all the other cognitive measures, uncorrelated with cannabis use over the last 30 days both within the whole sample ($N = 80$, $r = -0{\cdot}17$, NS) and within the three drug-using groups ($N = 60$, $r = -0{\cdot}07$, NS).

An overall main effect of Group ($F_{3,76} = 15{\cdot}2$, $P < 0{\cdot}001$) reflected the fact that non-users performed significantly better than both regular users and currently abstaining users ($t_{76} = 5{\cdot}6$,

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$P < 0{\cdot}001$, and $t_{76} = 4{\cdot}5$, $P < 0{\cdot}001$, respectively) but did not differ from novice users ($t_{76} < 1$, NS). Regular and currently abstaining users did not differ from each other ($t_{76} < 1$, NS).

In the combined MDMA user (novice, regular, abstaining) groups, there was a strong correlation with lifetime consumption of MDMA but not with recency of use. This pattern was replicated when currently abstaining users were excluded. ANOVA comparing participants with four levels of lifetime consumption showed a main effect of consumption level ($F_{3,76} = 12{\cdot}0$, $P < 0{\cdot}001$); *post hoc* contrasts between consecutive dose levels indicated that while the drop in scores from 'no use' to '1–30 doses' was just short of significance ($t_{76} = 1{\cdot}54$, $P = 0{\cdot}13$), the scores of participants who had taken 31–50 doses were significantly lower than those of participants who had used 1–30 times ($t_{76} = 3{\cdot}1$, $P < 0{\cdot}005$). There was no significant difference in scores between '31–50 doses' and '$\geqslant 51$ doses' ($t_{76} < 1{\cdot}0$, NS).

DISCUSSION

This study confirms previous findings (Krystal *et al.* 1992; Curran & Travill, 1997; Parrott & Lasky, 1998; Parrott *et al.* 1998; Bolla *et al.* 1998; Morgan, 1999) that regular MDMA users show significantly poorer immediate verbal recall than non-users equivalent in age, gender, educational level, IQ and use of most other psychoactive drugs in the last month. The same pattern was seen for delayed recall of the same material, even when immediate recall was partialled out.

Novice and currently abstinent users likewise showed significantly poorer immediate recall than non-users; interestingly, the novice users showed a milder impairment than regular users while those who were currently abstinent performed at a similar level to regular users. With immediate recall taken into account, there was no evidence that novice or currently abstinent users showed any additional impairment of delayed recall relative to non-users. These data thus suggest a cumulative impact of MDMA consumption on immediate recall of verbal information, and indeed, within the combined drug-using groups (novice, regular and currently abstinent) lifetime consumption was found to be strongly inversely correlated with both immediate and delayed recall scores ($r = -0{\cdot}48$ and $-0{\cdot}51$ respectively). The observed relationship with delayed recall was partly but not entirely secondary to that with immediate recall: with the latter partialled out, the negative correlation between lifetime consumption and delayed recall remained significant both in the combined users group ($r = -0{\cdot}23$, $P < 0{\cdot}05$) and in the current (novice and regular) users ($r = -0{\cdot}37$, $P < 0{\cdot}02$).

There was in addition evidence of some recovery of function over the first 15 days or so after taking MDMA. Thus there was a strong positive correlation ($r = 0{\cdot}47$) between duration since last dose and immediate recall scores in the current (novice and regular) MDMA users. This relationship became curvilinear when the currently abstaining users were included in the analysis: these participants, who had been abstinent for longer than those in the other two groups, tended to score less well. Closer examination suggested that this apparent decline in performance might be attributable to this group having a relatively high level of past MDMA consumption. Thus, the impairments observed in the sample as a whole might reflect a combination of protracted acute effects of MDMA use which remit over several weeks and more persistent (possibly permanent) effects resulting from cumulative use. This possibility is consistent with other data showing, for example, that levels of tryptophan hydroxylase (an enzyme which limits the rate of synthesis of serotonin) may be depleted for 3 weeks or even more following an acute dose of MDMA: Curran (2000) provides a valuable overview of this and other pharmacological mechanisms through which MDMA might produce both acute and long-term neurotoxic effects and notes the difficulty of separating out these influences on cognitive and psychological processes in recreational users who have taken MDMA within the last few weeks. Within the present dataset, a stepwise regression on the data from all 60 MDMA users (novice, regular and abstinent) confirmed that recency of MDMA use and total lifetime consumption were indeed significant independent predictors of immediate recall performance. Specifically, lifetime consumption accounted for 34% of the variance and time since last use accounted for an additional 5%. Neither cannabis use in the preceding month nor IQ emerged as significant predictors in this

analysis. Using the same predictors, an almost identical pattern was found for delayed recall; when immediate recall was included, however, it accounted on its own for over 80% of the variance and neither aspect of MDMA use accounted for a significant further proportion.

By contrast with the findings for verbal memory, none of the MDMA groups differed from the non-users on the Rey–Osterrieth test of visuospatial memory. It is unlikely that this lack of effect reflects relatively greater or lesser difficulty of this task than the verbal recall task, since none of the groups scored close to either floor or ceiling, and both tasks show normally distributed scores, with reasonably wide standard deviations, in standardization populations. Furthermore, the mean scores of the groups tested on the visuospatial test are well within the average range reported by Osterreith (1944). The observed pattern is, however, consistent with Parrott *et al.*'s (1998) suggestion that MDMA use may be associated with a preference for visual over verbal processing, and that this persists after the acute effects of MDMA have ceased. Interestingly, however, another recent study (Bolla *et al.* 1998) has found that within a group of abstinent users, those that had used more heavily showed greater impairment in delayed visual memory. Likewise, a small study comparing 10 non-users with 10 current and 10 former users found that some of the heaviest users showed very poor Rey–Osterreith performance (Turner *et al.* 1999) though the group effect failed to achieve significance. Within the present data there was a similar trend towards an association with lifetime consumption within the group of 16 abstainers ($r = -0{\cdot}40$, one-tailed $P = 0{\cdot}07$). This may suggest an organic basis to the observed impairments, with visual memory perhaps being more resistant to disruption by lighter drug use. Intriguingly, in the combined user groups (novice, regular and currently abstinent) there was a weak negative correlation ($-0{\cdot}25$, $P < 0{\cdot}05$) between duration of abstinence and visual recall; although this finding might be spurious, it could also be construed as indicating a transient MDMA-induced enhancement of visual processing.

Verbal fluency was included as a test of executive function, performance on which has been associated with bilateral activation of temporal and frontal cortex (e.g. Parks *et al.* 1988). Relative to non-users, regular and abstaining MDMA users, though not novice users, showed impairment. As with the measures of verbal memory, there was a strong correlation, within the drug-using groups, with lifetime consumption; in this case, however, there was no association with recency of MDMA use.

The differences between groups in verbal memory and verbal fluency cannot readily be attributed to differences in verbal language skills, since the groups were all comparable with one another in educational achievement and also on a measure of Verbal IQ (the Quick Test). Likewise, it seems unlikely that they reflect generalized impairments of attention or concentration, since the groups did not differ on the reversed digit span task, an index of working memory which is sensitive to these factors. While this test has not been used in previous studies with MDMA users, Curran & Travill (1997) found an acute effect of MDMA use on another test of working memory (Serial Sevens). All of the participants in the present study reported that they had not used MDMA within the 24 h prior to testing. It therefore seems likely that while MDMA may produce acute generalized cognitive effects, via disruption of attentional processes or working memory, these may be superimposed on a pattern of more specific impairments that may reflect localized structural damage or functional disruption outlasting the period of acute intoxication. Consistent with this, it is notable that the abstainers had not used MDMA for an average of 46 days yet they continued to show impairments of verbal recall and verbal fluency. The present data thus support Krystal *et al.*'s (1992) observation of impairments > 2 months after MDMA use.

Although MDMA users reported markedly more cannabis use in the previous month than did the non-users (all of whom reported zero consumption), frequency of cannabis use was unrelated to performance on any of the cognitive tests; this was the case whether the correlations were based on all 80 participants or just on the 60 participants in the MDMA-using groups. The observed between-groups differences in verbal memory and verbal fluency cannot therefore be attributed to differential cannabis use, a pattern which corroborates Morgan's (1999) findings in a comparison of polydrug users who

did and who did not include MDMA in their drug use. Thus, these two studies both point to a specific association of cognitive impairments with use of MDMA rather than with the use of illicit drugs more generally. While an ideal design would compare MDMA-using and non-MDMA-using groups equivalent in level of cannabis use, the fact that none of the non-MDMA users recruited here reported any use of cannabis may well reflect the reality that in a contemporary student population, where MDMA is widely used, dissociation of cannabis and MDMA use is atypical.

We cannot exclude the possibility that lifetime use of other drugs (not assessed within the present study) may have differed between groups and have contributed to the impairments observed here, although we consider it unlikely that many of the undergraduates constituting the bulk of the participants had extensive drug-using histories; indeed, very few reported any use, in the last month, of cocaine or amphetamine. This contrasts with a number of other recent studies of recreational MDMA use where substantial numbers of the participants have reported concurrent use of other psychomotor stimulants (e.g. Parrott & Lasky, 1998; Curran, 2000). Since users of these substances have recently been shown to be impaired on various aspects of decision-making (Rogers *et al*. 1999), arguably reflecting altered serotonergic and dopaminergic neuromodulation of prefrontal cortex, it is clearly important to control for other psychostimulant drug use in evaluating the impact of MDMA. Comparison of polydrug users who have used MDMA with polydrug users who have not would be one effective methodology for isolating the effects of MDMA, but in practice it is difficult to achieve this separation. Future research should therefore at least gather information about prior history of drug use of the participants and control for it statistically in the same way as was done here for recent drug use.

One obvious obstacle to interpretation of the present data is the lack of objective corroboration of self-reported drug use. This is a virtually insurmountable problem in this type of naturalistic study, where drug-testing procedures (e.g. assaying urine or blood) would be intrusive on the one hand and inconclusive concerning anything but very recent drug ingestion on the other. It is certainly possible that participants under-reported use of 'hard' drugs such as heroin or cocaine, though it is worth noting in this regard that there is, in any case, remarkably little convincing evidence that these drugs produce significant cognitive impairment. For example, Selby & Azrin (1998) found that cocaine users did not differ from well-matched controls on any of 15 tests tapping reasoning, memory, executive functions, attention, or psychomotor speed; by contrast, participants with a history of heavy alcohol use showed pronounced impairments.

Within the present study no measure was taken of participants' mood state; thus, we cannot directly exclude the possibility that observed impairments were to some degree secondary to dysphoric mood. Low mood is commonly reported during at least the first few days after MDMA use (e.g. Curran & Travill, 1997); however, Parrott & Lasky (1998) found in their prospective study of recreational users that mood had returned to normal by 7 days. This suggests that the impairments of verbal memory that were seen here in participants who had abstained for $\geqslant 30$ days are unlikely to be associated with low mood. However, even if this association did exist, the literature on depression and cognitive function suggests at most a very weak relationship (see meta-analysis by Burt *et al*. 1995) while many studies have found no correlation at all between clinical indices of mood and tests of visual and verbal memory including those used here (e.g. Hinkin *et al*. 1992).

The convergent evidence from this and other studies of enduring adverse effects of MDMA on cognitive functioning is extremely worrying when such large numbers of young people are taking the drug. In the present study, with a university educated sample who under normal circumstances would be expected to have a relatively restricted range of variation in intellectual abilities, between a quarter and a half of the variance in verbal recall and verbal fluency could be predicted by a very crude index of lifetime consumption. This is a startlingly high proportion, and the correlations were only marginally weaker when they excluded participants who had used regularly but were now abstaining. Although there was some indication of a slight improvement in performance on

verbal recall and verbal fluency with increasing duration of abstinence, it is not clear whether this reflects a reduction in transient intoxication effects or a more gradual recovery of underlying dysfunction. Since none of the abstainers had been free of MDMA for > 4 months – indeed the majority had abstained for only 2 months – the present study cannot clarify whether long-term abstinence is associated with an eventual reversal of the cognitive impairments that are evident in the short- to medium-term. A more benign possibility, which cannot adequately be resolved by the cross-sectional studies reported to date, is that the impairments shown by MDMA users in fact predate their drug use rather than being a consequence of it. These questions can only be addressed by prospective studies, with long follow-up periods; indeed, such studies are now essential if we are to understand and reduce the potentially devastating neurochemical and cognitive consequences of MDMA use.

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