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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. While 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 and 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.

Keywords: ecstasy (MDMA), inhibition, updating, executive, random generation, visuo-spatial.

There is 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 & Daumann 2006; Morgan, 2000; Reneman et al 2002). Morgan (2000, page 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, Collins, & Depue, 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 revealed 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 & 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.

Previous research from our laboratory (Fisk et al, 2004; Montgomery et al, 2005; Wareing et al 2004) utilising Miyake et al's conceptual framework, revealed 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 (2005) 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[1] and the random letter generation task used, restricted participants to producing 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 in order 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 demonstrated 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 demonstrated 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 .

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 seconds, 2 seconds, and 1 second) both within participants and ecstasy users group (with three levels; heavy, light, and nonuser) 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 utilising 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 (3 levels) between participants and the three measures of executive functioning as dependent variables. Orthogonal contrasts were employed in which heavy ecstasy users were compared to light users and the two ecstasy user groups combined compared with nonusers. 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 alpha level per comparison (Tabachnick & Fidell, 2001).

Participants.

Fourteen heavy ecstasy users (mean age 22.86; 9 male), 39 light ecstasy users (mean age 21.41; 19 male) and 28 non-user controls (mean age 20.71; 7 male) took part in the study. The heavy users group comprised all of those users with an estimated lifetime dose exceeding 400 tablets, (mean 1000.21, s.d., 786.41). Light users were those with an estimated lifetime dose of less than 400 tablets, (mean 149.69, s.d., 96.91). The cut off point of four hundred 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). Nonusers 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 $\alpha = .05$ and $\beta = .20$ (Hinkle et al, 1994). Participants were requested to refrain from ecstasy use for at least 7 days prior to 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 hours prior to testing. The level of use for each illicit substance, during the preceding 10 and 30 days may be found in Table 2.

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 employed 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 seconds. Participants were then required to recall the letters in 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 out 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 twelve 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 out of three trials.

Updating. Updating has been used extensively as a measure of prefrontal executive functioning (see for example, Fisk & Sharp, 2003; 2004; Miyake et al, 2000; Morris & Jones, 1990; Smith-Spark & 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 6 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 & Warr, 1996;

Salthouse & 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 every third trial. In order 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. In order 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 4 s, a second set at one letter every 2 s, and a third at one letter every 1 s. 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 1 reveals that age differed significantly between the groups. Tukey's test revealed that heavy users were significantly older than the other two groups, $p<.01$ and $p<.05$ in relation to nonusers and light users respectively. Light users and nonusers did not differ significantly from each other. The daily consumption of cigarettes differed significantly. While heavy users consumed significantly more than nonusers, $p<.05$, none of the other group differences were significant (via Tukey's test). Table 1 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 to non ecstasy users.

<Insert Table 1 about here>

Indicators of Drug Use. The vast majority of all of the groups had previous exposure to cannabis. Ninety-three percent 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 nonusers 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 percent of heavy ecstasy users and 33% of light ecstasy users indicated that they had previously used amphetamine. The equivalent figures for 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 2. 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 that was used was cannabis but the exposure to this drug was of a lower order compared to the other two groups. (Three 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 nonparametric analyses were used with the results revealing that most of the indicators of drug use set out in Table 2 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.

<Insert Table 2 about here>

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 & Warr, 1996), random letter generation performance declined 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[2].

<Insert Table 3 about here>

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 to the standard version, far more repeat sequences were produced in the consonant only version, F(1,77) = 102.37, p<.001. The interaction between type of task and rate of generation approached significance, F(2,154) = 2.89, p = .061. The effects of task on the number of repeat sequences was 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 = .054. Paradoxically participants' responses exhibited more redundancy in the standard version of the task compared to the consonant only version, F(1,77) = 8.29, p<.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<.05. It may be that there is a greater tendency to produce vowels is 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[3]. 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 declined 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 prevents 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 revealed 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 1 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 revealed a significant multivariate group effect, Wilks' lambda = .836, $F(6,150)=2.34$, $p<.05$. Regarding the univariate outcomes, as inspection of Table 1 reveals, 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 revealed that nonusers performed significantly better than the combined user groups on the computation span and spatial updating measures, $p<.05$ and $p<.01$ respectively, the difference approached significance for the verbal updating task, $p=.091$. However, the contrasts revealed that the two user groups did not differ from each other on any of the updating measures, $p>.05$ in all cases.

Statistic Controls for Group Differences in Background Variables and the Use of Other Drugs. As inspection of Table 2 revealed, ecstasy users (especially heavy users) consumed considerably more cannabis compared to 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 as well as 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 = .736, $F(6,114)=3.15$, $p<.01$. 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, $p<.05$ for spatial updating and computation span, and $p<.01$ for verbal updating. Difference contrasts revealed that nonusers performed significantly better than the combined user groups on all three measures, $p<.01$ for verbal updating and computation span and $p<.05$ 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, $p>.05$, 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, $p<.05$.

The absence of cocaine users among the non-ecstasy users made it impossible to control statistically for the potentially confounding effects of cocaine use since 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 of the aspects of cocaine use were associated with statistically significant correlations.

<Insert Table 4 about here>

Discussion

Utilising 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 demonstrated 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 consonants 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 demonstrated 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 10 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) have not revealed ecstasy-related deficits in random letter generation suggest that this aspect of cognitive functioning is unimpaired. Since 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, while we had demonstrated 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 as 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. In order 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 revealed that following control for group differences in cannabis consumption, ecstasy users performed significantly worse than nonusers 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 prior to the inclusion of the covariates. Similarly, the Helmert contrast on the original data revealed 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 .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 processes 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 while 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 utilised 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 to non ecstasy/polydrug users. Interestingly while the present paper 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 utilising 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). While analogous verbal tasks have been found to load on the updating process (Miyake et al, 2000; Fisk & Sharp, 2004), it is unclear whether this applies to the visuo-spatial working memory task that we employed 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 nonusers. The presence of deficits on both the verbal and visuo-spatial updating tasks is consistent with Baylis et al (2003) and Kane et al’s (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, forty two 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-naïve individuals. However, after correction for multiple comparisons, only the rrCBV decrease in the dorsolateral frontal cortex remained significant. Utilising 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) while 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 on the other hand 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 demonstrate 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 paper, due to 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 decline, 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, due to 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 to 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. While 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 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 be therefore be exercised in drawing inferences from the present results.

To summarise, the present paper 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 reveal ecstasy-related deficits. Thus while 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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Table 1: Background Variables

	Heavy Ecstasy users		Light Ecstasy Users		Non Ecstasy Users		F(2,78)
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
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<.05; ** p<.01

Table 2: Indicators of Illicit Drug Use

	Heavy Ecstasy Users				Light Ecstasy Users				Non Ecstasy Users			
	Median	Mean	S.D.	n	Median	Mean	S.D.	n	Median	Mean	S.D.	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
Cannabis (joints)	5200.00	6383.27	5830.32	11	320.00	1779.51	2971.07	37	22.00	262.13	507.44	23
Cocaine (grams)	75.75	127.52	144.64	6	0.00	17.51	35.84	21	0.00	0.00	0.00	25
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
Cannabis (joints)	15.08	15.59	12.76	11	2.40	5.96	9.97	35	0.17	1.60	2.84	23
Cocaine (grams)	0.44	0.52	0.47	6	0.00	0.14	0.29	21	0.00	0.00	0.00	25
Length of use (weeks)												
Ecstasy	271.00	300.82	136.12	14	148.00	176.29	108.55	39	-	-	-	-
Cannabis	260.00	342.14	184.14	13	268.00	283.56	145.16	33	172.00	172.83	106.63	21
Cocaine	217.22	240.63	136.35	14	121.00	137.65	79.50	27	-	-	-	-
Drugs Used During the 30 days Prior to Testing												
Ecstasy	0.00	2.61	4.09	14	0.50	1.73	2.60	39	0.00	0.00	0.00	28
Cannabis	24.00	56.31	75.15	13	3.00	22.80	45.00	38	0.00	7.04	29.30	26
Cocaine	0.25	0.45	0.55	10	0.00	0.25	0.66	30	0.00	0.00	0.00	27
Drugs Used During the 10 days Prior to Testing												
Ecstasy	0.00	0.68	1.49	14	0.00	0.32	0.86	39	0.00	0.00	0.00	28
Cannabis	0.50	6.75	12.50	14	0.00	2.79	6.03	39	0.00	1.14	3.57	28
Cocaine	0.00	0.10	0.18	14	0.00	0.08	0.24	39	0.00	0.00	0.00	28

Table 2 continued

	Overall Group Effect: Kruskal-Wallace (χ)	Heavy Ecstasy Users versus Light Users: Mann-Whitney U value
Total Use		
Ecstasy (Tablets)	χ(df=2, N=81) = 70.26***	0.00***
Cannabis (joints)	χ(df=2, N=71)= 16.65***	113.50*
Cocaine (grams)	χ(df=2, N=52) = 28.37***	16.50**
Average Weekly Dose		
Ecstasy (tablets)	χ(df=2, N=80) = 65.49***	46.00***
Cannabis (joints)	χ(df=2, N=69) = 13.37**	108.50*
Cocaine (grams)	χ(df=2, N=52) = 27.43***	21.00*
Length of use (weeks)		
Ecstasy		115.50**
Cannabis	χ(df=2, N=67) = 10.29**	178.50
Cocaine		91.00**
Drugs Used During the 30 days Prior to Testing		
Ecstasy	χ(df=2, N=81) = 19.07***	272.00
Cannabis	χ(df=2, N=77) = 9.77**	205.50
Cocaine	χ(df=2, N=67) = 13.65**	109.00
Drugs Used During the 10 days Prior to Testing		
Ecstasy	χ(df=2, N=81) = 5.80	251.50
Cannabis	χ(df=2, N=81) = 6.25*	235.00
Cocaine	χ(df=2, N=81) = 7.48*	246.00

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	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Redundancy												
4 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second	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 second			0.71	0.83			1.23	1.86			1.18	1.49
2 second			1.29	1.49			1.49	2.76			1.61	2.06
1 second			2.79	3.02			3.18	3.43			3.04	2.25

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)	.295**	-.234*	-.235*	80
Cannabis (joints)	.040	.035	-.020	70
Cocaine (grams)	.246	.014	-.183	51
Average Weekly Dose				
Ecstasy (tablets)	.316**	-.279*	-.288**	79
Cannabis (joints)	.011	.036	-.020	68
Cocaine (grams)	.251	.013	-.188	51
Length of use (weeks)				
Ecstasy	.075	.147	.081	53
Cannabis	-.121	-.127	-.031	43
Cocaine	.183	.079	-.017	66
Drugs Used During the 30 days Prior to Testing				
Ecstasy	.117	-.125	-.305**	80
Cannabis	.106	.039	-.055	76
Cocaine	.024	.069	-.166	66
Drugs Used During the 10 days Prior to Testing				
Ecstasy	-.084	.008	.036	80
Cannabis	.123	-.093	-.194	80
Cocaine	.032	.009	-.169	80

Sample sizes vary due to 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.

** $p<.01$; * $p<.05$

[1] Wareing et al's participants estimated their total lifetime use by responding on an eleven point ordinal scale. Most participants (15 out 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 four year period would yield a total lifetime use figure of approximately 1000 tablets.

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

[3] In relation to alphabetically ordered pairs, although non significant the F value exceeded 1, $F(2,77) = 1.35$, $p>.05$