Psychopharmacology

10.1007/s00213-003-1561-4

Original Investigation

Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users

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Received: 6 September 2002 **Accepted:** 4 June 2003 **Published online:** 30 August 2003

Abstract

Rationale Establishing whether cognitive changes follow long-term use of MDMA ("ecstasy") in humans has been difficult because of possible confounds with other drug use, particularly cannabis. Convincing evidence may be only obtained using experimental designs that account for such confounds.

Objective In the present study, cognitive/behavioural measures were used to investigate whether long-term MDMA use or long-term cannabis use is responsible for the changes sometimes observed in recreational MDMA users.

Method Tests of attention and memory were administered to subjects who used both MDMA and cannabis, cannabis only, or neither drug.

Results The main finding was that cannabis users, whether or not they also used MDMA, showed significantly impaired memory function on word free-recall and on immediate and delayed story recall compared to non-users.

Conclusions The findings highlight the importance of controlling for other drug use (particularly cannabis) when investigating persistent effects of MDMA in humans.

Keywords Cannabis - MDMA - Human users - Memory and attention effects

Introduction

MDMA ("ecstasy") is a recreational drug that has become widely used throughout the past decade in both Europe and the USA (see Parrott *2001* for review). The drug has complex neuropharmacological effects through stimulating acute release of serotonin, dopamine,

noradrenaline, acetylcholine and histamine (McDowell and Kleber *1994*; Liechti and Vollenweider *2001*), and has been shown to be neurotoxic at high or repeated doses to serotonin systems within the brain of primate and other animal species (Fischer et al. *1995*; Ricaurte et al. *2000*). Brain imaging techniques have recently been used to identify long-term changes in the brain of human recreational MDMA users (McCann et al. *1998*; Semple et al. *1999*) with some evidence of similar serotonergic system dysfunction Such findings raise an important question. Are the observed structural and metabolic changes reflected in cognitive/behavioural changes in human recreational users of MDMA and, if so, is the overall level of usage important? The majority of animal neurotoxicity studies have used high and repeated dosing to produce altered physiological and behavioural change, but a few studies have found changes after low doses which, after applying inter-species scaling formulae, approach those typically self-administered in humans (Ricaurte et al. *2000*; McCann and Ricaurte *2001*). It is important, therefore, to include level of drug usage as a factor in research into the cognitive consequences of recreational MDMA use. Studies on the possible persistent cognitive/behavioural consequences of recreational use in humans are increasing, but have been hampered by the impossibility of using double-blind, placebo-controlled, repeated dose regimens (on ethical grounds) and by the methodological difficulties of finding suitable control populations with which to compare MDMA users. The fact that MDMA users are usually polydrug users with a long history of cannabis, LSD, cocaine and other amphetamine use (Fox et al. *2001*) has led some researchers to abandon the traditional no-drug control group, resorting instead to correlational and other measures for assessing the link between level of prior MDMA use and degree of cognitive/psychiatric symptomatology (Davison and Parrott *1997*; Dafters et al. *1999*). Others have attempted to compare MDMA users with non-MDMA users matched in terms of other drug use (Morgan *1999*; Rogers *2000*). Cannabis use is a particularly important confound, since the majority of MDMA users are heavy users of cannabis, which could have effects on a range of cognitive functions that may be wrongly attributed to MDMA use (Croft et al. *2001*;Solowij et al. *2002*). Even where MDMA users and non-users matched for cannabis use have been compared, conflicting results have been reported. One study which compared subjects who used both MDMA and cannabis, subjects who used cannabis but not MDMA, and subjects who used neither drug on a battery of cognitive tasks, found significant deficits in performance on memory, word fluency and speed of processing in the combined drug-taking groups relative to the no drug controls, but no differences between the cannabis users who did or did not use MDMA (Croft et al. *2001*). In contrast, Gouzoulis-Mayfrank et al. (*2000*), using a similar group design, found no differences between the cannabis users and no-drug controls on any task, but significant differences between the users of both MDMA and cannabis and those who used only cannabis on several tests of cognitive function and memory, with the MDMA users showing deficits. It is also possible that there are cognitive deficits associated with use of both drugs, but which differ in a qualitative way. Thus, it is possible that MDMA use is associated primarily with deficits in attention and/or task shifting, as might be predicted from reports of increased impulsivity (Morgan *1998*, *2000*), while cannabis use may be more strongly associated with learning and memory deficits. Alternatively, both drugs may contribute to the same general deficit, such as memory, but in qualitatively different ways. This idea is given some support by a recent web-based study that used on-line drug-use and memory function questionnaires and regression analysis to factor out the contribution of cannabis. Although, the technique used allows for the possibility of multiple submission by individuals or frivolous/fraudulent entries the data is indicative of independent memory impairment associated with use of cannabis and MDMA, with cannabis use being associated more commonly with reports of "here and now", prospective memory lapses, while MDMA use was more commonly associated with long-term memory problems (Rodgers et al. *2001*).

The experiment reported here attempts to discover whether there are long-term

psychological and/or cognitive changes associated with MDMA or cannabis use. Given the difficulty of finding MDMA users who do not use other illicit substances, particularly cannabis, our study used subjects who were long-term cannabis users but who differed in terms of their use of MDMA. Thus, we compared regular cannabis users who were non-users, regular cannabis users who were light or heavy users of MDMA, and subjects who had used neither drug. Comparison of MDMA users with non-users who are matched for cannabis use should reveal MDMA-specific deficits, whilst comparison of cannabis-using subjects, whether or not they also use MDMA, with subjects who use neither drug should reveal cannabis-related deficits. Performance on a battery of health/personality measures, attention/task-shifting problems and memory problems was measured.

Materials and methods

Subjects

Subjects were university students or their friends contacted using the "snowball effect" (Callow *1996*). Subjects were recruited on the basis of initial telephone interview followed by use of a detailed, instructed, drug history questionnaire given on the first of two experimental sessions. Subjects recorded their prior use of level of drug use in the previous week, month, year and lifetime. These figures were used to assign subjects to four groups. Subjects in the Cann+E (heavy) group were regular cannabis users who had a cumulative lifetime use of at least 50 MDMA tablets, subjects in the Cann+E (light) group were regular cannabis users with a lifetime use of less than 50 MDMA tablets, subjects in group Cann-only were regular cannabis users with no experience of MDMA and subjects in the No-drug control group had used neither drug previously. All subjects stated that they had abstained from MDMA use for at least 7 days and from cannabis for 48 h prior to testing as requested during recruitment. The study was approved by the local ethics committee and performed in accordance with the standards laid down in the 1964 Declaration of Helsinki. The subjects gave written informed consent prior to participation. Table 1 shows subject demographics.

Table 1. Subject characteristics and drug usage. Drug histories are reported as total lifetime consumption (+SD) of alcohol (standard units), MDMA (tablets), cannabis (joints), cocaine (g), amphetamine (tablets), heroin ("fixes"), and LSD (tablets)

	No-drug control		Cannabis		Cann+E (light)		Cann+E (heavy)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	21.16	(4.19)	21.87	(2.87)	22.89	(2.66)	24	(3.33)
IQ (NART)	117.77	(3.77)	116.88	(2.78)	117.8	(3.00)	118.7	(3.09)
n	19	(9 male)	15	(8 male)	19	(10 male)	16	(7 male)
Alcohol	795.3	(1054.5)	826.2	(495.7)	1147.4	(559.3)	1404.6	(611.4)
Cannabis	0	(0)	1023.1	(670.7)	1252.9	(1078.1)	1680.7	(838.2)
MDMA	0	(0)	0	(0)	20.21	(10.5)	363.8	(532.7)
Amphetamine	1.2	(4.6)	1.7	(3.3)	16.8	(14.2)	65.1	(87.1)
Cocaine	0.05	(0.23)	2.2	(3.9)	13.0	(19.5)	180.9	(443.7)
Heroin	0	(0)	0	(0)	3.6	(13.8)	7	(17.3)
LSD	0.3	(1.2)	3.3	(7.9)	4.8	(7.0)	128.9	(369.1)

There was no significant difference between the cannabis groups in lifetime use of cannabis [$F(2,47)=2.17$, $P=0.125$] or recent frequency of use (joints in past month) [$F(1,47)=2.41$, $P=0.10$], but the groups did differ in terms of the duration of cannabis use [$F(2,47)=5.65$, $P=0.006$]. Mean durations (years) were 9.4, 8.2 and 6.0 for the Cann+E (heavy), Cann+E (light) and Cann-only groups, respectively. A Tukey's HSD test showed that group Cann+E (heavy) had used the drug for significantly longer than the Cann-only group but not longer than the Cann+E (light) group. With regard to MDMA use, heavy users of MDMA had used the drug for longer (mean 6.9 years) than light users (mean 4.2 years). This difference was also significant ($t=3.198$), $P=0.003$). Heavy MDMA users had used more MDMA in the past month than light users ($t=2.62$, $P<0.05$) and took more tablets at a single session on average (2.28 tablets and 1.47 tablets, respectively), although this difference just failed to reach significance ($t=1.91$, $P=0.063$). Overall, as Table 1 shows, MDMA users had used more of all other drugs (alcohol, amphetamines, cocaine and LSD) than non-users, and the lifetime use of these drugs were therefore included as covariates in the group analyses.

Cognitive and psychological tests

The following tests were used: National Adult Reading Test—NART (Nelson and O'Connel *1978*), which involves reading aloud 50 words of decreasing frequency in the English language. The correct pronunciation of these words is held to have been acquired in the past, since they cannot be derived using standard rules of pronunciation. Thus, the score provides a measure of premorbid intelligence; General health Questionnaire—GHQ (Goldberg *1978*); Beck's Anxiety Inventory—BDI (Beck et al. *1988*); and the EPQR—short version of the Eysenck questionnaire to assess Extraversion, Neuroticism, Psychoticism and L, a measure of stability, along with the Impulsivity, Venturesomeness and Empathy questionnaire—IVE (Eysenck and Eysenck *1991a*, *1991b*). This last test was used because of previous reports of enhanced impulsivity in MDMA users (Morgan *1998*, *2000*).

Memory tests

The following tests were used: forward digit span test in which subjects attempt to repeat letter strings they have heard (5–9 letters). Correct sequences are counted; free recall test—subject listens to 30 words of equal frequency in the English language then writes down as many as he/she can remember in any order; Rivermead behavioural memory test (Immediate), in which subjects listened to a brief taped news story and then reported immediately as much of the story as they could recall onto audio tape, subsequently analysed for the number of key components correctly recalled; and Rivermead behavioural memory test (Delayed). Recall of the same story but after a 30-min delay, filled with other tasks.

Attention/executive function tests

The following tests were used: rule shift cards test—part of the Behavioural Assessment of the Dysexecutive Syndrome—BADS (Nelson *1976*), a derivative of the Wisconsin Card Sorting Task involving a sudden change to a new sorting rule, which is designed to examine frontal lobe function; visual elevator task—subtest 4 of the Test of Everyday Attention—TEA (Robertson et al. *1994*), a test of attentional switching and cognitive flexibility in which subjects have to mentally count up and down as they follow the movements of an elevator which changes direction frequently through a series of visually presented "floors". Subjects are given a raw score out of ten, and a scaled score; matching consonant lists—subjects were presented simultaneously with two strings of consonants and had to indicate as quickly as possible whether the strings wre identical

or not. Eight trials were given; and matching familiar figures test (Cairns and Cammock *1978*)—on each of 20 trials, subjects view a sample geometric shape and attempt to identify a matching choice figure from a displayed selection as quickly as possible. This task involves a trade-off between speed and accuracy in a sustained attention problem, and increasing errors have been attributed to increased impulsivity in drug users (Morgan *1998*, *2000*)

The NART test, the drug-use questionnaire and health and personality tests were administered in the first of two experimental sessions. The remaining battery of attention and memory tests was administered in a second session 1 week later.

Results

Table 2 shows the results of a series of one-way ANOVAs for each dependent variable with group assignment as the single between-subject factor and with alcohol, amphetamine, cocaine and LSD use as covariates. Significant *P*-values are marked with an asterisk, the means were graphed (see Fig. 1) and were examined further in two ways. First, post-hoc tests (Tukey HSD) were used to test whether either of the MDMA-using groups differed from the cannabis-only group, from each other or from the No-drug control group, and second, the three cannabis-using groups were combined together for comparison with the No-drug control group in separate *t*-tests. In this way we hoped to distinguish effects due to MDMA use from those due to cannabis use.

Table 2. Overall group difference tested using one-way ANOVAs with lifetime consumption of alcohol, amphetamine, cocaine and LSD as covariates

Test	**Mancova**	
Health and personality	***F* (*df* 3,61)**	***P***
NART-based IQ	0.844	0.470
General Health Questionnaire, GHQ	0.773	0.510
Beck's Anxiety Index, BAI	1.02	0.390
EPQ-short (Psychoticism)	6.28	0.00087*
EPQ-short (Extroversion)	1.17	0.330
EPQ-short (Neuroticism)	1.1	0.350
EPQ-short (Lie scale)	2.33	0.080
IVE (Impulsivity)	0.511	0.67
IVE (Venturesomeness)	1.03	0.380
IVE (Empathy)	0.33	0.800
Memory		
Digit span	0.96	0.420
Free recall	8.7	0.00007*
Story recall (Immediate)	3.26	0.027*
Story recall (delayed)	4.5	0.006*
Attention and task-switching		
Matching consonant strings (time)	0.31	0.820

Test	Mancova	
Health and personality	***F* (*df* 3,61)**	***P***
Matching consonant strings (errors)	0.155	0.925
Matching familiar figures (time)	1.24	0.300
Matching familiar figures (errors)	0.55	0.650
Visual elevator scaled score	3.72	0.016
Visual elevator scaled time	1.75	0.166
Rule shift score	1.03	0.380

*Significant difference at $P<0.05$

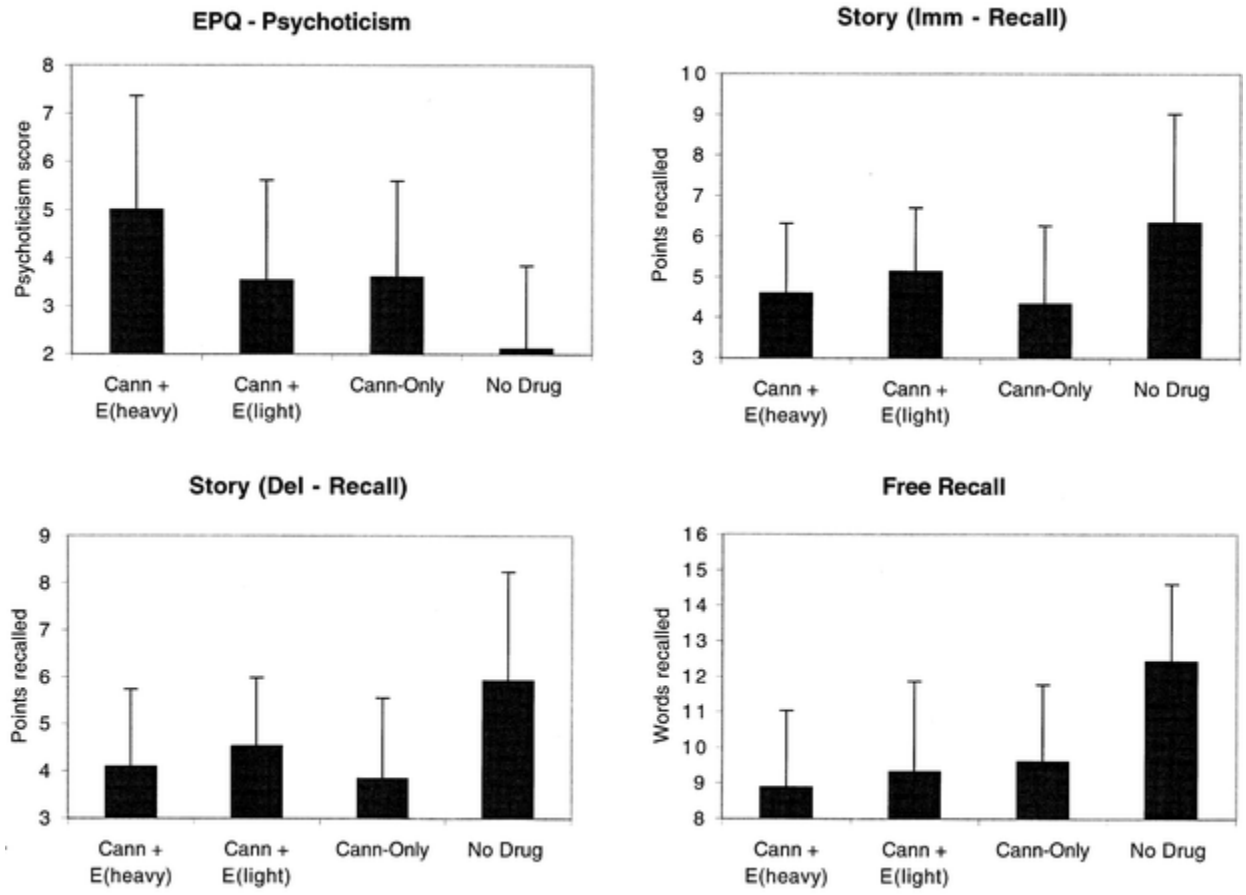

Fig. 1. Group means (+SD) for the four variables which showed a significant group effect

ANOVA revealed significant overall group differences in one personality measure and in three memory tasks; the EPQ(short)-psychoticism scale, immediate passage recall, delayed passage recall, and free recall. In each case, post-hoc Tukey tests showed that the individual MDMA-using groups did not differ from each other, from the the Cannabis-only group or from the No-drug control group ($P<0.05$ in each case). However, the combined drug-using groups differed significantly from the No-drug controls (independent *t*-tests, $P<0.005$ in each case) showing an increased level of psychoticism and impaired performance on the three tests of episodic memory. In the visual elevator task (VEAS), neither post-hoc tests nor the combined group comparison found any significant differences.

Discussion

Our results show that the significant differences occurred predominantly between the combined drug group and the No-drug control. This was true of three memory tests—the free recall task and both the immediate and delayed version of the story recall task, and also the EPQ-psychoticism score. In no task was there a difference between subjects who used both MDMA and cannabis and those who used cannabis only. The results therefore provide very little support for an effect of recreational MDMA use on cognitive or memory function. Our results are thus in agreement with those of previous studies which have reported cognitive deficits in users of cannabis alone or cannabis and MDMA (Wareing et al. *2000*; Croft et al. *2001*; Solowij et al. *2002*) and with those reporting no MDMA-related cognitive deficits when other drug use is controlled for (Dafters et al. *1999*; Croft et al. *2001*). It is also likely that failure to find evidence of MDMA's detrimental effects on cognition is under-reported, due to the reluctance of scientific journals to publish non-significant findings.

Our finding that cannabis users appear to have impairments on memory tasks is in agreement with recent published findings. For example, Block and Ghoneim (*1993*) have reported that relative to a matched group of non-drug-using controls, heavy cannabis users had significant impairments in memory retrieval along with deficits in verbal expression and mathematical reasoning. Similarly, a large prospective study using younger and older populations of Costa Rican cannabis users and matched controls found that prolonged use of cannabis is associated with deficits in free recall and list-learning tasks (Fletcher et al. *1996*). In addition, although our results provided no evidence for an effect of cannabis use on attentional tasks, there is evidence for subtle attentional changes associated with cannabis use when physiological measures are used. Thus, changes in event-related potentials, particularly those involving the positive potential at around 300 ms following a stimulus (P300), have been interpreted as indicating problems with stimulus selection and the filtering out of irrelevant information in cannabis users (Solowij et al. *1995*).

There are a number of important caveats and methodological problems which apply to all studies of long-term effects of recreational drug use in humans. The rational for the design of the present study is that if MDMA use is responsible for the deficits found in the combined drug group, then it would be expected that subjects who use both MDMA and cannabis should perform more poorly than those who use only cannabis. If cannabis is responsible, the two groups should not differ. Clearly, our data support the latter interpretation. However, other possibilities exist. It is possible that there are complex interactive effects resulting from use of both cannabis and MDMA that somehow mask MDMA's effects. In other words, cannabis use may attenuate effects that would be produced by MDMA alone. Such an effect is not implausible and it has been argued that it could operate via a cannabis-induced downregulation of dopamine release that might protect against ecstasy neurotoxicity (Croft et al. *2001*). While such an interaction is possible, it does not invalidate our main conclusion which is that people who use both MDMA and cannabis, which includes the vast majority of MDMA users, do not exhibit greater cognitive or memory deficits than those who use cannabis only. The complexities of polydrug use do not stop with cannabis. Studies show that as polydrug use widens it also intensifies, with the heaviest users of MDMA being also the heaviest users of cannabis, alcohol, tobacco and other stimulants (Milani et al. *2000*; Parrott et al. *2001*). This was clear from our own subject pool (see Table 1). While the difference was only significant in the case of amphetamine, MDMA users used more of all drugs listed than the Cannabis group.

Another methodological issue in human drug research concerns the optimum period of

abstention from drug use prior to testing. Should the abstention period be short, which clearly allows for possible residual effects, or long, which allows for the development of withdrawal effects? We decided to use a minimum abstention period of 7 days in the case of MDMA to avoid the documented mid-week rebound "depression" effect (Curran and Travill *1997*; Parrott and Laski *1998*) and a shorter 48-h period for cannabis use which avoided possible withdrawal effects and helped to maintain subject participation. It should also be pointed out that the effect of possible residual drug effects cannot be ruled out in the present study, since drug screens were not carried out on subjects prior to testing. Despite the methodological caveats discussed above, our results have demonstrated cognitive changes in regular users of MDMA and cannabis. Subjects who used cannabis, with or without MDMA, showed deficits on three memory tests but not on any of the attention or task-shifting tests. This finding suggests that some previous reports of MDMA-induced memory problems may have been due to the effects of cannabis use that were not controlled for.

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