Montgomery, C, Fisk, JE, Newcombe, R and Murphy, PN

The differential effects of ecstasy/polydrug use on executive components: shifting, inhibition, updating and access to semantic memory

The Differential Effects of Ecstasy-Polydrug use on Executive Components: Shifting, Inhibition, Updating and Access to Semantic Memory.

Catharine Montgomery, John E. Fisk, and Russell Newcombe

Liverpool John Moores University

Phillip N. Murphy

Edge Hill College of Higher Education

Running head: Updating function deficits in ecstasy users.

Corresponding author:

Dr John E Fisk

School of Psychology

Liverpool John Moores University

15-21 Webster Street

Liverpool L3 2ET

United Kingdom

Telephone: 44 (0) 151 231 4035; Fax: 44 (0) 151 231 4245

e-mail: j.e.fisk@livjm.ac.uk

Abstract

Rationale/Objectives: Recent theoretical models suggest that the central executive may not be a unified structure. The present study explored the nature of central executive deficits in ecstasy users. Methods: In Study One, 27 ecstasy users and 34 nonusers were assessed using tasks to tap memory updating (computation span; letter updating) and access to long-term memory (a semantic fluency test and the Chicago word fluency test). In Study Two, 51 ecstasy users and 42 nonusers completed tasks that assess mental set switching (number/letter and plus/minus) and inhibition (random letter generation). Results: MANOVA revealed that ecstasy users performed worse on both tasks used to assess memory updating, and on tasks to assess access to long-term memory (C- and S-letter fluency). However, notwithstanding the significant ecstasy-group related effects, indices of cocaine and cannabis use were also significantly correlated with most of the executive measures. Unexpectedly, in Study Two, ecstasy users performed significantly better on the inhibition task producing more letters than nonusers. No group differences were observed on the switching tasks. Correlations between indices of ecstasy use and number of letters produced were significant. Conclusions: The present study provides further support for ecstasy/polydrug related deficits in memory updating and in access to long-term memory. The surplus evident on the inhibition task should be treated with some caution as this was limited to a single measure and has not been supported by our previous work.

Keywords: ecstasy, MDMA, cannabis, cocaine, memory updating, switching, inhibition, executive function.

Introduction

The increasing popularity of the recreational drug ecstasy (MDMA) is of much concern. The drug elicits pharmacological effects through the release of serotonin (among other neurotransmitters) in the brain (McDowell & Kleber, 1994) and has a strong neurotoxic potential on serotonergic terminals in animals (Ricaurte et al, 1992, 2000), which may also occur in humans (Bolla et al, 1998; Klugman et al, 1999; Reneman et al, 2001). Thus, it may follow that these serotonergic depletions manifest themselves as disturbances in mood (e.g. Curran and Travill, 1997; Fox et al, 2001) and cognition (e.g. Bolla et al, 1998; Morgan, 1999; Wareing et al, 2000; Wareing et al, 2004a; Wareing et al, 2004b).

Cognitive deficits in ecstasy users are reported frequently over a wide range of tasks. The working memory system in general, and the executive system in particular appear to be affected. However, it remains unclear why ecstasy users may be impaired in some "executive function" tasks, and not others. Fox et al (2001) assessed the performance of a group of ecstasy users who reported experiencing cognitive deficits, and those who did not report such problems. Paradoxically, non-problem users were found to have significantly longer Tower of London (TOL) planning times than the problem users and the control group. Both ecstasy groups made significantly more errors than controls on a spatial working memory task, while higher use of ecstasy was associated with longer TOL planning times. Testing executive function and spatial working memory, Fox et al (2002) found that ecstasy users performed worse than controls on verbal fluency, spatial working memory, attention shifting and pattern recognition. Moving on to verbal working memory, Wareing, et al (2004a) found that previous and current users of ecstasy were impaired on a computation span task, requiring the concurrent processing and updating of information in working

memory. The main effect of ecstasy remained significant after control for the use of other drugs. However, no ecstasy related deficits were observed on the reading span task, which supposedly uses the same mechanism. Wareing, et al (2000) also found ecstasy users to be impaired in a random letter generation task, but no such effect was found in a subsequent study (Fisk et al, 2004). While the results of such studies suggest global working memory deficits in ecstasy users, some studies fail to find ecstasy related cognitive deficits. Turner, et al (1999) found that ecstasy users were unimpaired on the WCST (replicated by Fox et al, 2001), while Morgan et al, (2002) found ecstasy users to be unimpaired in word fluency, Stroop, and Subtracting Serial Sevens among other tests. Von Geusau et al. (2004) also found that ecstasy users were unimpaired on the stop signal reaction time task (believed to measures response inhibition).

Recent theoretical models of executive functioning postulate that the central executive is fractionated, with its different components performing separate tasks with varying degrees of competence. 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"), and how they contributed to executive tasks. Structural equation modelling revealed that the three executive functions were moderately correlated with each other, but clearly separate, and they contribute differently to performance on various executive prefrontal tasks. 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.

Furthermore, utilising Miyake et al's conceptualisation, we have suggested in previous studies that it is the updating component of working memory, and not the shifting and inhibition elements that are most susceptible to the effects of ecstasy (Montgomery et al, 2004; Montgomery et al, 2005; Montgomery et al, in press; Wareing et al, 2004a). Consistent with this proposition, Verdejo-Garcia et al (2005) found that ecstasy use was an important contributory factor in deficits in working memory updating among a clinical sample of poly-substance abusers. Similarly research from our own laboratory demonstrates that ecstasy users are impaired on tasks such as computation span (Fisk et al 2004), which is also known to load on the updating executive function (Fisk & Sharp, 2004). Equally it appears that tests sensitive to the shifting and inhibition elements do not appear to be as consistently susceptible to the effects of ecstasy (e.g. Fisk et al, 2004; Fox et al, 2001; Fox et al, 2002; Godolphin & Parrot, 1999, cited in Parrot, 2000; Gouzoulis-Mayfrank et al, 2000; McCardle et al, 2004; Thomasius et al, 2003; but also see von Geusau et al 2004).

To date there has been no systematic investigation of whether or not ecstasy users are impaired in the different aspects of executive functioning identified by Miyake et al (2000). Existing research findings are piecemeal and have not always made use of the traditional measures of the different executive subcomponents identified by Miyake et al (2000). Therefore, the present study sought to ascertain the nature of executive function deficits in a sample of recreational ecstasy users. We aimed to use "pure" measures of each of the three postulated executive functions (updating, shifting and inhibition), and provide further clarification of the nature of executive deficits in ecstasy users. In a study of cognitive ageing, Fisk and Sharp (2004) provided further support for Miyake et al's model. Factor analysis revealed

that certain tasks loaded on each of the three components identified by Miyake et al, but there was also a distinct executive function loading on another factor, which Fisk and Sharp termed access to long-term memory (although age was not a significant predictor of performance on "access" tasks). Previous research has shown that ecstasy users exhibit deficits in word fluency, which is reliant on the executive function of access to long-term memory (Baddeley, 1996). However, this task also reveals equivocal results, with some studies finding ecstasy related deficits and others not (e.g. Bhattachary and Powell, 2001; Curran and Verheyden, 2003; Croft et al, 2001; Fox et al, 2002; Heffernan et al, 2001). Thus the present study also sought to further investigate word fluency deficits among ecstasy users. The verbal fluency task used here, the Chicago word fluency test, is an established measure of prefrontal executive functioning (Kolb & Whishaw, 1985). The test imposes longer time limits and places further constraints on the categories used, thereby increasing the potential load on executive resources.

Poorer performance in certain tasks may provide further support for frontal lobe impairments among ecstasy users. For example, while performance on a switching task has been linked to the anterior cingulate cortex (Posner and Raichle, 1994), the left frontal lobe (Rogers et al, 1998) and the bioccipital and parietal lobes (Moulden et al, 1998), performance on a response inhibition task has been linked to the pre-frontal cortex (Casey et al, 1997; Kiefer et al, 1998), and damage to the inferior frontal gyrus (Aron et al. 2003). Likewise, deficits in updating may support an MDMA related deficit in the dorsolateral prefrontal cortex (Goldman-Rakic, 1996) or the left fronto-polar cortex (Van-der-Linden et al, 1999).

We are aware that there are other postulated executive functions. The four we have picked to investigate are low-level behaviours that are easily operationally

defined, and easy to measure (unlike for example planning). It is also likely that other more complex executive tasks will rely on these functions.

Therefore, the present study sought to systematically investigate ecstasy related deficits in the shifting, inhibition, updating, and access to long-term memory elements of the central executive. Given the nature of ecstasy poly-drug use, it is possible that any observed deficits in cognitive functioning may be in part attributable to the concomitant use of "other" drugs (e.g. Croft et al. 2001). Indices of the frequency and intensity of other drug use will be collected and where possible, we shall attempt to evaluate the impact of these on the executive measures included in the present study.

It was calculated that data collection using all the appropriate measures would take a considerable amount of time per session. Therefore to counter boredom and fatigue effects the tasks were divided into two research studies, Study One to investigate updating and access to long-term memory, and Study Two to investigate switching and inhibition.

STUDY 1

Study 1 investigated the updating executive component process and access to long-term memory. It was predicted that ecstasy users would perform worse than non-users on measures of updating (a running memory task and computation span) and on access to long-term memory (a word fluency task). The letter-updating task is widely accepted as an established pure measure of the memory updating function. The task is a key indicator of Miyake et al's conceptual framework, and has not been used in research with ecstasy users before. Although word fluency has been assessed in

samples of ecstasy users (e.g. Bhattachary and Powell, 2001; Fox et al, 2002), the task used in the present study is more likely to recruit executive prefrontal resources as it is a longer version than previously used and places further constraints on the categories thus making it harder for participants. To our knowledge, this task has not been used in research with ecstasy users before.

Method

Design.

With regard to the updating executive component process, a multivariate design was used, with ecstasy user group (2 levels) as the between groups variable, and the updating measures (letter updating and computation span) as the dependent variables. (For the letter-updating task, a single composite measure was calculated following the procedure adopted by Fisk and Sharp, 2004). Letter span was also measured and incorporated into ANCOVA, to remove the mediating effects of differences in simple span. A multivariate design was used for the word fluency tasks, with ecstasy user group as the between participants independent variable, and the three word fluency scores (semantic, "S" letter, and C" letter) as the dependent variables.

Participants

Twenty-seven ecstasy users (mean age 21.70; 14 male) and 34 non-user controls (mean age 21.59; 10 male) completed the updating and word fluency tasks. Participants were recruited via direct approach to university students, and the snowball technique (Solowij et al, 1992). With 27 ecstasy users, the present sample is

sufficient to detect a difference of between 0.75 and 1σ for α = .05 and β =.20 (Hinkle et al, 1994). Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 5 weeks, median abstinence period 2 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing.

Materials

Patterns of drug use and other relevant lifestyle variables were investigated via means of a background questionnaire. The questionnaire gauged the use of ecstasy and other drugs, as well as age, years of education, general health and other relevant lifestyle variables. 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).

Sleep Quality: A screening questionnaire and the Epworth Sleepiness Scale (ESS, Johns, 1991) were used to investigate any group differences in sleep quality. The ESS is a measure of subjective daytime sleepiness and contains eight items, which a participant has to score on a scale of 0 (would never doze off in this situation) to 3 (high chance of dozing off in this situation). A total score of all eight items was used in the analysis, and a high score was indicative of increased subjective daytime

sleepiness. The screening questionnaire contained a number of questions on sleep quality, e.g. hours per night.

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.

Consonant Updating: This task was based on the running memory task (Morris and Jones, 1990). In this computer-based task, the participant was presented with a random sequence of between 6 and 12 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 six consonants in the order in which they were presented. The participant experienced six trials at each of the four list lengths: 6, 8, 10, and 12 items. The order in which the lists were presented was randomised. A single composite score of updating was calculated as in Fisk and Sharp (2004).

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.

Semantic Fluency: In the semantic fluency task, participants were required to recall as many animal names as they could think of. This could be different species, or breeds within species. Participants were given four minutes for this task.

Chicago Word Fluency Test. Participants were instructed not to write any place names, peoples name or plurals in this test. Firstly participants were given five minutes to write down as many words as they could, beginning with the letter "S". Secondly, they were given four minutes to write down as many four-letter words beginning with "C" as they could. As plurals were not allowed, words such as " cats", and repetitions of words were excluded. Scores for all three fluency tasks were the number of appropriate words in each case.

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, sleep questionnaires, NART, letter span, consonant updating, semantic fluency, word

fluency, and Raven's progressive matrices. 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 ethical guidelines of the British Psychological Society.

RESULTS

The scores for background measures are set out in Table 1. An initial t-test revealed that there were no significant differences between the groups in age, pre-morbid intelligence, sleep (hours per night), years of education, self-rated health or Raven's Progressive Matrices (although the latter approached significance, $p=0.06$). Ecstasy users did however report higher subjective daytime sleepiness, measured by the Epworth Sleepiness Scale, $t(58)= 2.06$, $p<.05$.

<<Insert Table 1 About Here>>

The main effect of ecstasy use on memory updating was statistically significant, $F(2,58)= 3.19$, $p<.05$ for Pillai's Trace. Separate univariate analyses revealed that this was due to ecstasy users performing worse than controls on both the letter updating ($F(1,59)=5.15$, $p<.05$) and computation span ($F(1,59)=3.21$, $p<.05$, one-tailed) tasks. The main effect of ecstasy use on word fluency was also significant, $F(3,57)=3.20$, $p<.05$, for Pillai's Trace. This was due to ecstasy users' poorer performance on the "S" letter, $F(1,59)=6.15$, $p<.05$, and the "C" letter categories, $F(1,59)=8.81$, $p< .005$. There were no significant differences between the groups on the semantic fluency task.

<<Insert Table 2 About Here>>

Inspection of Table 3 shows that the use of other drugs was limited mainly to the use of cannabis, alcohol, and tobacco among the non-ecstasy group. The ecstasy users had a lifetime dose of cannabis twice that of the non-users (2634 joints to 1317 joints), in addition to using it more frequently (2.57 times a week, compared to 0.95 times a week), having smoked more in the last 30 days (22.66 joints compared to 9.58 joints), and having a larger average weekly dose (10.17 joints compared to 6.40 joints). In relation to the cannabis measures, t-test revealed that the group difference was statistically significant only for frequency of use variable: $t(25.56) = 2.56$, $p<.05$ (As Levene's test was significant, degrees of freedom have been adjusted accordingly).

<<Insert Table 3 About Here>>

Correlations with Indices of Drug Use.

Due to the small number of illicit drug users among the non ecstasy user group it was not possible to control statistically for the effects of other drugs through the use of ANCOVA. Therefore it is possible that some or all of the ecstasy-related effects might have been attributable to the effects of other drugs. To address this possibility, correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of lifetime use of each drug, the number of times each drug was consumed each week, the amount of each drug consumed within the last 30 days, and the average weekly dose (i.e. total amount consumed divided by the length of use in weeks) were all included[1]. For each of these a value of zero was

entered for nonusers of the drug in question. In addition, for each illicit drug, a categorical variable in which users and nonusers of each drug were coded as 0 or 1 respectively was included.

A full Bonferroni correction is not appropriate in this case, as the performance measures are intercorrelated (Sankoh et al. 1997). However multiple comparisons remain potentially problematic, therefore an intermediate level of correction has been used, with correlations being evaluated at $p<.01$. The results, set out in Table 4, show that ecstasy use was significantly correlated with a number of the performance measures. Total ecstasy use, average dose of ecstasy and amount used in the last 30 days were significantly negatively correlated with "C" letter fluency (at $p<.01$), while amount used in the last 30 days was also negatively correlated with "S" letter fluency ($p<.01$). Finally, the categorical ecstasy user/nonuser variable was significantly positively correlated "C" letter fluency at $p<.01$.

In relation to other drugs, total cannabis use, frequency of use and average cannabis dose were significantly negatively correlated with computation span ($p<.01$), and cannabis user/nonuser was significantly positively correlated with computation span ($p<.01$). Indices of cocaine use were also significantly negatively correlated with task performance: Total use, frequency of use and average dose with "C" letter fluency (at $p<.01$), frequency of use with "S" letter fluency ($p<.01$), and the user/nonuser variable with "C" letter fluency at $p<.01$.

<<Insert Table 4 About Here>>

It is clear from the correlations that aspects of cocaine use may have contributed or possibly caused the observed ecstasy-related deficits in word fluency observed in the present study. To evaluate the potentially confounding effects of cocaine we performed several analyses with a categorical cocaine user/nonuser

independent variable, with those reporting that they had ever tried cocaine, N=25 versus those who reported that they had never tried cocaine, N=36, which would enable us to compare effect sizes for ecstasy versus cocaine analyses. Cocaine user/nonuser was non-significant for letter updating, $F(1,59) = .95$, $p>.05$, and computation span, $F(1,59) = 1.81$, $p>.05$. With reference to word fluency, the multivariate cocaine-related effect was significant, $F(3,57) = 3.72$, $p<.05$. Separate univariate analyses revealed that cocaine users performed significantly worse on the "S" and "C" letter fluency tasks, $F(1,59) = 5.77; 11.33$, $p<.05$ and $p<.001$ respectively. To try and compare cocaine and ecstasy group-related effects on word fluency, we compared the effect sizes for the two sets of analyses (as cocaine user/nonuser was non-significant for computation span and letter updating, and ecstasy user/nonuser was, effect sizes for these analyses are not reported). The multivariate effect size was larger for cocaine user than for ecstasy user (partial Eta squared of 0.164 and 0.144 respectively), as was the "C" letter effect size (partial Eta squared of 0.161 and 0.130 respectively), the effect size for "S" letter fluency was marginally larger for ecstasy (partial Eta squared of 0.094) than for cocaine (partial Eta squared of 0.089). This is consistent with either a cocaine-related word fluency deficit, or an exacerbated cocaine/ecstasy deficit in word fluency, although it is still likely that performance on the letter updating and computation span tasks are related to aspects of ecstasy use.

Covariate Analyses.

As ecstasy users scored significantly higher than non-ecstasy users on the ESS and group differences on the Raven's Progressive Matrices approached significance (indicating a more pathological sleep pattern and higher IQ respectively), ANCOVA was conducted to investigate the possible mediating effects of sleep and intelligence

on memory updating and word fluency. The multivariate effects of the ESS were non-significant ($p>.05$), however, the effects of fluid intelligence were highly significant: $F(2,55) = 7.58$, $p<.001$, for Pillai's Trace. The main effect of ecstasy use on memory updating was enhanced after removing the variance due to fluid intelligence: $F(2,55) = 6.37$, $p<.005$, for Pillai's Trace. Univariate analyses revealed that although fluid intelligence was significantly associated with both computation span and updating performance: $F(1,56) = 9.00; 9.46$, $p<.005$ respectively, the effects of ecstasy use on computation span and updating were heightened when variance due to fluid intelligence was removed: $F(1,56) = 6.05; 9.37$, $p<.05$ and .005 respectively. Homogeneity of regression was achieved with respect to both covariates, $p>.05$ for the group covariate interaction in both cases.

With reference to word fluency, ANCOVA with ESS and Raven's Progressive Matrices scores as covariates revealed that the multivariate effects of these variables were non-significant ($p>.05$ in both cases). The multivariate ecstasy effect remained significant after control for these covariates, $F(3,54) = 2.36$, $p<.05$ one-tailed, for Pillai's Trace. Univariate analyses revealed that the effects of ecstasy use on "S" and "C" word fluency remained significant after control for ESS and Raven's scores: $F(1,56) = 4.04; 7.21$, $p<.05, .01$ respectively. Again, homogeneity of regression was achieved with respect to both covariates, $p>.05$ for the group covariate interaction in both cases.

Although there were no significant group differences in letter span, it was possible that the effect of ecstasy use on the letter-updating task could in part be mediated by letter span. To address this possibility letter span was entered as a covariate. The effects of letter span fell just short of significance: $F(1,58) = 3.47$, $p=.068$. The main effect of ecstasy use on letter updating remained significant after

control for letter span, $F(1,58) = 5.10$, $p<.05$. Homogeneity of regression was achieved with respect to this covariate, $p>.05$ for the group covariate interaction.

Finally, as there was a gender imbalance between the two groups, ANCOVA was performed with gender as a covariate. Although the multivariate effect of gender was significant for updating, $F(2,57) = 3.25$, $p<.05$ for Pillai's Trace, the multivariate effect of ecstasy use remained significant for updating after control for gender, $F(2,57) = 4.96$, $p<.01$, for Pillai's Trace. Subsequent univariate analyses revealed that the effects of ecstasy use on letter updating and computation span also remained significant, $F(1,58) = 7.57; 5.03$, $p<.01; .05$ respectively. The multivariate effect of gender on word fluency was non-significant ($p>.05$) and the multivariate effect of ecstasy use on word fluency remained significant after control for gender, $F(3,56) = 3.11$, $p<.05$, for Pillai's Trace. The effects of ecstasy use on S- and C-letter fluency remained significant after control for gender, $F(1,58) = 6.39; 8.79$, $p<.01; .005$ respectively. Homogeneity of regression was achieved with respect to this covariate, $p>.05$ for the group covariate interaction.

Implications: Study 1 supports an ecstasy-related deficit in memory updating and access to long-term memory that is not related to gender, intelligence, amphetamine use, or sleep quality. However, it is possible that access to long-term memory (as indexed by the word fluency scores) is also sensitive to aspects of cocaine use. Indeed Table 4 reveals that among ecstasy users, in the majority of cases outcome measures were more related to aspects of cocaine use than they were to the equivalent indices of ecstasy use. With regard to the updating executive component process, contrary to expectations, indices of cannabis use appear to be related to performance on the computation span task. It is equally noteworthy that while MANOVA yielded significant ecstasy-related group differences, none of the measures of ecstasy use

were significantly correlated with computation span nor letter updating performance at the adjusted level of $\alpha = .01$.

STUDY 2

Study 2 assessed the shifting and inhibition components of the executive. Two tests which tap shifting were used (plus-minus task, and number/letter task). Consistent with previous research that suggests ecstasy users are not impaired in switching (e.g. Fox et al, 2001; Turner et al, 1999) it was expected that both groups would have similar shift-cost latencies, and that ecstasy users would not perform worse than non-users in these tasks. Inhibition was measured via the random letter generation task (Baddeley, 1996). Again consistent with previous research (Fisk et al 2004) it was expected that ecstasy users would not perform worse than non-users on the random generation task.

Method.

Design.

A multivariate design was used for the switching measures with ecstasy user group (2 levels) as the between participants independent variable, and the shift cost latencies (seconds) as the dependent measures. Miyake et al (2000) found that random number generation loaded on the inhibition and updating components of the executive system. We used random letter generation to measure inhibition, which is analogous to the random number generation task but which Fisk and Sharp (2004) maintain loads on inhibition but not on updating. For the random generation task, MANOVA

was used with ecstasy user group as the between participants variable, and the four random letter generation scores as the dependent measures.

Participants

Fifty-one ecstasy users (mean age 21.96, 27 male) and 42 nonuser controls (mean age 20.83, 9 male) were recruited via direct approach to university students, and the snowball technique (Solowij et al, 1992). With 42 nonuser controls, the present sample is sufficient to detect a difference of between 0.5 and 0.75 σ for α = .05 and β =.20 (Hinkle et al, 1994). Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 22 weeks, median abstinence period 4 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing. None of the participants were involved in the first study.

Materials

Background questionnaires, intelligence tests and sleep quality tests were used as in Study 1.

Plus-minus task. The plus-minus task, adapted from Miyake et al (2000) consists of three lists of 30 two-digit numbers (the numbers 10-99, randomised). On the first list, participants were instructed to add three to each number, and write their answer in the box next to it. On the second list, participants were instructed to subtract three from each number. On the third list, participants were required to alternately add and subtract three from the list (i.e. add three to the first number, subtract from the second, and so on). List completion times were measured with a stopwatch. The cost

of shifting between adding and subtracting was calculated as the difference between the time for list three and the average of the times for lists one and two.

Number-Letter task. In the number-letter task, adapted from Rogers and Monsell (1995) and Miyake et al (2000), a number letter pair (e.g.D4) is presented in one of four quadrants on a computer screen. If the target is in the top half of the screen, the task is to indicate if the letter is a vowel (A, E, I, O or U) or a consonant. If the target is in the bottom half of the screen, the task is to indicate if the number is odd or even. The practise version of the task comprises three sets. The target is presented in the top half of the screen for 12 trials, then the bottom half for 12 trials, and then in a clockwise rotation around all 4 quadrants for a further 12 trials. The main task follows the same structure, except there are 64 targets in each block. Therefore, the trials in the first two blocks required no switching, while the third set did. The shift-cost was the difference between the average reaction times of the third block and the averages of the first two blocks.

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 alphabetical sequences, and to try to speak each letter with the same overall frequency. 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. The test yields four 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; third, a "redundancy" score, which measures the extent to which all 26 letters of the

alphabet are produced equally often (0% being truly random); and fourth, the number of letters produced. In the first three cases, higher scores indicate poor performance; in the fourth the opposite is the case. The scores for each separate variable, at each of the three generation rates, were standardised. A single score for each random generation measure was produced by averaging the standardised scores for the three production rates.

Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tasks 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, sleep quality questionnaires, NART, random letter generation, plus-minus task, number-letter task, and Raven's progressive matrices. 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 ethical guidelines of the British Psychological Society.

RESULTS/DISCUSSION

The scores for background variables are set out in Table 5. An initial t-test revealed that there were no significant differences between the groups in age, pre-morbid intelligence, Raven's Progressive Matrices, the Epworth Sleepiness Scale, sleep (hours per night), years of education, or self-rated health, so these are not discussed any further.

<<Insert Table 5 About Here>>

Contrary to expectations, the main effect of ecstasy on inhibition was statistically significant, $F(4,88) = 2.63$, $p<.05$ for Pillai's Trace. Separate univariate analyses revealed that this was due to ecstasy users producing more letters than non-users, $F(1,91)= 8.29$, $p<.005$. There were no differences between the groups on the other random letter generation scores of alphabetic sequences, repeat sequences and redundancy, $F < 1$ in all cases. The main effect of ecstasy use on switching was also non-significant, $F < 1$ for Pillai's Trace. Separate univariate analyses revealed that there were no significant between group differences in performance on the plus/minus task or the number letter task, $F < 1$ in both cases.

<<Insert Table 6 About Here>>

Inspection of Table 7 shows that the use of other drugs among the non-ecstasy group was limited mainly to the use of cannabis, alcohol, and tobacco. The ecstasy users had a lifetime dose of cannabis many times that of the non-users (3544 joints to 368 joints), in addition to using it more frequently (2.78 times a week, compared to 0.94 times a week), having smoked more in the last 30 days (41.14 joints compared to 17.29 joints), and having a larger average weekly dose (9.10 joints compared to 1.91 joints). A t-test revealed that all these differences between the groups except amount used in the last 30 days were statistically significant: $t(43.40; 40.80; 50.79) = 4.42; 3.27; 3.65$, $p<.005$, for total, frequency and average dose respectively. (As Levene's test was significant, degrees of freedom have been adjusted accordingly).

<<Insert Table 7 About Here>>

Correlations with Indices of Drug Use.

There was no evidence of any ecstasy-related deficit on the inhibition and switching measures, although it is possible that other illicit drugs might exert an influence. To address this possibility, correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of lifetime use of each drug, the number of times each drug was consumed each week, the amount of each drug consumed within the last 30 days, and the average weekly dose (i.e. total amount consumed divided by the length of use in weeks) were all included[2]. For each of these a value of zero was entered for nonusers of the drug in question. In addition, for each illicit drug, a categorical variable in which users and nonusers of each drug were coded as 0 or 1 respectively was included.

As in study 1, a full Bonferroni correction is not appropriate in this case, as the performance measures are intercorrelated (Sankoh et al. 1997). However multiple comparisons remain potentially problematic, therefore an intermediate level of correction has been used, with correlations being evaluated at $p<.01$. The results are set out in Table 8. Frequency of ecstasy use, average dose of ecstasy, and amount used in the last 30 days were significantly correlated with the number of letters produced ($p<.01$) . In all cases, increased ecstasy use was associated with more letters produced. No correlations with indices of other drug use were significant at $p<.01$.

<<Insert Table 8 About Here>>

Thus to summarize, the results of Study 2 suggest that ecstasy-related group differences are not apparent in task switching. Ecstasy users did however produce significantly more letters on the inhibition task, although there were no group

differences on the three other inhibition measures. This finding is not supported by previous research and should thus be treated with caution.

GENERAL DISCUSSION.

In the present paper, the conceptual framework of Miyake et al (2000) was used to assess executive function deficits in ecstasy users. The results demonstrate ecstasy/polydrug-group related deficits in memory updating and access to semantic memory. The ecstasy/polydrug users reached a lower level on the computation span task, and recalled fewer letters correctly on the letter-updating task. Ecstasy/polydrug users scored higher on an intelligence test and significantly higher on a sleep questionnaire, but the main effect of ecstasy/polydrug use remained significant after control for these covariates. Contrary to expectations ecstasy/polydrug users actually performed better than controls on the random letter generation task (used to measure inhibition), due to them producing more letters. There were no significant ecstasy/polydrug-related effects on the tasks used to measure switching. Thus the results of Studies 1 and 2 provide further support for ecstasy/polydrug-related deficits in memory updating (Montgomery et al, 2004; Verdejo-Garcia et al, 2005; Wareing et al, 2004a), and access to semantic memory, but not shifting (in contrast with von Geusau et al's 2004 findings) or inhibition.

The unanticipated effects of ecstasy on inhibition were due to ecstasy users producing more letters. However this should not be taken as evidence of an ecstasy related surplus since the three other measures of random letter generation: alphabetic and repeat sequences, and redundancy, failed to produce ecstasy group-related differences. Furthermore, other studies from our laboratory have not generated group-related differences in the random generation measures (Fisk et al, 2004).

With regard to the word fluency measures, there were no ecstasy/polydrug-related deficits on the semantic fluency category, and in addition, there were no significant correlations between the use of any drugs and semantic fluency. Ecstasy/polydrug users performed worse on the S- and C-letter categories (consistent with the results obtained by Bhattachary and Powell, 2001; Fox et al, 2002; and Heffernan et al, 2001). The deficit was more pronounced on the C-letter category. This may be because the further constraints (i.e. having to give four-letter words beginning with C) increase executive involvement, therefore making it more difficult. So, while ecstasy/polydrug users did not perform worse on the Semantic category (as this was relatively straightforward), performance declined as more rules were imposed on the categories. This finding suggests that ecstasy/polydrug group-related deficits are apparent in tasks that place greater demands on the central executive versus those where demands are relatively low. Poor performance on the word fluency task could represent a metacognitive deficit in ecstasy/polydrug users, whereby having no preestablished schema to achieve a particular goal in a novel situation such as this, they fail to select an appropriate strategy to solve the problem or find it difficult to monitor their performance and avoid breaking the rules (Ruff et al, 1997). The word fluency task used in the present study imposed a longer limit compared to the verbal fluency tasks used in other studies (e.g. Fox et al, 2002). Therefore it is possible that the impaired fluency may relate to attentional deficits (with ecstasy/polydrug users failing to maintain attention during this longer version e.g. Jacobsen et al, 2003; McCardle et al, 2004).

While the ecstasy/polydrug group were clearly impaired in access to semantic memory (as measured by the word fluency scores) it is difficult to attribute this deficit solely to ecstasy use. Indeed there is evidence that other drugs might play a key role.

Apart from ecstasy, aspects of cocaine use were also significantly associated with word fluency performance. Indeed it may be that the word fluency effects were a product of polydrug use. More specifically, since all of the cocaine users also used ecstasy it remains possible that the correlations observed relate to the joint use of the two substances. Equally while the present study suggests that there is a relationship between cocaine use and word fluency performance, this has only been demonstrated among ecstasy users. It remains to be seen whether the same pattern of associations apply among non-ecstasy users. Evidence of cocaine-related deficits in word fluency has been forthcoming (e.g. Strickland et al. 1993) and in view of the present findings an attempt to disentangle the relative effects of ecstasy and cocaine on this aspect of executive functioning would be an important area for future research.

The level of other drug use among ecstasy users also made interpretation of the memory updating results difficult. While the MANOVA and ANOVA analyses yielded significant group-related differences, surprisingly, none of the correlations between indices of ecstasy use and the updating measures were statistically significant at the corrected significance level $\alpha = .01$. Furthermore, measures of cannabis use rather than equivalent ecstasy use measures seem to be important predictors of computation span performance. While the significant relationship between computation span and aspects of cannabis use in consistent with cannabis related effects reported elsewhere (e.g., Croft et al, 2001) this finding should be treated with some caution as Fisk et al (2004) found that ecstasy-group related deficits in computation span remained statistically significant following control for various measures of cannabis (and other drug) use. Interestingly in contrast to the negative relationship between aspects of cocaine use and word fluency performance, measures

of cocaine use were not significantly correlated with letter updating and computation span performance.

It has been suggested that ecstasy related cognitive deficits may be due to the fact that ecstasy users get less sleep (e.g. Cole et al, 2002b). In the present study, there were no group differences in self-reported hours of sleep per night. There were significant differences on the Epworth Sleepiness Scale, with ecstasy/polydrug users scoring higher than nonusers (indicating that they were more likely to doze off during the day). However, ANCOVA with this as a covariate left the main effect of ecstasy/polydrug use on memory updating and semantic fluency significant, suggesting that cognitive deficits in ecstasy/polydrug users are not mediated by differences in sleep quality. Although all participants were recruited from the university population, the ecstasy/polydrug -related group differences in Raven's Progressive Matrices scores approached significance in Study 1, indicating that they have a higher IQ than nonusers. Controlling for differences in IQ increased the ecstasy-related deficits in updating and word fluency, suggesting that studies in which IQ has not been assessed may potentially underestimate the cognitive deficits (e.g. von Geusau et al, 2004). Although there was a gender imbalance between the user and nonuser groups, all significant main effects remained significant after control for gender. This suggests that in the present study, gender was not a significant contributory factor to cognitive impairment, and therefore contradicts some previous research findings (e.g. McCann et al, 1994; Liechti et al, 2001; Reneman et al, 2001; von Geusau et al, 2004).

The focus of the present study was intended to be ecstasy use. However, a number of other illicit drugs consumed by the participants tested here appear to have produced effects on the measures that were administered. How might these effects be

explained? As research has shown that concomitant use of amphetamine by ecstasy users reduces the density of nigrostriatal dopamine neurones (Reneman et al, 2002), it is possible that the apparent cocaine effects in the present study may relate to the exacerbatory effects cocaine also has on the dopamine system, in ecstasy users. Unfortunately, as 21 out of 27 ecstasy users had tried cocaine, with 14 of these able to estimate their lifetime usage (compared to 4 and 0 in the non ecstasy group) the degree of overlap was such that it was not possible to state definitively whether the significant relationships that were observed were due to cocaine use or to the combined effects of cocaine and ecstasy.

In Study 2, frequency of ecstasy use, average ecstasy dose, amount used in the last 30 days and the ecstasy user/non-user variable were significantly correlated with the number of letters produced. However, while this outcome cannot be ignored, it is noteworthy that none of the other random generation measures were significantly correlated with aspects of ecstasy use. Correlations between number of letters produced and other drugs were non significant.

Thus combining the results of Studies 1 and 2, it is possible that while ecstasy/cannabis related deficits are apparent in memory updating, and deficits in access to semantic memory are a product of cocaine use, ecstasy use or a combination of the two, the other executive components may be not be susceptible to the effects of ecstasy/polydrug use.

It is known that MDMA affects both serotonergic and dopaminergic systems (e.g. Kish et al, 2002), while cocaine may affect dopaminergic networks (Volkow et al. 2001) and cannabis the dopaminergic system (through interaction between the endocannabinoid and dopaminergic system, Ng Cheong Ton & Gardner 1986; Giuffrida et al. 1999). Thus this data is consistent with functional neuroimaging

studies indicating that ecstasy/polydrug-related neurotransmitter changes may be concentrated in the dorsolateral and parietal regions of the prefrontal cortex (Cohen et al, 1996), and in addition may give rise to significantly lower grey matter concentrations in multiple brain regions (bilateral BA 18 and cerebellum, left BA 21 and left BA 45, as well as the midline brainstem; Cowan et al. 2003). 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 (Van-der-Linden et al, 1999). Lesion studies have also implicated the left dorsolateral prefrontal cortex in impaired letter and category-based fluency (Stuss et al, 1998) and in impaired fluency among children (Levine et al, 2001). So it is likely that the deficits observed in the present study reflect reduced serotonergic/dopaminergic functioning in the prefrontal cortex. Although outside the scope of this study, it is possible that while ecstasy may affect memory updating and access through serotonergic depletions in the dorsolateral and parietal prefrontal regions (Cohen et al, 1996), cannabis may affect hippocampal areas resulting in deficits in short-term memory (e.g. Solowij et al, 1992; Solowij et al, 2002). Therefore, future research should concentrate on investigating the differential effects of each recreational drug on the different cognitive functions.

As with most studies in this area, there are a number of limitations. Due to the quasi-experimental design of the study, it is possible that the groups in each study may have differed on some variable other than ecstasy use. Some possibilities have been excluded such as intelligence (NART and Raven's) and aspects of sleep quality. Clearly there were differences in the use of other illicit drugs. Group differences in other variables such as general health, nutrition, or some premorbid condition predating drug use (Verheul, 2001) cannot be ruled out; neither could we guarantee

the purity of the tablets consumed by the ecstasy users in the present studies (Cole et al, 2002a); though in a recent review of the literature, Parrot (2004) reports that analysis of the contents of ecstasy tablets from amnesty bins in nightclubs revealed that purity of tablets is approaching 100% MDMA. 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; Morgan, 1999; Rodgers, 2000). All participants reported being drug free for at least 7 days (mean abstinence period was actually over 5 weeks for both groups, median abstinence period over 2 weeks), and we have no reason to believe this information to be false (participants were not informed that they would be excluded prior to testing). Due to the unreliable nature of our sample, it was not possible to test all of the participants in Study 1 and 2 on measures to assess all four target executive functions. However, the samples were matched for age and intelligence, so we have no reason to believe that the results would be different had we used one group. The mean abstinence period was also longer for Study 2 than Study 1 (22 weeks compared to 5 weeks), but as the period of ecstasy intoxication should have long passed (and the median period was over 2 weeks in both studies), and serotonin levels risen again, we did not think that this was an important factor.

The present studies provide further support for recent theoretical models of executive functioning suggesting that the central executive may not be a unified structure (e.g. Baddeley, 1996; Lehto et al, 1996 Miyake et al, 2000). Using a range of executive tasks to assess each of the four components, this study found that the effects of ecstasy/polydrug use on executive functions are not uniform, with ecstasy/polydrug users performing worse on the updating and access tasks, but not the shifting and

inhibition tasks which appear to be relatively unaffected by recreational ecstasy/polydrug use. This study highlights the importance of a multi-component approach to executive functions, not only in drug-related research, but in other neuropsychological testing populations, and is in line with other studies that provide support for the validity of this fragmented approach to executive functions (e.g. Fisk and Sharp, 2004).

In conclusion, the findings presented here suggest that cognitive impairments in ecstasy users may also be related to the concomitant use of other drugs. By way of summary ecstasy-related deficits in memory updating and access to semantic memory are apparent, although both also seem to be related to aspects of cannabis and cocaine use respectively. The study highlights the importance of a multicomponent approach to executive processes in samples of drug-users.

References.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003) Stop-signal inhibition disrupted by damage to the right inferior frontal gyrus in humans. Nature Neuroscience 6: 115-6

Baddeley AD (1996) Exploring the central executive. Quarterly Journal of Experimental Psychology 49A: 5-28

Bhattachary S, Powell JH (2001) Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or "ecstasy": Evidence for cognitive impairment. Psychological Medicine 31: 647-658

Bolla KI, McCann UD, Ricaurte GA (1998) Memory impairment in abstinent MDMA ("ecstasy") users. Neurology 51: 1532-1537

Bolla KI, Funderburk FR, Cadet JL (2000) Differential effects of cocaine and cocaine + alcohol on neurocognitive performance. Neurology 54: 2285–2292

Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, Castellanos FX, Haxby JV, Noll DC, Forman SD, Dahl RE, Rapoport JL (1997) A developmental functional MRI study of prefrontal activation during performance of a go/no-go task. Journal of Cognitive Neuroscience 9: 835-847

Cohen Z, Bonvento G, Lacombe P, Hamel E (1996) Serotonin in the regulation of brain microcirculation. Progress in Neurobiology 50: 335-362

Cole J, Bailey M, Sumnall HR, Wagstaff GF, King LA (2002a) The content of ecstasy tablets: Implications for the study of their long-term effects. Addiction 97: 1531-1536

Cole J, Sumnall H, Grob C (2002b) Sorted: Ecstasy facts and fiction. The Psychologist 15(9): 464-467

Cowan RL, Lyoo IK, Sung SM, Ahn KH, Kim MJ, Hwang J, Haga E, Vimal RLP, Lukas SE, Renshaw PF (2003) Reduced cortical gray matter density in human MDMA (ecstasy) users: a voxel-based morphometry study. Drug and Alcohol Dependence 72: 225-235

Croft RJ, Mackay AJ, Mills ATD, Gruzelier JGH (2001) The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology 153: 373-379

Curran HV, Travill RA (1997) Mood and cognitive deficits of 3,4-methylenedioxymethamphetamine (MDMA "ecstasy"): Weekend "high" followed by mid-week low. Addiction 92: 821.831

Curran HV, Verheyden SL (2003) Altered response to tryptophan supplementation after long-term abstention from MDMA (ecstasy) is highly correlated with human memory function. Psychopharmacology 169(1): 91-103

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. American Journal of Psychiatry 159: 1642–1652

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behaviour in humans. Drug and Alcohol Dependence 67: 157–167

Fisk JE, Montgomery C, Murphy P, Wareing M (2004) Evidence of executive deficits among users of MDMA (Ecstasy). British Journal of Psychology 95: 457-466

Fisk JE, Sharp C (2004) Age-related impairment in executive functioning: Updating, inhibition, shifting, and access. Journal of Clinical and Experimental Neuropsychology 26:

Fisk JE, Warr P (1996) Age and Working memory: the role of perceptual speed, the Central Executive and the phonological loop. Psychology and Ageing 11(2):

316-323

Fox HC, Parrot AC, Turner JJD (2001) Ecstasy use: cognitive deficits related to dosage rather than self reported problematic use of the drug. Journal of Psychopharmacology 15: 273-281

Fox HC, McLean A, Turner JJD, Parrott AC, Rogers R, Sahakian BJ (2002) Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. Psychopharmacology 162: 203-214

Giuffrida A, Parsons LH, Kerr TM, Rodriguez de Fonesca F, Navarro M, Piomelli D (1999) Dopamine activation of endogeneous cannabinoid signalling in the dorsal striatum. Nature Neuroscience 2:358-363

Goldman-Rakic PS (1996) The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. Philosophical Transactions of the Royal Society of London 351: 1445-1453

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HK, Fimm B, Sass H (2000) Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). Journal of Neurology, Neurosurgery and Psychiatry 68: 719-725

Heffernan TM, Jarvis H, Rodgers J, Scholey AB, Ling J (2001) Prospective memory, everyday cognitive failure and central executive function in recreational users of Ecstasy. Hum Psychopharm Clin Exp 16 (8): 607-612

Hinkle DE, Wiersma W, Jurs SG (1994) Applied Statistics for the Behavioral Sciences (3rd ed.). Boston MA: Houghton Mifflin Company

Jacobsen LK, Mencl WE, Pugh KR, Skudlarski P, Krystal JH (2003) Preliminary evidence of hippocampal dysfunction in adolescent MDMA ('ecstasy') users:

possible relationship to neurotoxic effects. Psychopharmacology 173: 383-390

Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14: 540–545

Kish SJ (2002) How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? Pharmacology, Biochemistry and Behaviour 71: 845-855

Kiefer M, Marzinzik F, Weisbrod M, Scherg M, Spitzer M (1998) The time course of brain activations during response inhibition: evidence from event-related potentials in a go/no-go task. Neuroreport 9: 765-770

Klugman A, Hardy S, Baldeweg T, Gruzelier J (1999) Toxic effect of MDMA on brain serotonin neurons. Lancet 353: 1269-1270

Kolb B, Whishaw IQ (1985) Fundamentals of Human Neuropsychology (2nd Ed). New York NY: WH Freeman & Co

Lawton-Craddock A, Nixon SJ, Tivis R (2003) Cognitive efficiency in stimulant abusers with and without alcohol dependence, Alcohol Clin. Exp. Res. 27(3): 457–464

Lehto J (1996) Are executive function tests dependent on working memory capacity? Quarterly Journal of Experimental Psychology 49(A): 29-50

Levin HS, Song J, Ewing-Cobbs L, Chapman SB, Mendelsohn D (2001) Word fluency in relation to severity of closed head injury, associated frontal brain lesions, and age at injury in children. Neuropsychologia 39(2): 122-131

Liechti ME, Gamma A, Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. Psychopharmacology 154: 161-168

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin Neurotoxicity after 3,4- Methylenedioxymethamphetamine (MDMA; ecstasy): a controlled study in humans. Neuropsychopharmacology 10: 129-138

McCardle K, Luebbers S, Carter JD, Croft RJ, Stough C (2004) Chronic MDMA (ecstasy) use, cognition and mood. Psychopharmacology 173(3-4): 434-9

McDowell DM, Kleber HD (1994) MDMA: Its history and pharmacology. Psychiatric Annals 24: 127-130

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD (2000) The unity and Diversity of executive functions, and their contributions to complex "frontal lobe" tasks: A latent variable analysis. Cognitive Psychology 41(1): 49-100

Montgomery C, Fisk JE, Newcombe R (2004) Further evidence for deficits in the updating executive component process of working memory in users of MDMA (Ecstasy). Proceedings of the British Psychological Society 12: 70

Montgomery C, Fisk JE, Newcombe R (in press) The Nature of Ecstasy-group related differences in Associative learning. Psychopharmacology

Montgomery C, Fisk JE, Newcombe R, Wareing M, Murphy PN (2005) Syllogistic reasoning performance in MDMA (ecstasy) users. Experimental and Clinical Psychopharmacology, 13.

Morgan MJ (1998) Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19: 252-264

Morgan MJ (1999) Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 141: 30-36

Morgan MJ (2000) Ecstasy (MDMA): A review of its possible persistent psychological effects. Psychopharmacology 152: 230-248

Morgan MJ, McFie L, Fleetwood LH, Robinson JA (2002) Ecstasy (MDMA): Are the psychological problems associated with it's use reversed by prolonged abstinence? Psychopharmacology 159: 294-303

Morris N, Jones DM (1990) Memory updating in working memory: The role of the central executive. British Journal of Psychology 81: 111–121

Moulden DJA, Picton TW, Meiran N, Stuss DT, Riera JJ, Valdes-Sosa P (1998) Event-Related Potentials when switching attention between task-sets. Brain and Cognition 37: 186-190

Nelson HE (1982) National Adult Reading Test (NART) Test Manual. Windsor, Berkshire, UK: NFER-Nelson

Ng Cheong Ton JM, Gardner EL (1986) Effects of delta-9-tetrahydrocannabinol on dopamine release in the brain: intracranialmicrodialysis experiments. Social Neuroscience Abstracts 13:135

Ornstein TJ, Iddon JL, Baldacchino AM, Sahakian BJ, London M, Everitt BJ, Robbins TW (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 23: 113–126

Parrott AC (2000) Human Research on MDMA (3,4-Methylene-dioxymethamphetamine) Neurotoxicity: Cognitive and Behavioural Indices of Change. Neuropsychobiology 42: 17-24

Parrot AC (2004) Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. Psychopharmacology (Berl) 173(3-4): 234-41

Posner MI, Raichle ME (1994) Images of Mind. New York, Sci. Am

Raven J, Raven JC, Court JH (1998) Manual for Raven's Progressive Matrices and Vocabulary Scales. Oxford, UK: Oxford Psychologists Press

Reneman L, Majoie CBLM, Schmand B, van den Brink W, den Heeten GJ (2001) Pre-frontal N-acetylaspartate is strongly associated with memory performance in (abstinent) Ecstasy users: Preliminary report. Biological Psychiatry 50: 550-554

Reneman L, Booij J, Lavalaye J, de Bruin K, Reitsma JB, Gunning BW, den Heeten, GJ, van der Brink W (2002) Use of amphetamine by recreational users of ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: A [123I]beta-CIT SPECT study-preliminary report. Psychopharmacology (Berl) 159: 335–340

Ricaurte GA, McCann UD (1992) Neurotoxic amphetamine analogues: effects in monkeys and implications for humans. Annals New York Academy of Sciences 648: 371-382

Ricaurte GA, Yuan J, McCann UD (2000) (+/-)3,4-Methylenedioxymethamphetamine (`Ecstasy')-Induced Serotonin Neurotoxicity: Studies in Animals. Neuropsychobiology 42(1): 5-10

Rodgers J (2000) Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology 151: 19-24

Rogers RD, Monsell S (1995) Costs of a predictable Shift between simple cognitive tasks. Journal of Experimental Psychology: General 124: 207-231

Rogers RD, Sahakian BJ, Hodges JR, Polkey CE, Kennard C, Robbins TW (1998) Dissociating executive mechanisms of task control following frontal lobe damage and parkinson's disease. Brain 121: 815-842

Roselli M, Ardila A (1996) Cognitive effects of cocaine and polydrug abuse. Journal of Clinical and Experimental Neuropsychology 18: 122–135

Ruff RM, Light RH, Parker SB, Levin HS (1997) The psychological construct of word fluency. Brain and Language 57: 394-405

Salthouse TA, Babcock RL (1991) Decomposing adult age differences in working memory. Developmental Psychology 27: 763-776

Sankoh AJ, Huque MF, Dubey SD (1997) Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Statistics in Medicine 16: 2529-42

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug. Br J Addict 87(8): 1161-72

Solowij N, Stephens RS, Roffman RA, Kadden T, Miller R, Christiansen M, McRee K, Vendetti B (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. J. Am. Med. Assoc. 287: 1123–1131

Strickland TL, Mena I, Villanueva-Meyer J, Miller BL, Cummings J, Mehringer CM, Satz P, Myers H (1993) Cerebral perfusion and neuropsychological consequences of chronic cocaine use. Journal of Neuropsychiatry and Clinical Neuroscience 5(4): 419-427

Stuss DT, Alexander MP, Hamer L, Palumbo C, Dempster R, Binns M, Levine B, Izukava D (1998) The effects of focal anterior and posterior brain lesions on verbal fluency. Journal of International Neuropsychol Soc 4: 265-78

Thomasius R, Petersen K, Buchert R, Andersen B, Zapletalova P, Wartberg L, Nebeling B, Schmoldt A (2003) Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. Psychopharmacology 167(1): 85-96

Turner JJD, Godolphin M, Parrot AC (1999) Cognitive Performance Profiles of current and former "ecstasy" (MDMA) users. Journal of Psychopharmacology 13: A24

Van der Linden M, Collette F, Salmon E, Delfiore G, Delgueldre C, Luxen A, Franck G (1999) The neural correlates of updating information in verbal working memory. Memory 7: 549-560

Verdejo-Garcia AJ, Lopez-Torrecillas F, de Arcos AF, Perez-Garcia M (2005) Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance abusers: A multiple regression analysis. Addictive Behaviours 30: 89-101

Verheul R (2001) Co-morbidity of personality disorders in individuals with substance use disorders. European Psychiatry 16: 274-282

Von Geusau NA, Stalenhoef P, Huizinga M, Snel J, Ridderinkhof KR (2004) Impaired executive function in male MDMA ("ecstasy") users. Psychopharmacology 175: 331-341

Verkes RJ, Gijsman HJ, Pieters MSM, Schoemaker RC, Visser S, Kuijpers M et al (2001) Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology 153: 196-202

Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D et al. (2001) Association of Dopamine transporter reduction with psychomotor

impairment in methamphetamine abusers. American Journal of Psychiatry 158:377-382

Wareing M, Fisk JE, Murphy P (2000) Working memory deficits in current and previous users of MDMA (“ecstasy”). British Journal of Psychology 91: 181-188

Wareing M, Fisk JE, Murphy P, Montgomery C (2004a) Verbal working memory deficits in current and previous users of MDMA. Human Psychopharmacology: Clinical and Experimental 19: 225-234

Wareing M, Murphy P, Fisk JE (2004b) Visuospatial memory impairments in users of MDMA ('ecstasy'). Psychopharmacology 173: 391-397

Table 1

Age, Years of Education, Intelligence and Sleep Quality for Ecstasy Users and Nonusers in Study 1.

	Ecstasy users		Non Ecstasy Users	
	Mean	S.D.	Mean	S.D.
Age (years)	21.70	1.66	21.59	1.88
Years of Education	16.04	1.45	15.68	2.11
Raven's Progressive Matrices (maximum 60)	50.37	3.84	48.08	5.08
NART (maximum 50)	29.93	6.23	30.32	6.25
Hours Sleep per night	8.04	1.64	7.93	1.47
Epworth Sleep Scale (Maximum 24)	6.88	3.34	5.32	2.52
Self Report Health*	3.74	0.81	3.94	0.89
Letter Span Score	5.22	0.58	5.26	0.75
Weeks Since Last Used Ecstasy	4.97	7.27	-	-

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Table 2

Significance Levels (F values) For Main Effects in Study 1.

	Ecstasy Users		Non Ecstasy Users		F
	Mean	S.D.	Mean	S.D.	
Updating	2.14	0.50	2.45	0.54	5.16**
Computation Span	3.85	1.63	4.50	1.19	3.22*
Semantic Fluency	40.59	9.03	41.94	10.11	0.29
"S" Letter	40.19	10.86	46.85	10.07	6.15**
"C" Letter	11.48	5.37	16.00	6.30	8.81***

* $p<.05$, one-tailed
** $p<.05$, two-tailed
*** $p<.01$, two-tailed

Table 3.

Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users in Study 1.

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	n	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	345.96	365.76	27	-	-	-
Amphetamine (grams)	4.08	4.22	6	4	-	1
Cannabis (joints)	2634.18	2501.21	19	1317.41	1547.50	14
Cocaine (grams)	19.59	23.64	12	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.44	0.36	27	-	-	-
Amphetamine	0.03	0.03	3	-	-	-
Cannabis	2.57	2.58	20	0.96	0.94	14
Cocaine	0.32	0.23	12	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	3.12	3.11	26	-	-	-
Amphetamine (grams)	2	3.46	3	-	-	-
Cannabis (joints)	22.66	36.04	19	9.58	11.66	13
Cocaine (grams)	1.68	1.83	10	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	1.8	1.37	27	-	-	-
Amphetamine (grams)	0.12	0.23	6	0.01	-	1
Cannabis (joints)	10.17	9.19	18	6.40	11.00	14
Cocaine (grams)	0.16	0.26	12	-	-	-
Number Ever Used						
Amphetamine	12	-	-	1	-	-
Cannabis	22	-	-	18	-	-
Cocaine	21	-	-	4	-	-

Table 4.

Correlations between Measures and Indices of Drug Use: Study 1.

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total use	**N**	61	51	48	55
Updating		-.199	-.234	-.287	.034
Computation span		-.161	-.410*	-.093	.128
Semantic Fluency		-.075	-.045	-.194	.132
"S" letter		-.326	-.208	-.365	.205
"C" letter		-.351*	-.261	-.510*	.109
Frequency of Use	**N**	61	52	48	51
Updating		-.253	-.194	-.310	-.050
Computation span		-.168	-.398*	-.027	.023
Semantic Fluency		-.045	-.029	-.231	.139
"S" letter		-.274	-.182	-.389*	.049
"C" letter		-.313	-.226	-.465*	.029
Average dose	**N**	61	50	48	54
Updating		-.230	-.196	-.276	-.026
Computation span		-.151	-.401*	-.092	.146
Semantic Fluency		-.028	.002	-.180	.081
"S" letter		-.317	-.175	-.351	.154
"C" letter		-.347*	-.204	-.505*	.087
Current Use	**N**	61	61	61	61
Updating		-.171	-.049	-.197	.015
Computation span		-.168	-.281	-.027	-.034
Semantic Fluency		-.018	-.079	-.246	.037
"S" letter		-.330*	-.139	-.271	-.066
"C" letter		-.386*	-.178	-.287	-.099
Ever Used	**N**	61	61	61	61
Updating		.294	.163	.121	.028
Computation span		.192	.331*	.146	.193
Semantic Fluency		.044	.118	.096	-.049
"S" letter		.309	.250	.291	-.068
"C" letter		.368*	.210	.408*	.017

* Correlation significant at $p<.01$

Table 5

Age, Years of Education, Intelligence and Sleep Quality for Ecstasy Users and Nonusers in Study 2.

	Ecstasy users		Non Ecstasy Users	
	Mean	S.D.	Mean	S.D.
Age (years)	21.96	2.11	20.83	1.45
Years of Education	15.62	1.94	15.07	1.92
Raven's Progressive Matrices (maximum 60)	46.66	6.53	47.83	5.47
NART (maximum 50)	28.67	6.53	28.71	4.90
Hours Sleep per night	7.92	1.45	8.09	1.13
Epworth Sleep Scale (Maximum 24)	6.48	3.54	7.63	3.22
Self Report Health*	3.54	0.88	3.83	0.70
Weeks Since Last Used Ecstasy	22.15	40.71	-	-

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Table 6

Mean Scores and Significance Levels for Measures in Study 2.

	Ecstasy Users		Non Ecstasy Users		F
	Mean	S.D.	Mean	S.D.	
Random Letter Generation (standardised scores)					
Alphabetic Sequences	0.0568	0.7719	-0.0720	0.7821	0.63
Repeat Sequences	0.0005	0.6453	-0.0007	0.6955	0.00
Redundancy	-0.0490	0.6341	0.0622	0.9591	0.45
Number of Letters	0.1967	0.4203	-0.2495	1.0137	8.29***
Switching Tasks					
Plus/Minus task Switch Cost (seconds)	28.63	19.46	29.58	18.18	0.06
Number/Letter Switch Cost (seconds)	39.27	18.14	38.52	18.98	0.04

*** $p<.01$, two-tailed

Table 7.

Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users in Study 2

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	n	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	373.87	542.91	52	-	-	-
Amphetamine (grams)	90.85	127.19	16	-	-	-
Cannabis (joints)	3544.16	4410.04	40	367.54	622.96	13
Cocaine (grams)	57.12	92.39	21	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.27	0.29	52	-	-	-
Amphetamine	0.04	0.13	14	-	-	-
Cannabis	2.78	2.65	40	0.94	1.36	13
Cocaine	0.71	1.57	21	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	2.18	3.17	52	-	-	-
Amphetamine (grams)	0.04	0.13	14	-	-	-
Cannabis (joints)	41.14	59.45	40	17.29	42.97	12
Cocaine (grams)	0.83	0.87	21	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	1.46	1.40	52	-	-	-
Amphetamine (grams)	0.26	0.37	14	-	-	-
Cannabis (joints)	9.10	11.58	40	1.91	3.37	13
Cocaine (grams)	0.30	0.38	21	-	-	-
Number Ever Used						
Amphetamine	19	-	-	0	-	-
Cannabis	46	-	-	23	-	-
Cocaine	41	-	-	4	-	-

Table 8: Correlations between Measures and Indices of Drug Use.

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total use	**N**	93	76	67	85
P/M switch cost		-.015	-.136	.196	.106
N/L switch cost		.124	.143	.212	.077
Redundancy		.028	-.032	.051	.042
Repeat sequence		.084	.004	.131	.139
Alpha sequence		.080	.010	.113	-.137
Number of Letters		.228	.174	.018	.032
Frequency of Use	**N**	93	76	67	85
P/M switch cost		-.043	-.125	.108	.220
N/L switch cost		.071	.050	.144	.139
Redundancy		-.079	-.145	.041	.034
Repeat sequence		-.062	-.169	.100	.044
Alpha sequence		.106	-.110	.025	-.105
Number of Letters		.335*	.186	.078	-.051
Average dose	**N**	93	76	67	83
P/M switch cost		-.025	-.167	.186	.115
N/L switch cost		.060	.122	.210	.025
Redundancy		.035	-.056	.048	-.029
Repeat sequence		.053	-.017	.129	.097
Alpha sequence		.071	.033	.120	-.159
Number of Letters		.283*	.199	.018	.034

Table 8: continued
Correlations between Measures and Indices of Drug Use.

Current Use	**N**	Ecstasy 93	Cannabis 93	Cocaine 93	Amphetamine 93
P/M switch cost		-.106	-.045	.133	.197
N/L switch cost		.041	.062	.068	-.025
Redundancy		-.109	-.100	-.057	.013
Repeat sequence		-.155	-.033	.075	.055
Alpha sequence		-.021	-.048	.062	-.071
Number of Letters		.344*	.116	.000	.102
Ever Used	**N**	93	92	92	92
P/M switch cost		.051	.118	-.007	-.073
N/L switch cost		-.063	-.062	-.176	-.052
Redundancy		.028	.050	-.142	.077
Repeat sequence		-.022	.055	-.118	-.056
Alpha sequence		-.134	.069	-.029	.129
Number of Letters		-.258	-.037	-.018	-.023

* Correlation significant at $p<.01$

[1] Those in the nonuser group who reported that they had ever used amphetamine or cocaine (N= 1 and 4 respectively) felt that they were unable to estimate their pattern of use accurately.
[2] Those in the nonuser group who reported that they had ever used amphetamine or cocaine (N= 1 and 4 respectively) felt that they were unable to estimate their pattern of use accurately.