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ORIGINAL INVESTIGATION

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The relative contributions of ecstasy and cannabis to cognitive impairment

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Abstract *Rationale:* (±)-3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'), a commonly used recreational drug, has typically been found to be related to poor cognitive function in humans. However, cannabis consumption may not have been adequately controlled for in these studies. *Objective:* The present study was designed to further elucidate the relation between MDMA and cannabis in cognitive impairment. *Methods:* Subjects who had used neither MDMA nor cannabis (controls; *n*=31), cannabis but not MDMA (cannabis users; *n*=18) and both MDMA and cannabis (MDMA/cannabis users; *n*=11) were compared on a battery of neuropsychological tests. *Results:* The cannabis and MDMA/cannabis groups did not differ on any of the tests, whereas the combined cannabis and MDMA/cannabis groups performed more poorly than controls on tests of memory, learning, word fluency, speed of processing and manual dexterity. Further, apart from speed of processing where higher MDMA consumption predicted slower processing, covariate analysis revealed that the deficits were more closely related to cannabis than MDMA usage. *Conclusion:* The results suggest that cannabis is an important confound in studies of MDMA-related cognitive impairment, and that previously reported cognitive impairment in MDMA users may have been caused by coincident cannabis use.

Keywords Cognitive impairment · Cannabis · Δ9-THC · Ecstasy · MDMA

Introduction

'Ecstasy', or (±)-3,4-methylenedioxymethamphetamine (MDMA), is currently one of the most popular recreational drugs in the western world. The drug causes a massive neurocellular release of serotonin (5-HT), likely due to an efflux of cytoplasmic 5-HT and concurrent 5-HT transporter facilitation (Huether et al. 1997), and it is this that is thought responsible for MDMA's psychotropic properties (Liechti et al. 2000). Exposure to the drug has been shown to impair 5-HT neurone integrity in rat (Commins et al. 1987; Mockler et al. 1987; O'Shea et al. 1998) and non-human primate (Ricaute et al. 1988; Scheffel et al. 1998; Hatzidimitriou et al. 1999), and 5-HT impairment has been demonstrated in human recreational users (McCann et al. 1994, 1998). This 5-HT impairment is extensive, with reductions in somatosensory cortex, caudate nucleus, putamen, hippocampus, hypothalamus and thalamus, and so concern has been raised regarding the cognitive consequences of MDMA use.

Corresponding to these studies, recreational MDMA users have been found to perform worse than controls on a number of cognitive tests related to memory and learning (Bolla et al. 1998; Parrott et al. 1998; Klugman et al. 1999; McCann et al. 1999; Morgan 1999; Wareing et al. 2000). However, there are a number of complexities that make generalisations regarding the effect of MDMA on cognition problematic. For example, other researchers have failed to find cognitive deficits (Morgan 1998; Dafters et al. 1999), and Bolla et al. (1998) found that the MDMA users with higher verbal intelligence exhibited dose-related memory enhancement. A further complexity is that there is ambiguity as to whether reported deficits have been related to MDMA *per se*, as studies have typically compared MDMA users who had used other drugs as well, with controls who were relatively drug free (or whose drug use details were not specified).

Cannabis use is a particular problem for MDMA research because it is common for MDMA users to consume cannabis to alleviate the negative experience that occurs when the MDMA-related euphoria is diminishing. Thus a large number of MDMA users have also used a substantial quantity of cannabis, making it difficult to recruit MDMA users who have not also used cannabis.

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Cannabis may confound MDMA studies in two ways. Firstly, the main psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol, has been shown to interact with the dopamine (DA) system (Bloom 1982; Malone and Taylor 1999; Tanda et al. 1999; Nava et al. 2000), and DA has been shown to largely determine MDMA-related 5-HT impairment in rat (Stone et al. 1988; Aguirre et al. 1998; Sprague et al. 1998). Thus cannabis may interact with MDMA in determining 5-HT deficit in recreational users. Secondly, rat hippocampus is impaired following chronic cannabis administration (Scallet 1991; Ameri et al. 1999), and as the hippocampus plays a significant role in the exclusion of extraneous stimuli (Miller and Branconnier 1983; Sun et al. 1999), cannabis may also impair cognitive function. Corresponding to this, learning and short-term memory deficits have been reported in chronic cannabis users (Schwartz et al. 1989; Fletcher et al. 1996).

Accounting for such confounds as polydrug use is particularly important given that animal studies have failed to show memory and learning impairments resulting from MDMA-related 5-HT depletion. For instance, Slikker et al. (1989) found that although MDMA produced significant 5-HT depletion in rat and monkey forebrain (50% and 80%, respectively) behaviour was not affected, and Ricaurte et al. (1993) found that recent memory was not impaired by MDMA administration alone. Malleret et al. (1999) even found spatial memory *enhancement* in 5-HT1B knockout rats, suggesting that the demonstrations of memory, learning and manual dexterity impairments in human MDMA users may not be expected on the basis of MDMA-related 5-HT depletion alone. Further, Vollenweider et al. (1999) have found opposite MDMA-related sensorimotor effects in rats and humans, suggesting that our knowledge of the relation between MDMA toxicity and cognitive function is far from clear.

There have been attempts to overcome this difficulty. Klugman et al. (1999) selected subjects whose MDMA use was both substantive (mean = 235 tablets) and long term (mean = 4.3 years) and who used other drugs only irregularly. None of the cognitive learning and memory deficits disclosed in MDMA users showed correlations with frequency or amount of cannabis use, whereas cannabis use correlated negatively with verbal word fluency. Morgan (1999) attempted to overcome this difficulty by demonstrating short-term memory impairment in ecstasy users relative to polydrug-user controls. Although a useful strategy, groups in that study were not matched on LSD or cannabis use (although not statistically significant, MDMA users used cannabis 48% more frequently and had a lifetime exposure 65% greater than polydrug-user controls). Lifetime exposure to LSD was ruled out as a confound through covariate analysis, yet although cannabis consumption correlated negatively with performance, it was not used as a covariate because it fell short of significance (P=0.058). Further, the correlations observed between MDMA consumption and immediate recall (r=–0.47; P=0.019) were no stronger than the correlations observed between cannabis consumption and immediate recall (r=–0.48; P=0.016), suggesting that cannabis use may have been as important as MDMA use to the observed deficits.

The present study was designed to help delineate the respective effects of cannabis and MDMA on human cognitive function, and to allow a direct comparison with previous results; it primarily employed the tests from Klugman et al. (1999). As we were unable to recruit MDMA users who had not consumed large quantities of cannabis, we followed the method of Morgan (1999), comparing cannabis/MDMA users to MDMA-na cannabis users on a series of cognitive tests. Poorer performance in the MDMA/cannabis group relative to the cannabis group would suggest that the reported cognitive deficits in MDMA users are related to their MDMA and not their concurrent cannabis use. It is more difficult to interpret a negative finding – where no difference is found between the cannabis users who have and have not used MDMA, and this possibility will be discussed after.

Materials and methods

Participants

Thirty-one drug-na controls, 11 MDMA/cannabis users and 18 cannabis users were recruited through ‘word of mouth’ notices in the local area and advertisements in the London magazine ‘Time Out’. They were screened in a telephone interview to determine drug and neurological history. Subjects with neurological or psychiatric histories were excluded. Users were instructed to abstain from cannabis and MDMA for 48 h prior to testing. Subject demographics and drug histories are given in Table 1. This study was approved by and conducted in accordance with the local ethics committee. Subjects gave written informed consent before participating in the study.

Neuropsychological tests

- Warrington recognition memory tests for words and faces (Warrington 1984). ‘Words’: a word is presented visually every 2 s whereby the subject reports to the experimenter whether they have pleasant associations with the word (‘yes’ or ‘no’). A total of 50 words are presented, after which 50 *pairs* of words are presented and the subject is asked to say which of each pair comes from the previously presented list (one and only one word from each pair comes from the previous list). ‘Faces’: similar to ‘words’ except that stimuli are faces rather than words. The maximum score for each test is 50.
- Grooved pegboard (Klove 1963). Subjects put 25 grooved pegs into 25 non-uniform matching holes as fast as they can, using one hand only. This is scored as ‘time to completion’, with separate scores for the right and left hand. ‘Left pegboard’ here refers to the time taken using the right hand (as this involves the left hemisphere of the brain), while ‘right pegboard’ refers to left-hand scores.
- Spatial and non-spatial associative learning test (Petrides 1985). Subjects are asked to learn associations between six spatial pairs (‘spatial’) or six colour pairs (‘non-spatial’). The task begins with the subject guessing, and learns the prompted associations through feedback from the experimenter – ‘yes’ or ‘no’. The task finishes when the subject correctly reports 18 consecutive associations, and the number of guesses that it takes to get to this point is the subject’s score (although the maximum guesses allowed is 180).

Table 1 Subject ages, NART-estimated full-scale IQs, level of education, drug histories and reported abstinence periods are shown. Drug histories are reported as total lifetime consumption, where units are 'joints', 'tablets', 'grams', 'tablets' and 'standard units' for cannabis, (±)-3,4-methylenedioxymethamphetamine (MDMA), cocaine, speed and alcohol, respectively. Education levels are coded '1' for O-levels (standard school education to approximately 15 years), '2' for A-levels (standard school education to approximately 17 years) and '3' for university education

	Control		MDMA/cannabis		Cannabis	
	Mean	SD	Mean	SD	Mean	SD
Age	23.5	6.8	25.7	4.7	26.6	8.1
Estimated IQ	115.2	4.7	116.2	3.6	115.2	4.1
Education	2.57	0.63	2.50	0.65	2.43	0.79
Cannabis	0.5	0.8	10964.9	13235.5	7762.4	14480.9
MDMA	0	0	41.9	49.3	0.6	1.3
Cocaine	0	0	6.4	6.1	5.7	13.3
Speed	0	0	20.4	29.7	12.1	19.0
Alcohol	3875.3	4407.8	3484.0	3254.0	5309.8	6517.5
Cannabis abstinence	–	–	47.3	15.5	66.5	42.4
n	31 (17 females)		11 (6 females)		18 (4 females)	

- Forward and backward digit span (Weschler and Stone 1974). The subject is asked to repeat sequences of digits back to the experimenter either forwards ('forward') or backwards ('backward'). The length of the sequences increase with the subject's success, and subjects obtain points for each sequence repeated in the correct order.
- Verbal fluency (Benton and Hamsher 1978). Subjects are asked to generate as many words as they can in 60 s, either starting with a specified letter ('FAS'), or belonging to a specified category ('animals'). High scores indicate greater verbal fluency.
- Stroop (Stroop 1935). Subjects are timed as they read out a list of colour words (i.e. 'blue', 'red', 'green' and 'yellow') as fast as they can. The colour words are either in black ink ('Stroop A'), giving a measure of speed of processing, or in incongruous colours ('Stroop B'), giving a measure of the interference caused by the incongruity.
- Coughlan list and design learning (Rey 1964). 'List': a list of 15 words is read out, after which the subject has to recall as many of these words as possible. The same list is then read out four more times (or truncated if the subject remembers all 15 words for two consecutive list presentations), after which a new list is read out and recall again requested. This new list serves as an interference task, and following it the original list is read out and recall again requested. The first lists are designated 'list1to5', the interference list 'listB', and the final list 'list6'. Scored as number correctly recalled, lists 1–5 provide measures of list learning, list B of immediate list recall and list 6 of delayed recall. Design learning follows the same format, differing only in that a design is shown that the subject is asked to redraw, rather than lists read out that the subject is asked to recall.
- National adult reading test (NART; Nelson 1982): Subjects are asked to read 50 words aloud. The pronunciations of these words need to have been learnt in the past as they cannot be derived using standard rules of pronunciation. The accuracy of pronunciation thus provides a measure of premorbid verbal intelligence.

Test procedure

Testing consisted of blocks A, B and C. Block B consisted of questionnaires (Thayer, Speilberger state/trait, personality syndrome questionnaire, Cloninger TPQ, drug history), always occurred second and will not be discussed. The order of A and C was counterbalanced across subjects and randomly assigned. Block A consisted of Warrington 'words' and 'faces', 'left' and 'right' pegboard, 'spatial' and 'non-spatial' associative learning and 'NART'. Block C consisted of 'forward' and 'backward' digit span, 'FAS' and 'animals' verbal fluency, 'Stroop A', 'Stroop B' and Coughlan 'list' and 'design' learning.

Upon arrival at the hospital, subjects were informed of the ensuing protocol and completed a consent form. They then completed the tasks in a quiet comfortable room. After the experiment subjects were paid UK£10 plus travel expenses. Half of the subjects were offered monetary reward for performing above average on the tests (UK£5) to explore the role of motivation. None of the tests discussed in this paper were affected by the motivation condition and thus this distinction will not be considered further. After testing was completed, subjects were paid and then informed that their results would be more valuable if we knew exactly how many hours that they had abstained from cannabis. A number of subjects reported less than the requested 48-h cannabis abstinence period, resulting in a minimum abstinence period of 17 h for included subjects (see Table 1).

Results

Means and standard deviations for the groups are shown in Table 2. Data were normalised using the following transformations, where ln = natural log: twords = 1/(51-words); tnonspatial = ln(nonspatial); tstroopA = ln(StroopA+5); tspatial=ln(spatial); tlist6=1/(17-list6); tdes1to5=1/(48-des1to5); tage=ln(ln(ln(ln(age)))). Between-group ANOVAs failed to find group differences in sex [$F(2,57)=2.67$; $P=0.077$], 'tage' [$F(2,57)=2.81$; $P=0.068$], 'NART' [$F(2,57)=0.24$; $P=0.790$] or education levels [$F(2,57)=0.63$; $P=0.537$]. All subjects reported abstaining from MDMA for at least 1 week before testing, and cannabis abstinence levels did not differ between the two drug groups [$F(1,27)=1.94$; $P=0.175$].

Cannabis versus MDMA

For each test score, ANCOVAs tested for group differences where the covariates 'tage', 'NART' and 'sex' were included if they were significant predictors at $\alpha=0.10$. Directional tests were used, predicting that those who have used both MDMA and cannabis would perform more poorly than those who have only used canna-

Table 2 Means and standard deviations are given for controls, MDMA/cannabis and cannabis only groups separately

Test	Control		MDMA/cannabis		Cannabis	
	Mean	SD	Mean	SD	Mean	SD
Warrington 'faces'	43.0	3.3	40.9	5.6	40.7	3.7
Warrington 'words'	48.3	2.3	45.5	7.0	48.3	1.8
Spatial associative learning	57.7	36.1	81.9	51.9	76.2	45.2
Non-spatial associative learning	46.9	30.1	74.8	44.1	74.4	38.0
Stroop A	16.7	2.4	19.5	4.9	17.9	2.7
Stroop B	19.5	3.8	22.1	5.2	21.5	4.2
Digit span – forward	10.5	1.8	9.2	1.6	9.6	1.5
Digit span – backward	9.3	2.2	8.0	2.6	7.9	1.8
Word fluency – FAS	48.9	11.6	44.4	9.4	48.0	11.1
Word fluency – animals	26.6	4.2	21.7	5.2	24.4	6.0
Coughlan – list 1to5	62.4	7.7	57.2	11.3	56.3	9.0
Coughlan – list 6	13.2	1.6	12.2	2.7	11.8	3.0
Coughlan – list B	8.5	2.7	7.3	2.6	6.5	2.2
Coughlan – design 1to5	39.9	6.5	40.4	4.2	34.9	8.6
Coughlan – design 6	8.2	1.7	7.7	2.5	7.3	2.1
Coughlan – design B	6.7	2.0	6.5	2.1	7.3	2.1
Pegboard – left	56.5	6.6	59.2	6.8	65.5	7.7
Pegboard – right	63.4	8.5	62.2	8.8	66.6	7.9

Table 3 Statistics are shown for the comparisons of the MDMA/cannabis with the cannabis group, and for the control with the combined drug groups, for each of the cognitive tasks. Note that for the comparison of cannabis and MDMA/cannabis groups, differences are not in the predicted direction (the cannabis only group performed worse than the MDMA/cannabis group)

Test	Comparison					
	MDMA vs cannabis			Control vs drug users		
	df	*F*	*P*	*df*	*F*	*P*
Warrington 'faces'	1,27	0.02	0.441	1,57	6.34	0.008[b]
Warrington 'words'[a]	1,27	1.54	0.113	1,57	1.03	0.157
Spatial associative learning[a]	1,27	0.11	0.372	1,56	0.21	0.078
Non-spatial associative learning[a]	1,26	0.17	0.343	1,58	10.97	0.001[b]
Stroop A[a]	1,27	1.19	0.143	1,57	3.42	0.035[b]
Stroop B	1,26	0.01	0.469	1,55	0.88	0.176
Digit span – forward	1,27	0.40	0.265	1,57	3.90	0.027[b]
Digit span – backward	1,27	0.02	0.445	1,57	2.83	0.049[b]
Word fluency – FAS	1,27	0.82	0.186	1,58	0.64	0.214
Word fluency – animals	1,27	1.36	0.127	1,58	6.11	0.008[b]
Coughlan – list 1to5	1,27	0.06	0.417	1,56	5.06	0.014[b]
Coughlan – list 6[a]	1,27	1.18	0.143	1,57	2.30	0.066
Coughlan – list B	1,27	0.73	0.200	1,55	2.41	0.063
Coughlan – design 1to5[a]	1,26	4.25	0.025[b]	1,57	0.83	0.188
Coughlan – design 6[a]	1,27	0.76	0.195	1,57	1.84	0.091
Coughlan – design B	1,27	0.64	0.216	1,57	1.61	0.105
Pegboard – left	1,26	4.78	0.019[b]	1,56	8.88	0.002[b]
Pegboard – right	1,26	1.88	0.091	1,56	0.07	0.396

[a] Denotes data that has been transformed
[b] Denotes significant differences between the groups (assuming α=0.05)

bis. As is shown in Table 3, there were no differences between the MDMA/cannabis and cannabis groups in the predicted direction (although the MDMA/cannabis group performed better than the cannabis only group on Coughlan 'design 1to5' and 'left pegboard').

Drug users versus controls

For each test score, ANCOVAs tested for group differences between the two drug groups combined (users) and the drug-na controls (controls). The covariates 'tage', 'NART' and 'sex' were included if they were significant predictors at α=0.10. Directional tests were used, predicting that the combined drug group would perform more poorly than the drug-na group. As is shown in Table 3, drug-na controls performed better than the combined drug group on 'faces', 'non-spatial' associative learning, 'forward' and 'backward' digit span, Coughlan 'list1to5', 'animals' and 'left pegboard'.

To determine whether subjects' drug histories were related to the above group differences, for each test score where a significant difference was found, four more ANCOVAs were performed. That is, for each of 'tStroopA', 'faces', 'non-spatial', 'forward', 'backward', 'list1to5', 'animals' and 'left pegboard', four ANCOVAs were performed, differing from those given in Table 3 in that each *also* contained one of the following drug-use indices as a covariate (total cannabis, total MDMA, frequency of cannabis and frequency of MDMA consump-

Table 4 Displayed are results from the second set of covariate analyses comparing the combined drug-user group to controls. 'Original statistics' are taken from Table 3, and 'new probabilities' are the probabilities obtained from the original statistics, differing only in that they included an extra covariate. The extra covariates were total lifetime consumption of cannabis and of MDMA ('total'), and monthly consumption of cannabis and of MDMA ('frequency'). It can be seen that cannabis-use indices had greater effect on significance values than MDMA-use indices

Test	Original statistics			New probabilities			
	df	*F*	*P*	Cannabis		MDMA	
				Total	Frequency	Total	Frequency
Stroop A	1,57	3.42	0.035	0.05	0.21	0.31	0.24
Warrington 'faces'	1,57	6.34	0.008	0.21	0.38	0.03	0.03
Spatial associative learning[a]	1,56	0.21	0.078	0.38	0.23	0.16	0.15
Non-spatial associative learning[a]	1,58	10.97	0.001	0.29	0.01	0.01	0.01
Digit span – forward	1,57	3.90	0.027	0.15	0.43	0.13	0.12
Digit span – backward	1,57	2.83	0.049	0.42	0.32	0.09	0.12
Word fluency – animals	1,58	6.11	0.008	0.15	0.39	0.06	0.05
Coughlan – list 1to5	1,56	5.06	0.014	0.43	0.07	0.02	0.02
Pegboard – left	1,56	8.88	0.002	0.04	0.05	0.01	0.01

[a] Denotes data that has been transformed

tion). Results are given in Table 4 where it can be seen that cannabis was more closely related to the deficits than MDMA on all tests except for Stroop A.

Discussion

The results demonstrate a number of cognitive deficits in chronic MDMA/cannabis users relative to drug-na controls, relating to learning, memory, verbal word fluency, speed of processing and manual dexterity. As such, the results are consistent with past demonstrations of poorer cognitive performance in MDMA/cannabis users than controls (Bolla et al. 1998; McCann et al. 1998; Parrott et al. 1998; Klugman et al. 1999; Morgan 1999; Wareing et al. 2000).

Two lines of evidence suggest that the deficits in the drug group discussed above were not related to MDMA consumption. The first is that if MDMA – or the interaction of MDMA and cannabis – was responsible for the above cognitive deficits, then it might be expected that people who used both MDMA and cannabis should perform more poorly than those who had only used cannabis, whereas if cannabis caused the deficits then there should be no difference between the groups. Thus finding that the MDMA/cannabis group did not perform worse than the cannabis group suggests that the poorer performance in the drug group was not caused by MDMA. The second piece of evidence is that the poorer performance of MDMA/cannabis users was affected very little by covarying either frequency of use or total MDMA consumption – that is, differences remained significant for most tests, whereas covarying for indices of cannabis consumption removed most significant differences between the groups.

There were exceptions to the above pattern in that measures of working memory (forward and backward digit span) were affected by covarying for MDMA, and the index of left hemisphere manual dexterity (pegboard) was not affected by covarying for cannabis use. These test scores were *more closely* related to cannabis than MDMA though, suggesting that cannabis was at least as important to the poorer test scores as MDMA. Another exception was speed of processing, as indexed by Stroop A. This was affected more by MDMA than cannabis consumption covariates, suggesting that this may be related to MDMA. Apart from the last index, the results are therefore consistent with Morgan (1998) and Dafters et al. (1999) who failed to find MDMA-related cognitive deficits.

However, another possible explanation for the lack of difference between the MDMA and MDMA/cannabis groups is that MDMA *does* cause cognitive impairment, and that the lack of difference was due to a complex interaction between the drugs. For instance, it may be that MDMA causes more cognitive impairment when used on its own than was observed in this study, but that the cannabis use attenuated the MDMA effect, making it comparable to the cannabis group. This explanation makes sense in that cannabis affects DA function (Bloom 1982; Malone and Taylor 1999; Tanda et al. 1999; Nava et al. 2000), and MDMA-induced 5-HT deficit is largely determined by DA integrity (Stone et al. 1988; Aguirre et al. 1998; Sprague et al. 1998). Therefore it is feasible that cannabis-related DA downregulation might protect the user against MDMA-related 5-HT impairment. A similar interaction might also occur in that MDMA induces DA release (Steele et al. 1987), and this may attenuate cannabis-related cognitive impairment, a possibility consistent with the current findings of better performance on 'left hemisphere pegboard' and 'Coughlan design learning' by the MDMA/cannabis group relative to the cannabis group. Such an interpretation would not affect the main finding of the study – that it is important to account for cannabis use in human MDMA research – but it does highlight the difficulty in determining causation in polydrug-related deficits.

It should be noted that even if the above caveat was rejected, causation of impairment would not have been demonstrated. That is, even where impairments were more closely related to cannabis use than MDMA, this may be for example, a result of self-medication (Dixon et al. 1991; Jansen 1999). Further, that the MDMA/cannabis users performed better on two tests than the sub-

jects who had used only cannabis (and less of it) suggests that naturally occurring differences in cognitive abilities may have played a role in the results. However in relation to the role of cannabis in studies of MDMA-related cognitive impairment, causation is not relevant because where cannabis is not controlled for, a relation between cannabis and cognitive impairment is enough to make it a confound. It should also be noted that the drug users only abstained from cannabis for 48 h before testing, and so it may be argued that the findings are related to residual cannabis intoxication. It is difficult to determine how larger abstinence periods would affect the results, because as well as decreasing the chance of observing acute effects, withdrawal effects would also be greater. However such an interpretation would only affect conclusions relating to the overall differences between controls and users because the two user groups had comparable abstinence periods. This interpretation would thus not affect the main finding of the study – that it is important to account for cannabis use in human MDMA research.

There were failures to replicate Klugman et al.'s (1999) results and so we shall consider them individually, and as that paper is a study summary, we shall refer to the more detailed account of those results in Klugman et al. (manuscript in preparation). Firstly, the present results are not consistent with findings of MDMA-related deficits in spatial associative learning or right hemisphere manual dexterity in the Klugman et al. study. Regarding spatial associative learning, the drug group in the present study had non-significantly poorer scores than the controls (P=0.08; see Table 2). The control group mean in the present study (57.7) was comparable to that of Klugman et al. (57.9), suggesting a comparable testing regime, but as the quantities of MDMA used in the present study were considerably less than those used by Klugman et al., this leaves open the possibility that more MDMA is required to produce the magnitude of impairment found by Klugman et al.. Covariate analysis failed to resolve this issue as covarying for either cannabis or MDMA use reduced the difference between the groups (Table 4). The lack of group difference on the right pegboard was more clearly a failure to replicate Klugman et al., as the only suggestion of impairment was on the cannabis only group, with the MDMA/cannabis users marginally faster than controls. Differences were also found in digit span and verbal fluency (animals) in the present study that were not found by Klugman et al., suggesting that these were related to subjects' cannabis consumption. The role of cannabis consumption in verbal fluency is further supported in that Klugman et al. found cannabis and verbal fluency to be negatively correlated.

Regarding the pattern of cognitive deficits found in the drug-user group, learning deficits were evidenced in poorer performance on the non-spatial associative learning task. That there was a near significant deficit on the spatial learning task suggests that this may not be a discreet learning impairment. Left but not right hemisphere manual dexterity was impaired in users, suggesting a discreet left hemisphere motor co-ordination impairment in the users, and thus not the general slowing of function that might be expected if the drug users were acutely intoxicated or suffering withdrawal symptoms. Memory deficits in the users were evidenced in poorer performance on delayed face recognition and immediate free recall of words (Coughlan lists 1–5), and on forwards and backwards digit span. That the groups did not differ on word recognition or Coughlan design learning again may suggest that they do not suffer a global memory deficit, but a number of discrete deficits.

The above suggests that previous findings of cognitive impairment in MDMA users may have noted impairments attributable to cannabis rather than MDMA because they did not adequately account for cannabis. Thus the 5-HT deficits found in recreational MDMA users may not be related to the cognitive impairments previously described. This demonstrates the need to account for cannabis use in human MDMA research, and suggests that caution should be applied in interpretation of previous studies of chronic MDMA use and cognition, as cannabis use may have determined the reported impairments.

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