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Evidence for selective executive function deficits in ecstasy/polydrug users

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Abstract

Previous research has suggested that the separate aspects of executive functioning are differentially affected by ecstasy use. Although the inhibition process appears to be unaffected by ecstasy use, it is unclear whether this is true of heavy users under conditions of high demand. Tasks loading on the updating process have been shown to be adversely affected by ecstasy use. However, it remains unclear whether the deficits observed reflect the executive aspects of the tasks or whether they are domain general in nature affecting both verbal and visuo-spatial updating. Fourteen heavy ecstasy users (mean total lifetime use 1000 tablets), 39 light ecstasy users (mean total lifetime use 150 tablets) and 28 non-users were tested on tasks loading on the inhibition executive process (random letter generation) and the updating component process (letter updating, visuo-spatial updating and computation span). Heavy users were not impaired in random letter generation even under conditions designed to be more demanding. Ecstasy-related deficits were observed on all updating measures and were statistically significant for two of the three measures. Following controls for various aspects of cannabis use, statistically significant ecstasy-related deficits were obtained on all three updating measures. It was concluded that the inhibition process is unaffected by ecstasy use even among heavy users. By way of contrast, the updating process appears to be impaired in ecstasy users with the deficit apparently domain general in nature.

Key words

ecstasy (MDMA); executive; inhibition; random generation; updating; visuo-spatial

Introduction

There is a cause to believe that among the many illicit drugs commonly in use, ecstasy in particular causes long-term impairment to cognitive processes through its effects on the serotonin system (Gouzoulis-Mayfrank and Daumann, 2006; Morgan, 2000; Reneman, *et al*., 2002). Morgan (2000, p. 234) has noted that 'it has been proposed that it (serotonin) may play an orchestrating role in cognition'. More specifically, the serotonin system is believed to underpin working memory processes through its modulation of the dopaminergic systems that support prefrontal executive processes (Luciana, *et al*., 1998; Robbins, 2000).

Recent investigations of executive functioning suggest that the central executive is fractionated. For example, Miyake, *et al*. (2000) studied the separability of three supposed executive functions: mental set shifting (shifting), information updating and monitoring (updating), and inhibition of pre-potent responses (inhibition). Structural equation modelling showed that the three executive functions were clearly separate and appeared to contribute differentially to performance on higher-level tasks that are known to be reliant on prefrontal cortical resources. For example, the Wisconsin Cart Sort Task (WCST) was linked to the shifting component, the Tower of Hanoi to the inhibition component, random number generation to both the inhibition and updating components and operation span to the updating component.

Using factor analysis, Fisk and Sharp (2004) provided further support for Miyake *et al*.'s model, finding that reading span and computation span (analogous to Miyake *et al*.'s operation span task), letter updating (Morris and Jones, 1990) and a visuo-spatial serial recall task (Brooks, 1967) all loaded on a single factor corresponding to Miyake *et al*.'s updating executive process. Aspects of random letter generation loaded on a separate factor corresponding to Miyake *et al*.'s inhibition executive process, while WCST measures loaded on a third factor (equivalent to Miyake *et al*.'s switching executive process). Additionally, a fourth factor emerged which Fisk and Sharp termed access to semantic memory and on which verbal fluency tasks loaded.

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Previous research from our laboratory (Fisk, *et al*., 2004; Montgomery, *et al*., 2005; Wareing, *et al*., 2004) using Miyake *et al*.'s conceptual framework, showed ecstasy-related deficits in memory updating (computation span and letter updating) and access to long-term memory (verbal fluency). No differences were observed on tasks assessing the switching (the plus–minus and number letter task) and inhibition (random letter generation) component processes. However, inconsistencies in this area of research have emerged. From our own laboratory, while Wareing, *et al*. (2000) found ecstasy users to be impaired in random letter generation, we have failed to obtain this outcome in subsequent studies (Fisk, *et al*., 2004; Montgomery, *et al*., 2005). Similarly, the ecstasy-related deficits in relation to the updating process that emerged from our own research (Montgomery, *et al*., 2005) have not have been replicated by Dafters (2006) using the keeping track task.

Clearly these inconsistencies require explanation and warrant further research. Wareing, *et al*.'s (2000) participants had an atypically high-estimated lifetime ecstasy dose exceeding 1000 tablets[a] and the random letter generation task used, restricted participants to produce only consonants. In our later study (Fisk, *et al*., 2004), those we tested had an appreciably lower lifetime exposure to the drug (with a mean of 343 tablets) and we administered the original version of the task (Baddeley, 1966) in which any letter of the alphabet may be produced. It is possible therefore that ecstasy might impair the inhibition process but only at high doses and only when the processing load is substantial. To resolve this ambiguity, it would be desirable to administer both versions of the random generation task to a group of high dosage users to establish whether group-related deficits are indeed limited to the consonants only version of the task.

Questions have also emerged concerning our previous results, which reported ecstasy-related updating process deficits. First, at six letters, the maintenance element of the updating task exceeded the letter span of the majority of participants that we tested. Consequently many participants may have adopted a free recall recency–based strategy negating the need for updating (Collette, *et al*., 2006; Smith-Spark, *et al*., 2003). It would be desirable to repeat our original experiment ensuring that the maintenance component of the task does not exceed the letter span of our participants. Second, we have recently reported ecstasy-related deficits in visuo-spatial working memory tasks (Wareing, *et al*., 2005), although it is unclear which executive component processes may be implicated in this regard. Recent conceptualisations of executive function tasks suggest the processing component of these is domain general (e.g., Bayliss, *et al*., 2003; Kane, *et al*., 2004). If the updating component does reflect some domain general process, it would be expected that the impairments that we have observed in verbal updating would also manifested in visuo-spatial updating.

[a] Wareing *et al*.'s participants estimated their total lifetime use by responding on a 11 point ordinal scale. Most participants (15 of 20) responded in the maximum 200+ category. Other data indicate that users had consumed a mean of 377 tablets during the most recent 12-month period of use. Users also indicated a mean length of use of 4 years. It is unlikely that this level of use was maintained throughout the entire period. Assuming a constant absolute rate of increase over the 4-year period would yield a total lifetime use figure of approximately 1000 tablets.

Method

Design and analysis

For the random letter generation tasks, a three-way mixed ANOVA design was used with type of task (with two levels; standard version and consonant only version) and rate of letter generation (with three levels; 4, 2 and 1 s) both within participants and ecstasy users group (with three levels; heavy, light and non-user) between participants. Dependent variables were the number of alphabetically ordered pairs, the number of repeated pairs and redundancy. For the consonants only random generation task, the number of vowel intrusions was analysed using a mixed ANOVA design with user group between participants and rate of letter generation within.

With regard to the updating executive component tasks, verbal and spatial updating and the computation span task, a multivariate (MANOVA) design was used with user group (three levels) between participants and the three measures of executive functioning as dependent variables. Orthogonal contrasts were used in which heavy ecstasy users were compared with light users and the two ecstasy user groups combined compared with non-users. Orthogonal contrasts were used as they allow inter-group comparisons to be made while controlling the Type 1 error rate without the need to adjust the α-level per comparison (Tabachnick and Fidell, 2001).

Participants

Fourteen heavy ecstasy users (mean age 22.86; nine men), 39 light ecstasy users (mean age 21.41; 19 men) and 28 non-user controls (mean age 20.71; seven men) took part in the study. The heavy users group comprised all those users with an estimated lifetime dose exceeding 400 tablets, (mean 1000.21, SD, 786.41). Light users were those with an estimated lifetime dose of less than 400 tablets, (mean 149.69, SD, 96.91). The cut-off point of 400 tablets was determined by trial and error so as to produce a high use group with a mean lifetime dose of 1000 tablets, as this was the level of exposure characterising the ecstasy users in our previous study (Wareing, *et al*., 2000). Non-users were those who indicated that they had never used ecstasy. Participants were recruited via direct approach to university students and the snowball technique (Solowij, *et al*., 1992). With 14 ecstasy users, the present sample is sufficient to detect a difference of 1.25 σ for $\alpha = 0.05$ and $\beta = 0.20$ (Hinkle, *et al*., 1994). Participants were requested to refrain from ecstasy use for at least 7 days before testing. The mean period of abstinence was actually 22 and 27 weeks for heavy users and light users, respectively; median abstinence period 5.5 and 4 weeks, respectively. Participants were also requested not to use any other illicit drugs for at least 24 h before testing. The level of use for each illicit substance during the preceding 10 and 30 days may be found in Table 1.

Measures

Patterns of drug use and other relevant lifestyle variables were investigated via means of a background questionnaire. The questionnaire assessed the use of ecstasy and other illicit drugs, as well as age, years of education and other relevant lifestyle variables including the average number of cigarettes consumed daily and the weekly consumption of alcohol. In relation to other drugs, participants were asked a range of questions including frequency and duration of use and the last time that they had used each drug. Participants were also questioned concerning their history of drug use, and using a technique used by Montgomery, *et al*. (2005) these data were used to estimate total lifetime use for each drug. Average weekly dose and the amount of each drug consumed within the previous 30 days were also assessed. Fluid intelligence was measured via Raven's Progressive Matrices (Raven, *et al*., 1998), and premorbid intelligence was assessed via the National Adult Reading Test (NART, Nelson, 1982).

Letter span

Consonants were presented sequentially on a computer screen for 1.25 s. Participants were then required to recall the letters in

Table 1 Indicators of illicit drug use

	Heavy ecstasy users				Light ecstasy users				Non-ecstasy users				Overall group effect: Kruskal–Wallace (χ)	Heavy ecstasy users versus light users: Mann–Whitney *U* value
	Median	Mean	SD	*n*	Median	Mean	SD	*n*	Median	Mean	SD	*n*		
Total use														
Ecstasy (tablets)	628.00	1000.21	786.41	14	142.00	149.69	96.91	39	0.00	0.00	0.00	28	χ(df = 2, *n* = 81) = 70.26***	0.00***
Cannabis (joints)	5200.00	6383.27	5830.32	11	320.00	1779.51	2971.07	37	22.00	262.13	507.44	23	χ(df = 2, *n* = 71) = 16.65***	113.50*
Cocaine (g)	75.75	127.52	144.64	6	0.00	17.51	35.84	21	0.00	0.00	0.00	25	χ(df = 2, *n* = 52) = 28.37***	16.50**
Average weekly dose														
Ecstasy (tablets)	2.87	3.49	2.05	14	0.73	0.99	0.68	38	0.00	0.00	0.00	28	χ(df = 2, *n* = 80) = 65.49***	46.00***
Cannabis (joints)	15.08	15.59	12.76	11	2.40	5.96	9.97	35	0.17	1.60	2.84	23	χ(df = 2, *n* = 69) = 13.37**	108.50*
Cocaine (g)	0.44	0.52	0.47	6	0.00	0.14	0.29	21	0.00	0.00	0.00	25	χ(df = 2, *n* = 52) = 27.43***	21.00*
Length of use (weeks)														
Ecstasy	271.00	300.82	136.12	14	148.00	176.29	108.55	39	-	-	-	-	-	115.50**
Cannabis	260.00	342.14	184.14	13	268.00	283.56	145.16	33	172.00	172.83	106.63	21	χ(df = 2, *n* = 67) = 10.29**	178.50
Cocaine	217.22	240.63	136.35	14	121.00	137.65	79.50	27	-	-	-	-	-	91.00**
Drugs used during the 30 days before testing														
Ecstasy	0.00	2.61	4.09	14	0.50	1.73	2.60	39	0.00	0.00	0.00	28	χ(df = 2, *n* = 81) = 19.07***	272.00
Cannabis	24.00	56.31	75.15	13	3.00	22.80	45.00	38	0.00	7.04	29.30	26	χ(df = 2, *n* = 77) = 9.77**	205.50
Cocaine	0.25	0.45	0.55	10	0.00	0.25	0.66	30	0.00	0.00	0.00	27	χ(df = 2, *n* = 67) = 13.65**	109.00
Drugs used during the 10 days before testing														
Ecstasy	0.00	0.68	1.49	14	0.00	0.32	0.86	39	0.00	0.00	0.00	28	χ(df = 2, *n* = 81) = 5.80	251.50
Cannabis	0.50	6.75	12.50	14	0.00	2.79	6.03	39	0.00	1.14	3.57	28	χ(df = 2, *n* = 81) = 6.25*	235.00
Cocaine	0.00	0.10	0.18	14	0.00	0.08	0.24	39	0.00	0.00	0.00	28	χ(df = 2, *n* = 81) = 7.48*	246.00

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

the order in which they were presented. The task commences with three sets of two letters and is then increased to three sets of three, four, five, etc., until the individual fails on at least two of three trials. *Digit span* was administered in a similar manner except that the letters were replaced with digits.

Spatial span

The participants were informed that they would be presented with a pattern consisting of blank squares and were told that some of the squares would be filled one a time with Xs. They were asked to remember the position of each of the cells so highlighted and to write down the positions of all the cells in the order in which they were filled. There were 12 positions that could be filled with Xs and these were set out on the computer screen in a Corsi-type fashion. The number of positions highlighted increased gradually over the course of the experiment. There were three trials at each level of the task. The participant proceeded to the next level until he/she failed on at least two of three trials.

Updating

Updating has been used extensively as a measure of prefrontal executive functioning (see for example, Fisk and Sharp, 2003, 2004; Miyake, *et al.*, 2000; Morris and Jones, 1990; Smith-Spark and Fisk, 2007; Van der Linden, *et al.*, 1999). The participant's letter span, 'n', was determined. In the consonant updating task, the participant was presented with a random sequence of between n and $n + 6$ consonants on a computer screen. Twenty-four such lists were presented, and in each case the participant was unaware of the number of consonants to be presented. The task was always to recall the most recent 'n' consonants in the order in which they were presented. Thus the maintenance element of the task was limited to the individual's actual span. This contrasts favourably with our previous study where at six letters the maintenance requirement exceeded the span of most of our participants. The participant experienced six trials at each of the four list lengths: n, $n + 2$, $n + 4$ and $n + 6$ items. The order in which the lists were presented was randomised. A single composite score of updating was calculated by computing the average number correct for each serial position over the six trials at each list length. The resulting figures were then averaged over list length and serial position.

The spatial updating task was analogous to consonant updating except that it involved the serial recall of cells that were highlighted sequentially, one at a time, in a Corsi style display. The participant's spatial span, 'n', was determined. In the updating task the participant was presented with a random sequence of between n and $n + 6$ cells highlighted on a computer screen in a Corsi style configuration. Twenty-four such sequences were presented, and in each case the participant was unaware of the number of cells that were highlighted. The task was always to recall the most recent 'n' cells in the order in which they were presented. As in the consonant task, the participant experienced six trials at each of the sequence lengths. The order in which the lists were presented was randomised. A single composite score of updating was calculated using the same procedure as outlined for the consonant updating task.

Computation span

Computation span has been used extensively as an indicator of working memory functioning in the cognitive ageing literature (Fisk and Warr, 1996; Salthouse and Babcock, 1991) and it is similar to the operation span measure used by Miyake, *et al.* (2000) in their investigation of executive processes. Participants were required to solve a number of arithmetic problems (e.g., $4 + 7 = ?$) by circling one of three multiple-choice answers as each problem was presented. They were also required to simultaneously remember the second digit of each presented problem. At the end of each set of problems, the second digits had to be recalled in the order in which they were presented. The number of arithmetic problems that the participant had to solve, while at the same time remembering each second digit, gradually increased as the test proceeded. For each of the first three trials, only a single problem was presented. For the next three trials, two problems were presented. Subsequently, the number of problems presented per trial increased by one for every three trials. To proceed, the participant was required to be correct in at least two of the three trials at the current level. Computation span was defined as the maximum number of end digits recalled in serial order, with the added requirement that the corresponding arithmetic problems had been solved correctly. To take account of individual differences in the non-executive maintenance component of the task, the load on executive resources was computed as the percentage difference between the computation and digit span scores. Large percentage differences are indicative of poor executive functioning.

Random letter generation

A computer display and concurrent auditory signal was used to pace responses. Participants were asked to speak aloud a letter every time the signal was presented. They were told to avoid repeating the same sequence of letters; to avoid producing alphabetically ordered sequences and to try to speak each letter with the same overall frequency. In the standard version of the task, participants were permitted to produce any letter of the alphabet. In the other version, they were told to produce only consonants (i.e., to avoid the letters a, e, i, o and u). For each version of the task, individuals attempted to produce three sets of 100 letters; one set at a rate of one letter every four seconds, a second set at one letter every two seconds and a third at one letter every one second. The order in which the sets were generated was randomised. The experimenter recorded the responses on an answer sheet. Each version of the test yields three scores. First, the number of alphabetically ordered pairs;

second, a repeat sequences score corresponding to the number of times that the same letter pair is repeated and third, a ‘redundancy’ score, which measures the extent to which all 26 letters of the alphabet are produced equally often (0% being truly random). In addition to these three, the consonant only version of the task yielded an additional score, the number of vowel intrusions. In all cases, higher scores are indicative of poor performance.

Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tests were administered under laboratory conditions, and a computer running MS-DOS was used for the computer-based tasks. The tests were administered in the following order: background questionnaire, random letter generation (the order in which the two different versions was completed was alternated), digit, letter and spatial span, computation span, letter and spatial updating, Raven’s progressive matrices and the NART. Participants were fully debriefed, paid £15 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the Declaration of Helsinki.

Results

Background measures

The groups did not differ significantly in terms of weekly alcohol consumption, the number of years of education and the Raven’s and NART measures. Inspection of Table 2 shows that age differed significantly between the groups. Tukey’s test showed that heavy users were significantly older than the other two groups, $P < 0.01$ and $P < 0.05$, in relation to non-users and light users respectively. Light users and non-users did not differ significantly from each other. The daily consumption of cigarettes differed significantly. Although heavy users consumed significantly more than non-users, $P < 0.05$, none of the other group differences were significant (via Tukey’s test). Table 2 also contains mean simple span scores (digit, letter and spatial) for each of the three groups. Ecstasy users were unimpaired on these measures in fact scoring marginally higher compared with non-ecstasy users.

Indicators of drug use

The vast majority of all of the groups had previous exposure to cannabis. Ninety-three per cent of heavy ecstasy users, 87% of light users and 75% of non-ecstasy users indicated that they had used cannabis. Cocaine use was also common among ecstasy users. All heavy ecstasy users and 72% of light ecstasy users indicated that they had previously used cocaine. However, only 11% of non-users had had any exposure to this drug. Other drugs that had been previously used included amphetamine and LSD but use of these was less prevalent and limited to the ecstasy user groups. Sixty-four per cent of heavy ecstasy users and 33% of light ecstasy users indicated that they had previously used amphetamine. The equivalent figures for lysergic acid diethylamide (LSD) were respectively, 64% and 13%. For those drugs where it was possible to quantify the level of use a number of relevant measures are set out in Table 1. Heavy ecstasy users also consumed substantial quantities of cocaine and cannabis. Light ecstasy users also used these drugs but to a lesser extent. Among non-ecstasy users, the only illicit drug used was cannabis but the exposure to this drug was of a lower order compared with the other two groups. Three

Table 2 Background variables

	Heavy ecstasy users		Light ecstasy users		Non-ecstasy users		$F(2,78)$
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	22.86	2.38	21.41	2.05	20.71	1.37	5.91**
Years of education	15.11	2.66	14.87	3.11	15.55	2.24	<1
Cigarettes (number smoked per day)	7.82	10.35	5.94	6.45	2.50	3.99	3.67*
Alcohol (units per week)	22.36	12.23	20.86	11.78	16.70	13.17	1.32
Raven’s Progressive Matrices (maximum 60)	45.86	7.19	46.74	5.96	49.36	5.06	2.25
NART (maximum 50)	27.86	8.39	28.72	5.67	29.14	5.02	<1
Digit span	6.86	1.03	6.89	1.17	6.60	1.47	<1
Letter span	5.21	1.05	5.46	0.94	5.04	0.84	1.75
Spatial span	4.57	0.85	4.92	0.77	4.57	0.96	1.71
Computation span (% cost)	49.04	28.75	41.32	25.21	29.43	23.00	3.23*
Consonant updating	3.99	0.71	3.83	0.83	4.22	0.61	2.23
Spatial updating	4.01	0.56	4.03	0.66	4.48	0.75	3.97*

*$P < 0.05$; **$P < 0.01$.

non-ecstasy users indicated that they had used cocaine on one or two previous occasions but were unable to quantify the amount. For the most part, the measures of drug use were not normally distributed. In many instances the median response was zero and more generally the distributions were positively skewed. In addition, the group variances were generally heterogeneous. As a consequence, non-parametric analyses were used with the results showing that most of the indicators of drug use set out in Table 1 differed significantly between the groups. With regard to differences between the two ecstasy user groups, heavy users scored significantly higher than light users in terms of total lifetime and average weekly consumption of both cannabis and cocaine. Heavy users had used ecstasy and cocaine significantly longer than light users although length of cannabis use did not differ significantly between the two ecstasy user groups. Also there were no significant differences between heavy and light ecstasy users in terms of their use of illicit drugs in the previous 10 and 30 days.

Inhibition process measures

Outcomes for the different versions of the random generation task are set out in Table 3. Not surprisingly and in line with previous research (Fisk and Warr, 1996), random letter generation performance decreased significantly as the rate of letter generation increased, $F(1.74, 133.84) = 109.20$; $F(1.57, 120.51) = 32.71$; $F(1.58, 121.45) = 110.73$; for redundancy, repeat and alphabetically ordered pairs respectively, $P < .001$ in all cases[b].

It had been anticipated that the consonant only version of the task would be more difficult than the standard version and therefore that performance would be worse. This expectation was only partially borne out. Compared with the standard version, far more repeat sequences were produced in the consonant only version, $F(1,77) = 102.37$, $P < 0.001$. The interaction between type of task and rate of generation approached significance, $F(2,154) = 2.89$, $P = 0.061$. The effects of task on the number of repeat sequences were most evident at the slower generation rates. Also consistent with the increased difficulty associated with the consonants only version, at the one second rate, participants generated fewer letters when completing this version compared with the standard version. This difference approached significance, $F(1, 77) = 3.83$, $P = 0.054$. Paradoxically participants' responses exhibited *more* redundancy in the standard version of the task compared with the consonant only version, $F(1,77) = 8.29$, $P < 0.01$. Furthermore, this tendency was especially evident at the faster generation rates and produced a significant interaction between type of task and rate of letter generation, $F(1.78, 137.18) = 4.30$, $P < 0.05$. It may be that there is a greater tendency to produce vowels in the standard version of the task making these over represented and inflating redundancy.

With regard to ecstasy-related effects, for both versions of the task in all aspects of random letter generation, the scores were similar between the groups. Consistent with the trends evident in the means, none of the group main effects were statistically significant, for each of the four analyses (redundancy, repeat sequences, alphabetical sequences and vowel intrusions), $F < 1$. Also in each case, the interactions between group and rate of letter generation and between group and type of task were non-significant, $F < 1$ for both interactions, in each of the three analyses[c]. Similarly for vowel intrusions, the interaction between group and rate of generation was non-significant, $F < 1$. The number of letters produced was close to ceiling (i.e., 100 letters) for all groups at the four and two second generation rates in both the standard and consonant only versions of the task. Although performance decreased at the one second rate for both task versions, this was equally apparent for all groups. The maximal number of letters generated by most participants at the four and two second rates prevent meaningful analysis. However, ANOVA with group between participants, type of task within and the number of letters generated at the one second rate as the dependent variable showed no significant difference between the groups, neither was the group by task interaction significant, $F < 1$ in both cases. Thus, to summarise, the present results provide no evidence of ecstasy-related differences on either version of the random generation task, and by implications, no group difference in the inhibition process on which random letter generation is known to load.

Updating process measures

The percentage reduction in capacity associated with the concurrent processing component of the computation span task is set out in Table 2 along with the outcomes for the spatial and verbal (consonant) updating tasks. All three measures are believed to load on the updating process. For each of these three indicators of executive functioning, non-ecstasy users outperformed both ecstasy user groups. Non-users exhibited substantially lower costs in relation to the processing component of the computation span task. They also exhibited more efficient updating both in relation to verbal and visuo-spatial stimuli. MANOVA with user group between participants and the three measures of the updating process as dependent variables showed a significant multivariate group effect, Wilks' lambda = 0.836, $F(6,150) = 2.34$, $P < 0.05$. Regarding the univariate outcomes, as inspection of Table 2 shows, the group differences were statistically significant for both computation span and spatial updating. However, the group difference for the verbal updating task failed to reach significance. Difference contrasts showed that non-users performed significantly better

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[b] Where Mauchly's test of sphericity was significant, Greenhouse-Geisser epsilon adjusted degrees of freedom have been used.

[c] In relation to alphabetically ordered pairs, although non-significant the F value exceeded 1, $F(2,77) = 1.35$, $P > 0.05$

Table 3 Performance on random generation measures

	Heavy ecstasy users				Light ecstasy users				Non-ecstasy users			
	Basic version		Consonants only		Basic version		Consonants only		Basic version		Consonants only	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Redundancy												
4 s	4.93	1.82	4.78	2.53	4.06	2.34	4.00	1.72	4.02	1.97	4.49	2.14
2 s	5.95	2.46	5.95	1.94	5.66	2.31	5.01	2.05	5.84	2.10	5.11	2.26
1 s	8.93	3.02	7.05	3.00	7.87	2.61	7.17	3.02	8.42	3.15	7.37	2.15
Repeat sequences												
4 s	10.71	3.12	16.00	3.26	8.95	3.76	14.05	4.76	7.78	3.12	14.14	4.28
2 s	11.79	3.87	16.86	3.61	11.64	3.89	16.72	6.41	11.48	3.02	16.54	4.77
1 s	15.86	7.18	19.07	8.40	15.51	6.42	18.23	5.89	14.33	5.53	18.39	6.15
Alphabetic sequences												
4 s	4.50	3.03	5.07	2.50	5.31	5.24	4.62	3.88	3.33	2.82	3.79	3.37
2 s	6.29	2.87	6.79	3.58	8.18	5.50	7.10	5.08	7.70	4.85	6.96	4.62
1 s	11.14	5.14	10.86	5.55	13.38	10.15	11.87	6.51	11.22	4.79	12.11	6.44
Number of letters generated												
4 s	100.00	0.00	100.14	0.36	100.03	0.28	100.15	0.43	99.89	0.32	100.11	0.50
2 s	99.36	1.74	99.93	1.00	99.26	2.33	99.15	3.08	98.85	2.09	98.79	3.08
1 s	91.86	7.51	90.00	11.73	92.77	7.96	89.74	9.51	88.81	10.47	88.43	10.15
Vowel intrusions												
4 s			0.71	0.83			1.23	1.86			1.18	1.49
2 s			1.29	1.49			1.49	2.76			1.61	2.06
1 s			2.79	3.02			3.18	3.43			3.04	2.25

than the combined user groups on the computation span and spatial updating measures, $P < 0.05$ and $P < 0.01$ respectively, the difference approached significance for the verbal updating task, $P = 0.091$. However, the contrasts showed that the two user groups did not differ from each other on any of the updating measures, $P > 0.05$ in all cases.

Statistic controls for group differences in background variables and the use of other drugs

As inspection of Table 1 showed, ecstasy users (especially heavy users) consumed considerably more cannabis compared with non-ecstasy users both in terms of long term and recent use. Similarly, age and cigarette consumption differed significantly between the groups. It is possible, therefore, that these variables and various aspects of cannabis use may have accounted for the ecstasy-related group differences that were obtained on the updating executive component measures. To control for this possibility, the MANOVA was repeated with measures of cigarette and alcohol use and the two long-term (total lifetime consumption and average weekly consumption) and two short-term measures of cannabis use (amount used in the last 10 and 30 days) included as covariates. The multivariate group effect remained significant, Wilks' lambda = 0.736, $F(6,114) = 3.15$, $P < 0.01$. Regarding the univariate outcomes, the group differences were all statistically significant with F values for verbal updating, spatial updating and computation span of 5.93, 3.62 and 4.07, respectively, on 2,59 degrees of freedom, $P < 0.05$ for spatial updating and computation span and $P < 0.01$ for verbal updating. Difference contrasts showed that non-users performed significantly better than the combined user groups on all three measures, $P < 0.01$ for verbal updating and computation span and $P < 0.05$ for spatial updating. Tests for homogeneity of regression were conducted for each covariate with respect to each of the dependent variables yielding a total of 18 analyses. In 16 of the 18 cases, homogeneity of regression was obtained, $P > 0.05$, for the covariate by group interaction in all cases. In two cases, homogeneity of regression was not obtained. In both cases, this was in relation to computation span where group by covariate interactions for average weekly cannabis consumption and for age were significant with F values of 4.81 and 4.38, respectively, on 2,62 degrees of freedom, $P < 0.05$.

The absence of cocaine users among the non-ecstasy users made it impossible to control statistically for the potentially confounding effects of cocaine use because it was not possible to test for homogeneity of regression. To evaluate the extent to which cocaine use (as well as ecstasy and cannabis use) was associated with performance on the updating executive component measures, we examined the correlations (Spearman's rho) between the different aspects of drug use and the outcomes on the updating measures. The results are set out in Table 4. It is clear that only aspects of ecstasy use were significantly correlated with the updating executive component measures. None

Table 4 Correlations between aspects of illicit drug use and updating executive component measures

	Computation span	Verbal updating	Spatial updating	*n*
Total use				
Ecstasy (tablets)	0.295**	−0.234*	−0.235*	80
Cannabis (joints)	0.040	0.035	−0.020	70
Cocaine (g)	0.246	0.014	−0.183	51
Average weekly dose				
Ecstasy (tablets)	0.316**	−0.279*	−0.288**	79
Cannabis (joints)	0.011	0.036	−0.020	68
Cocaine (g)	0.251	0.013	−0.188	51
Length of use (weeks)				
Ecstasy	0.075	0.147	0.081	53
Cannabis	−0.121	−0.127	−0.031	43
Cocaine	0.183	0.079	−0.017	66
Drugs used during the 30 days before testing				
Ecstasy	0.117	−0.125	−0.305**	80
Cannabis	0.106	0.039	−0.055	76
Cocaine	0.024	0.069	−0.166	66
Drugs used during the 10 days before testing				
Ecstasy	−0.084	0.008	0.036	80
Cannabis	0.123	−0.093	−0.194	80
Cocaine	0.032	0.009	−0.169	80

Sample sizes vary because of the fact that some users were unable to quantify aspects of their drug use. For the most part these were infrequent users or those who indicated that they had used on a small number of occasions and were uncertain of the quantity used and the time that had elapsed since use.
*$P < 0.05$; **$P < 0.01$.

of the aspects of cocaine use were associated with statistically significant correlations.

Discussion

Using a random letter generation task, it was hoped that the present investigation would determine whether ecstasy-related deficits were present in the inhibition process and if so whether these deficits were confined to heavy users. We also intended to show that the ecstasy-related deficits that had been reported in memory updating reflected the executive aspects of the task and generalised to the spatial modality. We found no significant ecstasy-related differences on either version of the random letter generation task. The consonant only version used here was the same as that used in our early research and as noted above this was associated with a significant group difference in our initial study (Wareing, *et al*., 2000). Average lifetime consumption of ecstasy tablets approximated 1000 in that study, which is appreciably higher than was apparent in our subsequent research. Furthermore, there is clear evidence that restricting the letter set to consonants only caused particular problems for the ecstasy users groups in Wareing, *et al*.'s (2000) study as they produced significantly more vowel intrusions under all generation rates. Thus, it had been conjectured that deficits might be found in the present study among heavy chronic users on the consonants only version of the task. However, the results presented here reported that this was not the case. The basis for the significant group difference in our original study (Wareing, *et al*., 2000) remains unclear. With just ten participants in each group, the sample sizes were small. Furthermore, in our previous study, we did not assess participants on measures of intelligence. Thus, it remains possible that the differences we observed might have been due to some premorbid factor other than drug use. The fact that the present study along with other recent results from our laboratory (Fisk, *et al*., 2004; Montgomery, *et al*., 2005) has not showed ecstasy-related deficits in random letter generation suggest that this aspect of cognitive functioning is unimpaired. Because random letter generation is an established measure of the inhibition process, it would seem reasonable to conclude that ecstasy use does not adversely affect this aspect of cognition.

Research from our own laboratory has suggested that ecstasy use may be associated with deficits in the updating process. Two measures of the updating function appear to be subject to ecstasy-related impairment, computation span and letter updating (Montgomery, *et al*., 2005). However, with regard to the latter, in our previous study participants were required to maintain a load of six letters while concurrently performing the updating task. It appears that this load exceeded the letter span of the majority of participants and for these individuals it would have been impossible to perform the maintenance element of the task. This raises the question of whether any serial rehearsal element and concurrent updating activity was actually occurring. It is possible that participants may have adopted a free recall strategy with a reliance on the recency component of the process. Baddeley and Hitch (1993) have argued that the recency phenomenon is distinct from the maintenance and processing functions of working memory. Thus, in our previous research, although we had reported an ecstasy-related deficit in letter updating, this may not have in fact reflected an executive function deficit. In an important early study of the updating process, Morris and Jones (1990) addressed this problem by running two experiments, the first with a load of six letters and the second with a load of four letters. However, reducing the load to four letters is not without problem because it makes it possible for those individuals with large letter spans to avoid updating all together by encoding and serially rehearsing the entire sequence where the presented sequence length allows this. To address this problem, in the present study, participants were required to maintain a load that was equivalent to their letter span. The orthogonal difference contrasts showed that following control for group differences in cannabis consumption, ecstasy users performed significantly worse than non-users on all three measures of the updating process, including the letter updating task, computation span and visuo-spatial updating. Having said this it must be conceded that the group difference for letter updating was non-significant before the inclusion of the covariates. Similarly, the Helmert contrast on the original data showed that users as a whole did not differ significantly from non-users in the letter updating task. However, the contrast was associated with a significance level of 0.091, which although non-significant on a two-tailed basis would have just been significant on a one-tailed basis. These results have features in common with those obtained by Wareing, *et al.* (2004). In their study, two verbal updating tasks were administered, reading span and computation span. The latter was used in the present study. The former requires the participant to process sets of sentences while simultaneously retaining the last word of each sentence that was presented. After all sentences have been processed, the participant recalls the last words in the order in which they were presented. Wareing, *et al.* (2004) obtained ecstasy-related deficits on the computation span measure, but on the reading span task, the group deficit, while present, only approached significance. Thus, although it can be argued with some degree of confidence that ecstasy users are impaired in the updating process, it remains unclear why deficits are not always found in the verbal modality.

The present results can be compared with those of Reay, *et al.* (2006) who also used Miyake *et al.*'s conceptual framework and reported a very similar pattern of results. Specifically, inhibitory processes were found to be unimpaired in ecstasy/polydrug users compared with non-ecstasy/polydrug users. Interestingly, while the present article relied on a verbal task (random letter generation) to assess inhibition, Reay *et al.* used a spatial inhibition task. Thus, it appears that inhibitory processes remain intact in ecstasy users in both verbal and spatial modalities.

It has been argued that the storage aspects of the working memory system are domain-specific while processing is domain-general in nature (e.g., Bayliss, *et al.*, 2003; Kane, *et al.*, 2004). Thus, verbal and visuo-spatial information would be stored by functionally separate systems, but the processing component of tasks using this information would be domain-general in nature. Given that ecstasy users have been found to exhibit deficits in verbal updating, the domain general nature of the process would imply that deficits should also be apparent in updating visuo-spatial information. In our previous research, we have found ecstasy users to be impaired in a visuo-spatial complex span task (Wareing, *et al.*, 2005). Although analogous verbal tasks have been found to load on the updating process (Miyake, *et al.*, 2000; Fisk and Sharp, 2004), it is unclear whether this applies to the visuo-spatial working memory task that we used previously. The present study has used an analogue of the verbal updating task in which individuals were required to maintain and update a spatial sequence, and it was established that ecstasy users were significantly impaired on this task relative to non-users. The presence of deficits on both the verbal and visuo-spatial updating tasks is consistent with Baylis, *et al.* (2003) and Kane, *et al.* (2004) view of working memory and it may be that the deficits observed reflect an ecstasy-related impairment in this domain general updating process.

The present findings may be viewed in the context of recent neuroscience research. Cowan, *et al.* (2003) observed significantly lower grey matter concentrations among ecstasy users in multiple brain regions (bilateral BA 18 and cerebellum, left BA 21 and left BA 45, as well as the midline brainstem). Other research suggests that ecstasy/polydrug-related changes may occur in the prefrontal and parietal regions of the neocortex (Daumann, *et al.*, 2004; De Win, *et al.*, 2007). For example, 42 weeks after receiving a single dose of ecstasy, De Win, *et al.* (2007) observed a reduction in relative regional cerebral blood volume (rrCBV) in the thalamus, dorsolateral frontal cortex, and superior parietal cortex in previously ecstasy-naive individuals. However, after correction for multiple comparisons, only the rrCBV decrease in the dorsolateral frontal cortex remained significant. Using single-voxel H-1 MR spectroscopy, Reneman, *et al.* (2002) found that *N*-Acetylaspartate (NAA)/creatine (Cr) and NAA/Choline (Cho) ratios, both markers of neuronal integrity, were significantly reduced in the frontal cortex of MDMA users. The magnitude of the reduction was significantly correlated with previous exposure to ecstasy. In an earlier study by the same authors, the ecstasy-related reduction in the NAA/Cr ratio in the prefrontal cortex was found to be significantly associated with impaired memory function (Reneman, *et al.*, 2001).

Memory updating has been particularly linked to the dorsolateral prefrontal cortex (Goldman-Rakic, 1996), whereas performance on the letter-updating task is most strongly associated with the left fronto-polar cortex (Collette, *et al.*, 2006;

Van der Linden, *et al.*, 1999). Random generation has also been found to rely on dorsolateral prefrontal resources (Collette, *et al.*, 2006). It is unclear, therefore, why serotonergic damage to the prefrontal cortex should affect one executive process while leaving the other unaffected. Updating requires that the individual maintains information in working memory while engaging in concurrent processing. Random generation, however, has only a minimal maintenance requirement. Perhaps it is the case that serontonergic damage particularly affects performance on executive tasks where there is a need to maintain information in working memory. The results of the present study clearly report that users are unimpaired in simple memory span tasks. It appears, therefore, that maintenance alone is not a problem but concurrent processing and maintenance does appear to be associated with ecstasy-related impairment.

As with most studies in this area, a number of limitations need to be acknowledged. First, it is not universally accepted that ecstasy produces neurotoxic effects in humans. Indeed the neuroscience evidence indicative of neurotoxicty is the subject of much debate (e.g., Cowan, 2007; Kish, 2002; Reneman, *et al.*, 2006). Thus, the underlying causes of ecstasy-related deficits remain unclear. In relation to the present article, because of the quasi-experimental design, it is possible that the groups may have differed on some variable other than ecstasy use. The groups differed significantly in age and although the tests administered are subject to age-related decrease, this does not typically occur until old age. None of the participants tested in the present study were more than 27 years old. Furthermore, when we controlled statistically for the effects of group differences in age, the ecstasy-related effects remained statistically significant. Group differences in other variables such as general health, nutrition or some premorbid condition predating drug use (Verheul, 2001) cannot be ruled out. Furthermore, because of limited resources we were unable to provide an objective measure of recent drug use (e.g., from hair or urine samples). However, most published studies testing cognitive deficits among ecstasy users have not used these techniques (e.g., Fox, *et al.*, 2002; Morgan, 1998; Rodgers, 2000). We were able to statistically control for group differences in both recent and longer-term aspects of cannabis use. Furthermore, aspects of ecstasy use were more closely correlated with the cognitive outcomes compared with the equivalent correlations with cocaine use. However, it must be acknowledged that a minority of the ecstasy users had in the past used amphetamine and a small number LSD. We cannot, therefore, entirely exclude the possibility that these drugs may have played some role in the results that were obtained. A further limitation relates to the measures themselves. Although there is broad agreement that the tasks reported here load on specific component executive processes, the evidence is not always consistent. For example, Miyake, *et al.* (2000) found that random *number* generation loaded on both inhibition and updating. However, in a later study, Fisk and Sharp (2004) found that random *letter* generation loaded on the inhibition process but not on the updating process. It is also clear that all tasks may load on some general executive resource (Miyake, *et al.*, 2000). Thus, it appears that subtle changes in task characteristics can result in an altered pattern of reliance on executive processes and some degree of caution must therefore be exercised in drawing inferences from the present results.

To summarise, the present article clearly augments the growing body of evidence indicating that while ecstasy users have deficits in prefrontal executive processes, these are only manifested in specific aspects of executive functioning. While the inhibition process is apparently spared, the updating process does appear to be impaired among ecstasy users. This impairment remains statistically significant following controls for group differences in aspects of cannabis consumption and it appears to be more closely associated with indicators of ecstasy use as opposed to other drugs such as cocaine. While apparently domain general in nature in so far as deficits appear to exist in both the spatial and verbal domains, the deficiency appears to be more readily detectible in the spatial domain.

Further research is needed to determine why ecstasy-related deficits are not always apparent on verbal memory updating tasks. The group difference obtained in the present study approached statistical significance, and it may be that a larger sample with increased power might be required to detect a difference, should one be found to exist. A larger sample would also potentially allow participants to be screened so that all groups were exactly matched in terms of simple span thereby ensuring that all participants are carrying the same load on phonological resources. Ecstasy-related deficits have also been observed in tasks putatively loading other executive processes such as access to semantic memory (Montgomery, *et al.*, 2005). It would be of value to conduct further studies to establish whether other tasks tapping this aspect of executive functioning show ecstasy-related deficits. Thus, although the present results are potentially of interest, clearly much additional research is needed before the effects of ecstasy use on this important aspect of cognitive functioning can be properly determined.

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