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Evidence for executive deficits among users of MDMA (Ecstasy)

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Random letter generation and computation span are tasks known to load on executive, prefrontal resources. Previous research suggests that Ecstasy users are impaired on random letter generation. The current study, employing a larger sample (44 current Ecstasy users, and 59 non-Ecstasy users), together with more effective statistical controls for other drug use, failed to replicate previous findings. Ecstasy users were unimpaired on all measures of random generation performance. A significant difference was obtained on the computation span measure, with Ecstasy users scoring significantly lower than non-Ecstasy users. This difference remained statistically significant following control for various indicators of the use of other drugs including cannabis. The results are discussed in terms of the potential effects that Ecstasy might have on different component executive processes.

In our previous paper (Wareing, Fisk, & Murphy, 2000) we found evidence for executive deficits among current and previous Ecstasy users. Ten current Ecstasy users (estimate lifetime consumption 1349 tablets), 10 previous users (estimated lifetime consumption 1280 tablets) and 10 drug-naive controls (matched with both groups for age, gender and education) were compared on a range of working memory tests. Executive functioning was measured using the random letter generation task. Random generation is a relatively demanding cognitive process and is known to place a continuous strain on executive resources (see Baddeley, 1996). Participants are asked to produce letters in a random sequence avoiding alphabetical or well-known sequences (e.g. CIA, BBC or FBI). They are also asked to try to produce each letter with the same overall frequency and additionally, in our study, participants were asked to produce only consonants. The task is repeated three times with, respectively, letters produced at one every 4 seconds, one every 2 seconds and one per second. Both user groups performed significantly worse than controls at the 1-second rate of production and produced more vowel intrusions at all three rates of generation (4, 2 and 1 second). Although these results are interesting

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they need to be treated with a certain degree of caution because our participants were largely, heavy, chronic users with an estimated lifetime consumption of the drug of around 1300 tablets. This is considerably higher than the equivalent figures reported in other studies. For example, Verkes and co-workers' heavy user group had an estimated mean lifetime consumption of 741 tablets, whereas the corresponding figure for the moderate users was 169 tablets (Verkes *et al.*, 2001).

Apart from the Wareing *et al.* (2000) study, what evidence is there for Ectasy-related deficits in working memory and more specifically in executive processes? Curran and Travil (1997) compared Ecstasy users with alcohol users on various measures on days one, two and five after the last use of Ecstasy. In the serial sevens subtractions task (SSS), which is believed to tap working memory and executive resources, Ecstasy users made significantly fewer subtractions than the alcohol group. However, no significant differences were found between the groups in the total number of errors made on the task. Recent research from our own laboratory demonstrated that current and previous Ecstasy users were impaired on measures of verbal and visuopatial working memory span (Wareing, Fisk, Murphy, & Montgomery, 2004; Wareing, Murphy, & Fisk, 2004), and on syllogistic reasoning (Montgomery, Fisk, Newcombe, Wareing, & Murphy, 2003). However, in these studies controls for the use of other drugs were not extensive and so the outcomes cannot be conclusively attributed to Ecstasy.

Gouzoulis-Mayfrank *et al.* (2000) tested combined Ecstasy–cannabis users (estimated lifetime consumption of Ecstasy 93 tablets), cannabis controls (matched with the Ecstasy group for cannabis consumption) and non-drug user controls (matched with both groups for age, gender and education) on a battery of cognitive tests. No cognitive impairments were established with regards to cannabis users, who did not differ significantly from controls on any of the tests. However, the combined Ecstasy–cannabis users performed significantly worse than both control groups, on a number of tests that are believed to load on executive resources, for example, in selective attention, tests involving logical thinking (LPS-4 Test) and problem solving (Mosaic Test).

Although these results are noteworthy, other studies have failed to find evidence for executive deficits. For example, Morgan, McFie, Fleetwood, and Robinson (2002), compared current Ecstasy users (estimated mean lifetime consumption 513 tablets for males, 93 for females) and previous users (estimated mean lifetime consumption 336 tablets for males, 577 for females) who had been abstinent from the drug for at least 6 months, with polydrug users and non-drug users on a range of tests measuring cognitive functioning. They found no significant group differences in relation to digit cancellation, Stroop performance and verbal fluency, all of which are believed to reflect aspects of executive functioning (although deficits on other non-executive measures were found). Fox and co-workers also report mixed results in relation to executive processes. For example, although users took longer in the planning phase of the Tower of London (ToL) task, the other measures of ToL performance revealed no Ecstasy-related differences (Fox *et al.*, 2002; Fox, Parrott, & Turner, 2001). More recently, although Thomasius *et al.* (2003) found that Ecstasy users committed significantly more perseverative errors than polydrug controls on the Wisconsin Card Sort Test (WCST), they were no worse than *drug-free* controls on this measure.

The varied pattern of results may, in part, reflect the fact that the executive may not be a unitary construct and, therefore, although Ecstasy users may experience deficits on some aspects of executive functioning, other areas might be spared. In this regard, Miyake and co-workers have shown that executive functions can be subdivided into at least three separate types of operation: updating, shifting and inhibition (Miyake *et al.*, 2000).

Updating involves evaluating incoming information and revising the existing contents of working memory as necessary by deleting what is no longer relevant and incorporating more recent salient information. Shifting is concerned with the individual's ability to shift attention between different subtasks or different elements of the same task. Inhibition is concerned with the individual's ability to withhold dominant, automatic or pre-potent responses when they are inappropriate. Although these three operations share some common element, Miyake *et al*. showed that they are separable with different executive tasks loading heavily on just one or two specific operations. For example, the WCST is believed to load on Miyake *et al*.'s shifting component executive process, random generation on the inhibition and updating components, whereas working memory span tasks appear to load on the updating component.

Miyake *et al*.'s findings are potentially important as they may provide an explanation as to why some of the above studies have found Ecstasy-related working memory and executive deficits, whereas others have not. If the executive is indeed fractionated as Miyake and others propose, then it is necessary to establish which components might be most susceptible to Ecstasy-related impairment and which might be less vulnerable in this regard. The available evidence would appear to suggest that tasks loading on the switching component of Miyake *et al*.'s model are unaffected by Ecstasy use. For example, both Fox *et al.* (2001) and Thomasius *et al.* (2003) found Ecstasy users to be unimpaired on the WCST, which Miyake *et al*. have associated with the switching component executive process. Furthermore, Fox *et al.* (2001) found that Ecstasy users were unimpaired on the three-dimensional intra-dimensional extra-dimensional set-shifting task (IDED) also believed to load on the switching component.

It remains unclear whether updating and inhibition, the other executive component processes identified by Miyake *et al*., are susceptible to Ecstasy-related deficits. There is agreement that random generation appears to load on the inhibition component of Miyake *et al*.'s conceptual framework. For example, Fisk and Sharp (in press) found that random *letter* generation loads on the inhibition function, but not on the other two components. By contrast, Miyake *et al.* (2000) found that random *number* generation loaded on both the inhibition and updating component processes. In our previous study (Wareing *et al.*, 2000), we established that Ecstasy users were impaired in random *letter* generation and so it seems reasonable to infer that the inhibition component executive process may be subject to Ecstasy-related deficits. However, as noted above, those individuals tested in our earlier study were heavy chronic polydrug users with an estimated lifetime consumption of over 1000 Ecstasy tablets. Thus, they were not representative of the typical Ecstasy user. Also the sample size was limited to just 10 individuals in each group. In addition, although we attempted to control for the effects of other drugs such as cannabis, through the use of ANCOVA, because none our control group had used cannabis, this meant that the tests we conducted for homogeneity of regression were effectively limited to the two user groups. An implication of this is that we cannot say with any degree of certainty that the results we obtained were due to Ecstasy.

Given the limitations of our earlier study, it is now desirable to replicate our initial results using a larger sample of more representative Ecstasy users and with more effective controls for the effects of other drugs. Furthermore, given that random letter generation appears to load exclusively on the inhibition function, it would be of value to establish whether deficits are also to be found on measures of the updating component executive process. Thus, the aim of the current study is to determine if typical users of the drug Ecstasy are impaired on measures that load on the inhibition and updating components of Miyake *et al*.'s conceptual framework, while statistically controlling for the potentially confounding effects other drugs, most noticeably, of cannabis. Because the available evidence (Fox *et al.*, 2001; Thomasius *et al.*, 2003) suggests that measures loading on the switching component are unaffected by Ecstasy use, this aspect will not be investigated further.

Tasks loading on both the inhibition and updating component executive processes were administered. These included random letter generation. In this task, participants were asked to produce letters in a random sequence avoiding alphabetical and well-known sequences (e.g. ABC, CIA, BBC or FBI). They were also asked to try to produce each letter with the same overall frequency. The task was repeated three times with participants respectively generating a letter every 4 seconds, every 2 seconds or one per second. Random generation yields a number of performance measures: (i) redundancy, which measures the extent to which each letter is produced with equal frequency; (ii) alphabetical; and (iii) repeat sequences (alphabetically ordered pairs or pairs of letters that are repeated). For all of these, a high score is indicative of poor performance. The fourth measure generated by the random generation task is the total number of letters generated. For this variable a high score is indicative of good performance. There is general agreement that alphabetical and repeat sequences load on the inhibition component executive process (Fisk & Sharp, in press; Miyake *et al.*, 2000). Consensus is lacking as to whether or not the redundancy measure loads on any of the component processes. While Miyake *et al*. found that with random number generation, redundancy appears to load on the updating component process, Fisk and Sharp (in press) found that this was not the case with random letter generation. The focus for the current study is therefore on alphabetical and repeat sequences in which the link with the inhibition component process is well established. The other random generation measures were included for completeness and to facilitate comparisons with our previous results (Wareing *et al.*, 2000).

In addition to random generation, the computation span task was administered. This is believed to load on the updating component executive processes (Fisk & Sharp, in press; Miyake *et al.*, 2000). Computation span requires the participant to retain a sequence of digits in serial order while simultaneously carrying out simple arithmetic computations. The individual's score is the maximum number of digits successfully recalled in the correct order. On the basis of our previous results, it was expected that Ecstasy users would perform worse than non-Ecstasy users on *all* executive measures and that the group difference would remain significant following statistical controls for various measures of other drug use.

Method

Design

With regard to the random generation task, a mixed design was utilized with user group (with two levels: Ecstasy users and non-Ecstasy users) between participants and the rate of letter generation (4-, 2- and 1- second rates) within. Dependant variables were redundancy, alphabetical sequences, repeat sequences, and the total number of letters generated. Each of these was analysed separately. For computation span, ANOVA was administered with user group between participants and the span score as the dependent variable. For all analyses, where significant group differences were obtained, various measures of other drug use were included as covariates.

Participants

In total, 103 individuals completed the tasks, average age 21.44 years, average number of years of full-time education 15.45. There were 44 Ecstasy users (mean estimated total lifetime use 343 tablets) and 59 non-users. Participants were initially recruited through direct approach to Liverpool John Moores University undergraduate students, including psychology majors and psychology–biology joint students. Subsequently, word-of-mouth referral was used with most participants being recruited by this means. Background data for each group is set out in Table 1.

Table 1. Age, years of education, intelligence and measures of illicit drug use

	Ecstasy users		Non-ecstasy users		
	Mean	SD	Mean	SD	*p*
Age	21.52	1.66	21.37	1.84	*ns*
Years of education	15.66	2.23	15.29	2.16	*ns*
Ravens Progressive Matrices	48.77	5.94	47.95	5.11	*ns*
NART	28.91	6.88	30.05	5.72	*ns*
Ecstasy					
Weeks since last used	10.90	27.86	—	—	N/A
Length of use (weeks)	183.27	103.11	—	—	N/A
Total number of tablets taken	343.38	376.94	—	—	N/A
Current use: times per week	0.44	0.38	—	—	N/A
Average (tablets per week)	2.14	2.57	—	—	N/A
Cannabis					
Per cent using in the last 3 months	84.1		4.58		
Weeks since last used	4.43	11.51	6.58	10.84	*ns*
Length of use (weeks)	307.84	120.80	250.78	151.37	*ns*
Total number of joints taken	3755.89	5451.32	1179.88	1477.37	$< .05$
Current use: times per week	2.85	2.71	0.81	0.87	$< .001$
Average (joints per week)	12.79	16.07	5.72	10.01	*ns*
Cocaine					
Per cent using in the last 3 months	54.5		5.1		
Weeks since last used	7.92	12.1	55.60	87.57	N/A
Length of use (weeks)	129.65	91.29	131.20	105.12	N/A
Total number of grams taken	38.48	61.63	—	—	N/A
Current use: times per week	0.53	0.48	—	—	N/A
Average (grams per week)	0.34	0.43	—	—	N/A
Amphetamine					
Per cent using the last 3 months	20.5		0.0		
Weeks since last used	55.56	77.92	260.00	—	N/A
Length of use (weeks)	221.50	142.09	303.00	—	N/A
Total number of grams taken	71.85	166.55	4.00	—	N/A
Current use: times per week	0.09	0.10	—	—	N/A
Average (grams per week)	0.25	0.41	—	—	N/A
Other drugs					
Alcohol (units per week)	21.91	15.58	11.90	9.14	$< .001$
Tobacco (number per day)	10.46	5.33	11.29	4.37	*ns*

ns = $p > .05$ two tailed non-significant

N/A = Significance levels are not computed where there are fewer than 10 participants in either group.

Materials
Fluid intelligence was measured through Raven's progressive matrices (Raven, Raven, & Court, 1998). Premorbid intelligence was assessed through the NART scale (Nelson, 1982). A background questionnaire used by Wareing *et al.* (2003) assessed the use of Ecstasy and other drugs, as well as age, years of education, other lifestyle variables and a measure of psychological health. In relation to illicit drugs, among other things, participants were asked to indicate their frequency of use, total consumption during the previous 30 days, average consumption per week and the last time that they had used each drug. Cigarettes smoked per day and units of alcohol consumed each week were also assessed. Using a measure developed by Wareing *et al.* (2003), participants also provided an indication of their history of drug use. These data were used to estimate total lifetime use for each drug. Executive functioning was assessed through random letter generation and computation span.

Random letter generation
In this task, participants were asked to speak aloud a letter each time they heard an auditory signal. They were asked to avoid generating alphabetical sequences and repeat sequences such as AB or BBC. They were also asked to try and produce each letter with the same overall frequency. Each participant produced three sets of 100 letters, at the rate of one letter per second, one every 2 seconds and one every 4 seconds. The order in which the sets were produced was randomized for each participant. The experimenter recorded participants' responses.

Computation span
Participants were presented with a number of arithmetic problems (e.g. $4 + 7 = ?$.) They were required to solve each problem as it was presented (by circling one of three multiple-choice answers), while at the same time remembering 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. As the test proceeded, the number of arithmetic problems that the participant had to solve, while at the same time remembering each second digit, gradually increased. The test commenced with three trials with just a single problem, followed by three trials each with two problems, and then three trials each with three problems, and so on. In order to proceed to the next level the participant was required to be correct in at least two of the three trials at the previous level. Computation span was defined as the maximum number of end digits recalled in serial order, subject to the additional requirement that the corresponding arithmetic problems had been solved correctly.

Procedure
Participants were asked to abstain from Ecstasy for at least 7 days prior to testing and from the use of all other illicit drugs for at least 24 hours prior to testing.[1] The tests were

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[1] *With the exception of cannabis, the typical period of abstinence for most users was in excess of one week; 90% of amphetamine users, 72% of cocaine users, and 50% of cannabis users had not used during the week prior to testing. The minimum 24-hour period of abstinence is sufficient to ensure that the results obtained are not due to intoxication. Barnett, Licko, and Thompson (1985) have established that measures of reaction time, selective attention and tracking return to baseline level within 10–12 hours after smoking cannabis and more recently Solowij (1998) used the same 24-hour period to determine that her participants were free of intoxication effects.*

administered in a laboratory setting, using an MS-DOS computer. A range of other measures was also administered, the results of which are outside the scope of this study and have been, or are to be, reported elsewhere (e.g. Fisk, Newcombe, Wareing, & Murphy, 2003; Montgomery *et al.*, in press; Wareing *et al.*, in press). The order in which the tasks were administered was varied so as to control for group differences in the effects of fatigue and boredom.

Results

Background variables and indicators of illicit drug use are reported in Table 1. There were no significant differences between the groups in relation to age, years of education and measures of intellectual functioning. Ecstasy users had smoked significantly more cannabis joints, $t = 2.51$, $df = 38.43$, $p < .05$ (Levene'e test, $p < .05$), and they smoked more frequently than non-Ecstasy users, $t = 3.90$, $df = 40.99$, $p < .001$ (Levene'e test, $p < .001$). They also consumed more units of alcohol per week, $t = 3.80$, $df = 64.73$, $p < .001$ (Levene'e test, $p < .01$). Just over half of Ecstasy users reported that they had consumed cocaine during the previous 3 months and 20% had consumed amphetamine at some time during the same period. Use of these two illicit drugs among non-Ecstasy users was rare.

Switching the focus to random generation performance, inspection of Table 2 reveals that, contrary to expectation, there were no substantial group differences on any of the measures. For the most part, Ecstasy users performed in a similar manner to non-Ecstasy users. *F*-values for the main effects of user group, generation rate and for the group-by-rate interaction, are presented in Table 3. Inspection of Table 3 reveals that there

Table 2. Executive performance by group: Computation span and random generation

	Ecstasy users		Non-ecstasy users	
	Mean	SD	Mean	SD
Computation span	3.64	1.60	4.61	1.50
Random generation measures				
Redundancy (%)				
4 second	4.55	1.85	4.25	1.93
2 second	6.15	2.47	5.79	2.53
1 second	7.92	2.51	7.85	3.19
Repeated sequences				
4 second	8.81	2.93	8.95	2.84
2 second	11.11	3.82	10.85	4.03
1 second	12.32	5.07	13.97	6.40
Alphabetical sequences				
4 second	3.86	2.41	4.02	3.29
2 second	7.32	3.56	7.03	4.39
1 second	9.52	5.11	9.83	5.28
Number of letters				
4 second	99.80	0.70	99.95	0.63
2 second	98.84	2.51	98.02	4.66
1 second	86.59	11.76	88.14	12.05

Table 3. *F*-values for the main effect of group, generation rate and the group by rate interaction

Dependent variable	Independent variable		
	User[a]	Rate[b]	User[b] by rate
Redundancy	0.40	79.61***	0.12
Repeat sequences	0.70	24.04***	1.46
Alphabetical sequences	0.01	73.56***	0.32
Number of letters	0.09	57.70***	1.93

[a] $df = 1, 101$.
[b] $df = 2, 100$ for Pillai's Trace.
$^{***}p < .001$.

were no statistically significant group differences on any of the measures and none of the interactions involving group was statistically significant.

With regard to computation span, relative to non-users, Ecstasy users registered lower scores on the measure (Table 2). Analysis of variance revealed that this difference was statistically significant, $F(1, 101) = 10.05, p < .01$, partial $\eta^2 = .090$. An ANCOVA was conducted with various measures of amphetamine, cannabis and cocaine use as covariates. For each of these three illicit drugs, estimates of lifetime consumption, frequency of use, average weekly dose and level of use during the preceding 30 days were included as covariates. The average number of cigarettes smoked per day and average number of units of alcohol consumed per week were also included. The main effect of group remained statistically significant, $F(1, 87) = 5.44, p < .05$, partial $\eta^2 = .059$. The deficit on the computation span measure therefore appears to be at least in part related to *Ecstasy* use and not solely an artefact of the use of other illicit drugs.[2]

Discussion

Our results reveal a different pattern than that obtained in our previous study. We show no reliable Ecstasy-related group differences in random generation performance. All random generation measures failed to yield statistically significant differences. It is possible that the differences between the current findings and our previous results were due to the vagaries of the small sample that was employed in our original study or to the fact that our attempts to control for cannabis and amphetamine use were more stringent in this study. Alternatively, it may be that deficits in random generation result from an unusually high lifetime dose of Ecstasy taken in conjunction with other neurotoxic illicit drugs.

Random generation is believed to load heavily on executive resources and thus the current results raise questions as to whether or not typical Ecstasy users are impaired in executive processes. However, as noted above, it is now believed that the executive is

[2] *Subsequent analyses revealed that homogeneity of regression was obtained for all the covariates tested. Specifically, the group by covariate interaction was non-significant in all cases. Homogeneity of regression could not be tested for some of the cocaine and amphetamine measures, as there were insufficient users of these among the non-Ecstasy group. However, we repeated the main analysis, excluding all users of cocaine and amphetamine and the Ecstasy-related group difference remained statistically significant,* $F(1, 73) = 8.78$, $p < .01$. *Furthermore, control for the various measures of cannabis use among this reduced sample still left the main effect of Ecstasy user group significant,* $F(1, 67) = 5.86$, $p < .05$.

not a unitary structure but instead consists of a number of separable component processes. According to Miyake *et al.* (2000) and Fisk and Sharp (in press), random generation loads prominently on the inhibition component executive process. It is noteworthy that the Stroop test is also believed to map onto the inhibition component of Miyake's proposed structure and Ecstasy use appears not to affect this task (Croft, Mackay, Mills, & Gruzelier, 2001; Morgan *et al.*, 2002;). Furthermore, according to Miyake *et al.*, another task believed to rely on the inhibition component of executive processes is the Tower of Hanoi test. This is similar to the Tower of London (ToL) test which also appears to be generally unaffected by Ecstasy use. For example, Fox *et al.* (2002) found that only one aspect of ToL performance was adversely affected by Ecstasy use, whereas Morgan (1998) found no evidence of Ecstasy-related impairment on the ToL task. Because the current study failed to find an Ecstasy-related deficit on the random generation task the available evidence suggests that Ecstasy may *not* be associated with any substantial impairment in this aspect of executive processing.

Contrasting with the random generation results, a robust group difference in computation span was obtained. Ecstasy use appeared to account for 9% of the variance in the computation span scores (partial $\eta^2 = .090$). Control for the effects of cannabis, cocaine and amphetamine use reduced the effect size by roughly one half but the effect nonetheless remained statistically significant. Like other working memory span measures, computation span has been found to load on the updating component executive process (Fisk & Sharp, in press; Miyake *et al.*, 2000). Previous studies from our laboratory have revealed Ecstasy-related deficits in working memory span (e.g. Wareing, Fisk, Murphy, & Montgomery, 2004). However, controls for the use of other illicit drugs were not as extensive as those employed in this study. For example, in the current study we controlled for measures of lifetime use, frequency of use, average weekly dose and consumption levels during the proceeding 30 days for amphetamine, cannabis and cocaine. We also controlled for alcohol and tobacco use. The results observed, therefore, appear to be related to some aspect of Ecstasy use. It also seems clear that although updating executive process appears to be impaired, the same is not true of the shifting and inhibition component processes. Thus, the current study offers the clearest evidence to date that Ecstasy users are impaired on one specific aspect of executive functioning, updating, and this deficit, at least in part, appears to be independent of the potential effects of other illicit drugs.

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