Prospective memory deficits in illicit polydrug users are associated with the average long term typical dose of ecstasy typically consumed in a single session.

Running Head: Prospective memory deficits in illicit polydrug users

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Title

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Abstract

Rationale Neuroimaging evidence suggests that ecstasy-related reductions in SERT densities relate more closely to the number of tablets typically consumed per session rather than estimated total lifetime use. In order to better understand the basis of drug related deficits in prospective memory (PM) we explored the association between PM and average long-term typical dose and long-term frequency of use. **Method** *Study 1*: Sixty five ecstasy/polydrug users and 85 non-ecstasy users completed an event based, a short-term and a long-term time based PM task. *Study 2*: Study 1 data were merged with outcomes on the same PM measures from a previous study creating a combined sample of 103 ecstasy/polydrug users, 38 cannabis-only users and 65 nonusers of illicit drugs. **Results** *Study 1*: Ecstasy/polydrug users had significant impairments on all PM outcomes compared to non-ecstasy users. *Study 2*: Ecstasy/polydrug users were impaired in event based PM compared to both other groups and in long-term time based PM compared to non illicit drug users. Both drug using groups did worse on the short-term time based PM task compared to nonusers. Higher long-term average typical dose of ecstasy was associated with poorer performance on the event and short-term time based PM tasks and accounted for unique variance in the two PM measures over and above the variance associated with cannabis and cocaine use. **Conclusions** The typical ecstasy dose consumed in a single session is an important predictor of PM impairments with higher doses reflecting increasing tolerance giving rise to greater PM impairment.

Key words: ecstasy, cannabis, cocaine, prospective memory, dose, tolerance.

The aim of the present paper is to identify which aspects of long term ecstasy/polydrug use are associated with drug-related impairments of prospective memory (PM). PM is an aspect of real-world memory that involves remembering to carry out intended actions in the future (Einstein et al. 2005). PM tasks include both short-term and long-term activities that are triggered by external events (event-based) or the passage of time (time-based). In short-term PM tasks, such as locking the car after leaving, there is a relatively short period of time between the external episode/prompt (leaving the car) and the appropriate behaviour (locking the doors). Long-term PM tasks, such as remembering to post a birthday card, have a longer time interval between the external episode/prompt (realization of a friend's birthday) and the desired behaviour (posting a card). As to the cerebral mechanisms involved in PM processing, there is a general consensus that medial temporal hippocampal structures feature prominently (Adda, Castro, Além-Mar e Silva, de Manreza, & Kashiara, 2008; Martins et al., 2007) as well as areas of the prefrontal cortex (PFC; Brooks, Rose, Potter, Jayawardena, & Morling, 2004; Burgess, Scott, & Frith, 2003; Katai, Maruyuma, Hashimoto, & Ikeda, 2003). Considering that ecstasy users (Kish et al. 2010) and cannabis users (Jager et al. 2007) exhibit abnormalities in these brain regions, it is plausible to suggest that people using these drugs may demonstrate PM impairment. This proposal has received support with several studies using both self report and laboratory based measures demonstrating PM deficits in temporarily abstinent illicit substance users (e.g., Hadjiefthyvoulou, Fisk, Montgomery, & Bridges, 2011a; Heffernan, Jarvis, Rodgers, Scholey, & Ling, 2001a; Montgomery & Fisk, 2007; Rendell, Gray, Henry, & Tolan, 2007). Furthermore, former users of ecstasy have also exhibited event and time-based impairments in PM on the "Virtual Week" task (Rendell, Mazur, & Henry, 2009) highlighting the possible long-term neurotoxic potential of MDMA use.

One key aspect that remains to be thoroughly explored is the presence of dose-related effects in relation to PM performance. It is important to demonstrate that these exist since in the absence of clear dose-related effects, any group differences that have been observed might more readily be attributed to some premorbid condition or lifestyle differences unrelated to drug use. However, in relation to ecstasy use and PM outcomes, there have been some problems with the way in which dose-related effects have been investigated. For example, in between group comparisons, using the self-report Prospective Memory Questionnaire (PMQ), while ecstasy/polydug related PM deficits have emerged in a number of studies, dose related effects have not been directly reported (Heffernan et al. 2001a; Heffernan, Ling, & Scholey, 2001b; Parrott et al. 2006). In other studies, lifetime use has been defined in a categorical manner in terms of the number of times that the drug has been previously used (e.g., 0, 1-9, 10-99, 100+ times). On this basis, lifetime use accounted for unique variance in long term PM problems on the PMQ, but not short term and internally cued PM problems (Rodgers et al. 2001). Montgomery and Fisk (2007) estimated lifetime use in terms of the number of tablets previously consumed but found no association between this variable and outcomes on the PMQ. Bedi and Redman (2008a) obtained estimates of lifetime ecstasy use (total number of tablets) from their participants as well as age of first use, and period of abstinence but none of these significantly predicted PMQ outcomes.

Using objective measures of PM, Zakzanis, Young and Campbell (2003) found that ecstasy users differed from nonusers on the 'appointment' and 'message' PM subscales of the Rivermead Behavioural Memory Test (RBMT). Furthermore, the scores on the appointment subscale were significantly related to the number of occasions of ecstasy use and to the frequency of use (although the significant outcome was based on a sample size of fewer than 20). Bedi and Redman (2008b) included short term time and event based PM tasks in their test battery but ecstasy/polydrug group differences were either absent or inconclusive and

dose related effects were not reported. Although Rendell et al. (2007) did not report effects in relation to lifetime dose, they found that frequent ecstasy users (using more than once a fortnight) performed worse than infrequent users (using less than one a month) who in turn performed worse than nonusers on all PM measures on the virtual week task. Hadjiefthyvoulou and co-workers found that lifetime ecstasy use (estimated number of tablets) was significantly associated with time and event based PM scores on the Cambridge Prospective Memory Test (CAMPROMPT) (Hadjiefthyvoulou et al. 2011a) and with performance on the RBMT and other short term time and event based PM tasks (Hadjiefthyvoulou et al. 2011b). However, these effects were no longer significant following controls for other drug use. It is also worthy of note that in these studies (Hadjiefthyvoulou et al. 2011a; 2011b; Montgomery & Fisk, 2007) non users were included in the samples (with use coded as zero). Indeed this practice is common in much of the ecstasy-related behavioural research (e.g., Medina, Shear & Corcoran, 2005; Montgomery, Fisk, Newcombe, & Murphy, 2005; Piechatzek et al. 2009; Reneman et al. 2001).

What this summary of the relevant literature demonstrates is that the issue of dose related effects in relation to laboratory measures of PM remains to be systematically investigated. For example, those studies quantifying use in a categorical manner may lose a degree of precision due to the ordinal nature of the scale and responses at the top end of the scale, e.g., 100+, do not reflect the actual differences among heavy users. Furthermore, when lifetime use is defined in terms of occasions of use, differences between individuals who might consume one tablet per occasion, versus others who might consume several tablets are masked. When dose-related effects are reported on the basis of distinctions between broadly defined groups, for example ‘heavy’ versus ‘moderate users’ or ‘frequent’ versus ‘infrequent users’ (e.g., Rendell et al. 2007), the group criteria are variable and even where the same criteria are used widely different cut off points may be adopted. Clearly, comparisons

between user groups defined in this manner might be useful but they are less informative than correlational indicators and make informed comparisons between studies difficult, if not impossible. Including non users of specific drugs in the sample (with their use coded as zero) when dose-related effects are evaluated is also potentially problematic since a significant correlation or regression coefficient may be due to the absence of use within the drug naïve participants (i.e., the group effect) rather than a trend **within** the drug using participants. Indeed when the correlation is limited to the drug users within the sample it may no longer be significant.

Lastly, it is also possible that that estimates of lifetime use which do not suffer from the limitations identified above may still fail to capture subtle differences in the patterns of use between ecstasy users. Consistent with this possibility, Morefield, Keane, Felgate, White, and Irvine (2011) found that there were pronounced differences in the consumption patterns of their sample in terms of the number of tablets consumed in a single session. Furthermore they found that a non linear relationship existed between the number of tablets consumed in a single session and MDMA plasma concentrations with the latter increasing exponentially with the number of tablets consumed. Thus for those consuming no more than a single tablet, MDMA plasma concentrations peaked and remained stable after an hour or so, while those consuming more than a single tablet experienced a dose related disproportionate rise in plasma levels which continued to increase through out the five hour period during which levels were monitored. Therefore, taking a single tablet often or multiple tablets infrequently may give rise to similar lifetime doses but have very different consequences in terms of the typical level and peak duration of blood plasma MDMA levels.

A potential implication of this is that more emphasis should be placed on the size of the typical dose rather than other measures such as frequency of use and lifetime dose. The importance of alternative measures has also emerged from neuroimaging studies. For

example, Thomasius et al. (2003) found that distribution volume ratios (DVRs) of SERT ligands in some sub-cortical structures were best predicted by the usual dose of ecstasy consumed at a typical party event, while in other instances DVRs were best predicted by the amount of ecstasy consumed in the 12 months prior to testing. Estimates of lifetime use and maximum dose of ecstasy were either non significant or accounted for significantly less unique variance.

The present study aimed to further investigate dose related effects on PM performance by using a timeline technique similar to that adopted by Medina et al. (2005) and Bedi and Redman (2008b) in order to examine long term dose related effects . For each illicit drug, we will obtain an estimate of the typical dose and frequency of use for each year since use commenced. These two variables have received relatively little attention previously. Furthermore they can be used to produce an estimate of lifetime use. In the analysis of dose related relationships presented here only users of specific drugs will be included. Non users will be excluded from these particular analyses and we will seek to maximise the size of the available sample by combining samples from different phases of data collection. In Study 1, a replication and extension of previous findings are presented. In Study 2, data from Study 1 will be augmented with equivalent data which, although collected in a previous study, has yet to be analysed. The resulting combined data set will allow us to more effectively investigate polydrug dose related effects. Specifically Study 2 will focus on the effects of the long term average number of tablets consumed in a single session and the long term average frequency of use.

STUDY 1

METHOD

Participants.

Participants included 65 ecstasy/polydrug users (27 females, 37 males, 1 not reported), and 85 non-ecstasy users (54 females) (for demographic details see Table 1). Females predominated among the non-ecstasy user group and males among the ecstasy/polydrug users, producing a significant gender effect, $\chi 2$ (1) =6.70, $p<.01$. Participants, who were university students studying in the United Kingdom, were recruited via direct approach. Fifty-seven of the participants included here took part in a previous study from our laboratory. However, their results on the laboratory PM tasks have not been previously reported and are presented here for the first time. None of the present sample reported use of ecstasy within the week prior to testing and none reported using any other illicit drug within the 24 hours prior to testing. All participants gave verbal consent and were tested in accordance with the national and local ethics guidelines and the Declaration of Helsinki.

Materials

The use of ecstasy and other drugs was assessed by means of a self-report questionnaire previously used in several studies from our laboratory. For all illicit drugs that were regularly consumed and for each year since they commenced drug use, participants estimated the typical dose that they ingested in a representative session and their typical frequency of use (number of sessions per week) during that year. These annual estimates were used to produce an estimate of total lifetime use. Participants also indicated their current frequency of use and the period of abstinence for each major illicit drug. Demographic variables including age, gender, and years of full time education were recorded and fluid intelligence was measured through Raven's progressive matrices (Raven, Raven & Court, 1998). The current use of cigarettes and alcohol were also recorded.

Laboratory Measures of Prospective Memory.

Pattern Recognition PM Task: This test utilises a processing speed task which was amended to include a parallel PM element. The task involved classifying pairs of patterns which increased in complexity as either the same or different while remembering to press the F1 key each time that the complexity level increased (purportedly to save the participant's scores). The task was repeated three times. The number of times the participant forgot to press F1 for each trial was calculated producing a laboratory event-based PM measure.

Fatigue Short-Term Time-Based PM Test: Following the briefing, participants were told that they should provide an indication of their level of fatigue (using the Karolinska Sleepiness Scale: Gillberg, Kecklund, & Akerstedt, 1994) every 20 minutes throughout the experiment or if this occurred during the completion of a task, to do so immediately after. The percentage of occasions on which this was done was calculated separately for the first and second half of the test session thereby producing two measures of short-term time-based PM. On each occasion, participants who forgot were reminded to fill in the questionnaire.

Mail Long-Term Time Based PM Test: During the test session participants learned a list of 15 words over five trails. A long-term PM element was added in which participants had to remember to return an answer sheet, in a prepaid envelope, to the experimenter with the words that they were able to recall after a delay of one, two, and three weeks from the time of testing. Participants scored 1 if the envelope was returned and 0 otherwise yielding a maximum possible score of three.

Full descriptions of the tasks may be found in Hadjiefthyvoulou et al. (2011b).

Procedure

The tests were administered under laboratory conditions. The Ravens intelligence test was administered first followed by the age/education questionnaire. Next the F1 event based task was administered and instructions for the long-term time based task were provided. The

fatigue short-term PM task was administered throughout the session and the drug use questionnaire was administered at the end. Participants were fully debriefed, given a 20 GBP supermarket (grocery store) gift card and given drug education leaflets. Participants also performed a range of other tasks that are beyond the scope of the present investigation.

Design and Statistics.

A between-participant design was used with drug user group (ecstasy/polydrug versus non-ecstasy user) as the independent variable. Dependent variables included all of the PM measures, i.e., the proportion of fatigue questionnaires completed during the first and second half of the test session, the number of times that participants forgot to press the F1 key for each of the three trials and the number of delayed recall tests participants remembered to mail back to the experimenter. Group differences were analysed via t test.

RESULTS AND DISCUSSION

Regarding background variables, inspection of Table 1 reveals that the two groups differed significantly in terms of age and the number of cigarettes consumed each day. Ecstasy/polydrug users were older and consumed more cigarettes. Furthermore, the ecstasy/polydrug group had a significantly higher level of lifetime cannabis use and a significantly shorter period of abstinence from the drug. Although ecstasy/polydrug users reported a higher current frequency of cannabis use, the difference was short of statistical significance. Ecstasy/polydrug users were significantly impaired on all but two of the PM measures and on these remaining two, the difference approached statistical significance (see Table 1).

The present results replicate the findings from our previous study. Ecstasy/polydrug users made significantly more errors (forgetting to press F1) on each of the three trials of the

event based task; they completed significantly fewer Karolinska fatigue questionnaires during both halves of the test session, with the deficit larger in magnitude during the second phase of testing; they also returned fewer delayed recall tests during the three weeks following the test session.

STUDY 2

Of the non-ecstasy users included in Study 1, over one third had used cannabis and 10% cocaine and the majority of these individuals appeared to be current users. Similar proportions were using these drugs among non-ecstasy users in our previous study. Since there is evidence to suggest that cannabis use is associated with self report (Fisk & Montgomery, 2008; Rogers et al. 2001) and laboratory based (McHale & Hunt, 2008; Montgomery, Seddon, Fisk, Murphy, & Jansari, 2012) PM deficits, the group difference evident in Study 1 and in our previous paper may actually underestimate the true difference between ecstasy/polydrug users and drug naïve individuals. Inclusion of a cannabis only user group and a group of nonusers of illicit drugs would clarify the nature of the ecstasy/polydrug related deficit and also allow us to directly test for group differences between cannabis-only users and nonusers of illicit drugs.

Most importantly, as outlined above, it has often not been possible to demonstrate clear long-term dose related effects of ecstasy and other illicit drugs on aspects of prospective memory. Rather than relying on single estimates of lifetime use, it may be useful to focus on other long-term aspects of use including the long-term dose (e.g., tablets, lines or joints typically consumed per session) or the long-term frequency of use. Merging the sample from Study 1 with that of our previous study will create a sufficiently large sample in order to explore the associations between these long-term measures of illicit drug use and the PM outcomes. A larger sample size will help establish whether measures such as long-term

average dose per session and frequency of use can explain variance in PM performance where more traditionally used measures of drug use such as total lifetime use, current frequency of use, period of abstinence, duration of use and average weekly long-term consumption may fail to reveal such a relationship.

METHOD

Participants.

One hundred and three ecstasy/polydrug users (51 females, 51 males, 1 not reported), 38 cannabis-only users (21 females), and 65 nonusers of illicit drugs (48 females) took part in this investigation (for demographic details see Table 2). The gender composition differed significantly between the groups with females predominating among the non illicit user group and a broadly even split among the cannabis only and ecstasy/polydrug users, $\chi 2\ (2) = 9.51$, $p<.01$. Participants, who were university students studying in the United Kingdom, were recruited via direct approach.

In addition to the individuals included in Study 1, 69 of the participants included in the present study also took part in our earlier study where we have previously reported some of the laboratory PM results for these individuals. Merging the samples together allowed us to include a cannabis only user group and a group of non-users of illicit drugs (in Study 1 the non-ecstasy user group contained a substantial minority of cannabis users and a small number of cocaine users). It also enabled us to create sufficient numbers of illicit drug users so that long and short-term dose-related effects could be properly investigated. None of the present merged sample reported use of ecstasy within the week prior to testing and none reported using any other illicit drug within the 24 hours prior to testing. All participants gave verbal consent and were tested in accordance with the national and local ethics guidelines and according to the Declaration of Helsinki.

Materials

The drug use and demographics questionnaires (and measures) were the same as those that featured in Study 1. In addition, in the present study, the historical annual estimates of typical dose per session and frequency of use for each year were considered separately and estimates of long-term dose (averaged over the number of years of use) and similarly the long-term average frequency of use were computed. This was done for each illicit drug that was regularly consumed.

Laboratory Measures of Prospective Memory

The same PM tasks were administered as in Study 1, that is, the F1 Short-Term Event Based Task, the Fatigue Short-Term Time Based Test, and the Mail Long-Term Time Based Test. Full descriptions of these may be found above.

Procedure

The procedure was the same as that outlined in Study 1.

Design/Statistics

A mixed design was used to analyse outcomes from the fatigue short-term time based PM task. The proportion of fatigue questionnaires completed in the first half and second halves of the test session were compared across the three participant groups (ecstasy/polydrug, cannabis only, and non-illicit drug user). To explore any differences on the F1 event based PM task (omitting to press F1) a mixed design was again used. The number of errors was compared across three separate trials and between the three participant groups (ecstasy/polydrug, cannabis only, and non-illicit drug user). Responses from the mail long-

term time based PM task were compared between the three user groups (ecstasy/polydrug, cannabis only, and non-illicit drug user) using a one way design. In all three analyses, gender and measures of current alcohol and cigarette use were included as covariates. With respect to the between participant comparisons, it was predicted, a priori, that non users would score significantly better than both cannabis only and ecstasy/polydrug users. For these two pairwise comparisons, an alpha value of .025, one-tailed, was selected. No prediction was made regarding the difference between the two drug using groups.

For those individuals using illicit drugs, associations between indicators of long and short-term drug use and the outcomes on the PM measures were investigated using correlation. It was predicted that increasing levels of illicit drug use would be associated with poorer PM performance and that PM performance would be positively associated with the period of abstinence.

While some means of controlling the Type 1 error rate is required it is now well established that full Bonferroni correction greatly inflates the likelihood of Type 2 error (Rothman, 1990). Where test results are conditionally dependent, (as is the case with the present study, where there are multiple interrelated outcome variables and multiple inter-correlated drug use measures) full Bonferroni correction is known to be inappropriate (Bland & Altman, 1995; Narum, 2006; Pike, 2010). Thus an alternative to full Bonferroni correction has been adopted here, which focusses on controlling the False Discovery Rate (FDR), a technique which is well suited to situations where the reported outcomes are not independent (Benjamini & Yekutieli, 2001). This involves controlling the proportion of occasions where true null hypotheses are falsely rejected giving rise to 'false discoveries'. Computational methods are available for calculating the critical value for alpha (also known as the q value) which controls the FDR at a given level (e.g., Pike, 2010). The FDR rate in the present study was set to .10 which implies that the proportion of significant outcomes which are actually

false discoveries is limited no more than 10%. In fact, in the present case, significant outcomes that were not in the predicted direction are also rejected which effectively reduces the FDR to .05. There is a related procedure for calculating the critical alpha value which limits the Family Wise Error rate (FWE) to .05 without greatly inflating the risk of a Type 2 error, as is the case with full Bonferroni correction (Benjamini & Yekutieli, 2001; Narum, 2006). It is this critical level and the related FDR which has been used to identify those outcomes in Tables 4 and 5 which can be regarded as statistically significant with the FWE <.05 and FDR<.10, two tailed.

RESULTS

Group differences on the background variables are set out in Table 2. Ecstasy/polydrug users were significantly older than nonusers. Both illicit drug using groups consumed significantly more units of alcohol per week than nonusers. Ecstasy/polydrug users smoked significantly more cigarettes each day compared with cannabis only and nonusers. In terms of illicit drug use, aside from ecstasy, most ecstasy/polydrug users regularly consumed cannabis and two-thirds of the group were regular cocaine users (see Table 3). On virtually all of the cannabis use measures set out in Table 3 ecstasy/polydrug users registered significantly greater cannabis use compared to cannabis only users.

The F1 event based PM task.

Examination of Table 2 reveals that relative to the other two groups, ecstasy/polydrug users committed more errors on this task by failing to press F1 at the end of each 30 second period on each of the three trials. Cannabis only users and non-illicit drug users performed similarly on this task. ANCOVA was administered with gender, daily cigarette and weekly alcohol

consumption as covariates. Mauchly's test of sphericity was statistically significant, p<.001, therefore Greenhouse-Geisser adjusted degrees of freedom have been used. The interaction between drug user group and trial was non significant, F<1. There was a significant effect of trial, F(1.45,268.40)=7.97, p=.002, η_p^2 = .041, and the groups differed significantly, F(2,185) = 7.28, p=.001, η_p^2 = .073. Pairwise comparisons revealed that ecstasy/polydrug users committed significantly more errors than drug naïve persons, and cannabis only users, p<.001 and p=.008 respectively. Drug naïve persons and cannabis only users did not differ significantly, p>.05. None of the covariates were statistically significant, p>.19, and homogeneity of regression was obtained in all three cases.

The fatigue short-term time based PM task. Inspection of Table 2 reveals that non illicit drug users did best, remembering to complete more fatigue questionnaires than the other two groups. Cannabis-only users performed worse than non illicit drug users but better than ecstasy users. ANCOVA with the same covariates included as in the previous analysis revealed a significant interaction between drug user group and test session, F(2,184)=7.42, p=.001, η_p^2 = .075. As is clear in Table 2, while both user groups performed worse than nonusers during the first half of the session, nonusers broadly maintained their performance in the second half while the performance of the drug using groups deteriorated further. For the sample as a whole, performance deteriorated between the first and second halves of the session, F(1,184)=35.25, p<.001, η_p^2 = .161. The overall group difference was significant, F(2,184)=25.43, p<.001, η_p^2 = .217. Pairwise comparisons revealed that, overall, both user groups performed significantly worse than nonusers, p<.001 in both cases. Furthermore, the ecstasy/polydrug group performed significantly worse than cannabis only users, p=.020, one tailed. None of the covariates were statistically significant, p>.20, for alcohol and nicotine

consumption, although gender approached significance as a covariate, F(1,184)=3.84, p=.052, η_p^2 = .020. Homogeneity of regression was obtained in all three cases.

The mail long-term time based PM task. As is clear from inspection of Table 2, non-illicit drug users remembered to return more delayed recall tests compared to the other two groups. Ecstasy/polydrug users again performed worse on this measure, with cannabis only users scoring in between. ANCOVA with the same three covariates failed to yield a statistically significant group difference, F(2,185)= 2.06, p=.131, η_p^2 = .022. However pairwise comparisons revealed that non illicit drug users scored significantly higher than ecstasy/polydrug users, p=.023 one-tailed. None of the other pairwise comparisons were statistically significant, p>.05. None of the covariates were statistically significant, p>.45, for gender and nicotine consumption, although alcohol consumption approached significance as a covariate, F(1,185)=3.39, p=.067, η_p^2 = .018. Homogeneity of regression was obtained in all three cases.

Associations between long-term drug use and PM. A key objective of the present paper was to examine the association between the various laboratory PM measures and the long-term average dose per session and long-term average frequency of use for ecstasy, cocaine and cannabis. The corresponding correlations are presented in Table 4. Inspection of Table 4 reveals that, without adjustment for multiple comparisons, the long-term average dose of ecstasy is significantly associated with all but one of the PM measures. Using Benjamini and Yekutieli's (2001) procedure for controlling the FWE, four of the eight correlations are statistically significant at FWE < .05, and using a two tailed FDR<.10 with m=48, five of the correlations are significant. It is also apparent that prior to adjustment for multiple comparisons, the long-term average frequency of cannabis use was significantly associated with the two time based PM measures, however, only the association with the

Fatigue short term measure remains significant after controlling the FWE and FDR at the levels indicated above.

Examination of the more traditional measures of illicit drug use set out in Table 5 shows that, prior to adjustment for multiple comparisons, a number of these were significantly associated with individual PM outcomes. The fatigue short term measure (during the first half of the test session) was significantly associated with five of the drug use variables, four relating to aspects of ecstasy use and one to cocaine. Similarly, F1 event based PM task performance in Trial 1 was significantly associated with five of the drug use variables, two relating to aspects of ecstasy use and three to cocaine. These account for most of the unadjusted significant outcomes in Table 5. However, it is important to note that following control of the FWE rate at less than .05 only two of these associations remained statistically significant. Furthermore controlling the FDR at 0.10, two tailed, left **none** of the associations statistically significant. Clearly both these methods for controlling Type 1 error are sensitive to the number of comparisons made (i.e., m=120 in Table 5). It might be argued that the number of comparisons should be treated separately for each aspect of drug use. FWE and FDR analyses were repeated on each separate block of 24 comparisons (i.e., m=24) and as with the full analysis in each case none of the outcomes achieved significance at a level which guaranteed FDR<.10. Similarly, for each separate block of 24 comparisons, only the same two correlations were such that FWE <.05, i.e., the association between total cocaine use and F1 event based PM performance in Trial 1 and between the average weekly consumption of ecstasy and performance during the first half of the Fatigue short term time based PM task.

For the seven statistically significant associations listed in Table 4 with the two tailed FDR<.10, partial correlations were conducted controlling for the long term average dose and frequency of use of the other main illicit drugs. Thus, the association between the relevant

PM measures and the long term average dose of ecstasy was estimated while controlling for long term average frequency of ecstasy, cannabis and cocaine use and long term average dose of cannabis and cocaine. Similarly the association between the relevant PM measures and the long term average frequency of cannabis use was estimated while controlling for the long term average frequency of ecstasy and cocaine use and long term average dose of ecstasy, cannabis and cocaine. The resulting partial correlations (df=53) between the long term average dose of ecstasy and respectively the fatigue time based total, and first half performances were -.267 and -.279, and between the long term average dose of ecstasy and respectively the F1 event based total, and Trial 3 outcomes were .269 and .290. These four remained significant with FDR<.10 (m=7, two tailed). However the remaining partial correlations between the long term average dose of ecstasy and F1 event based Trial 1 performance, i.e., .164, and between the long term average frequency of cannabis use and the fatigue time based total, and first half performance, respectively -.163, and -.169, were not significant at a level which controlled the FDR at less than .10. Furthermore, while these outcomes are informative none of the associations met the threshold for controlling the FWE at less than .05 two tailed (although on a one tailed basis one of the significant FDR outcomes met the FWE criterion, p=.016, and all of the remainder approached significance, $.02 \leq p \leq .025$, one tailed, compared with the critical value of .019).

General Discussion

The present findings are consistent with previous studies (Hadiefthyvoulou et al. 2011a; Heffernan et al. 2001a; Montgomery & Fisk, 2007; Rendell et al. 2007) and support the view that ecstasy/polydrug use is associated with deficits in short term time and event based PM and in long term time based PM. However, we demonstrate here that outcomes on both the event and time-based short term PM measures are significantly associated with long

term differences in the average dose of ecstasy consumed in a single session. Furthermore, the inclusion of a cannabis-only group showed that while ecstasy/polydrug users performed significantly worse than non illicit drug users on the FI event based task, cannabis-only users did not, which therefore suggests that the deficit here is due to some characteristic of polydrug use unrelated to cannabis consumption.

Interestingly cannabis-only uses were impaired in short term time based PM relative to drug naïve persons suggesting a direct effect of cannabis on this aspect of PM functioning. Indeed, both user groups exhibited significant deficits relative to drug naïve persons on the Fatigue PM measure during the second half of the test session. Furthermore ecstasy/polydrug users were significantly impaired relative to cannabis-only users on this measure. It is also of interest to note that the long term average **frequency** of cannabis use (among illicit drug users as a whole) was significantly associated with performance on the Fatigue PM measure (although interestingly this was during the first half of the test session).

Almost 90% of ecstasy/polydrug users in the present study also used cannabis and approaching 80% used cocaine, thereby raising the possibility that the effects on PM performance that we observed may be due to any one of these three major drugs, or to cocktail effects associated with their joint consumption. The evidence set out in Tables 4 and 5 appears to suggest that it is the long term average dose of ecstasy which is linked to most of the PM deficits that have been observed in the present paper. This appears to share statistically significant variance with most of the PM measures. Furthermore, when we controlled for the effects of cocaine and cannabis, the negative associations between the long term typical average dose of ecstasy (per session) and performance on two of the three PM measures remained statistically significant, at least at a two tailed FDR <.10.

A key aspect of the present results is the importance of the long term typical dose of ecstasy in a single session. This appears to be directly related to adverse outcomes on the PM

measures. This finding may be a corollary of the development of tolerance. Indeed, it has been demonstrated that the subjective effects of taking ecstasy diminish quite rapidly, leading many users to progressively increase their dose so as to maintain the intensity of the experience. In an extensive review of the literature Parrott (2005) attributes tolerance to serotonergic neurotoxicity. Consistent with this proposition, animal studies in rodents and primates have demonstrated long term reductions in serotonin, its metabolite 5-HIAA and in serotonin axon densities (e.g., Commins et al. 1987; Hatzidimitriou, McCann & Ricuarte, 1999) and neuroimaging studies in regular ecstasy users have demonstrated reduced SERT densities across the neocortex, and clear evidence of serotonin axonal damage and grey matter loss (Cowan et al. 2003; Kish et al. 2010). The progressive degeneration of the serotonergic system means that there are fewer sites for the drug to operate on thereby requiring increasing amounts to achieve the same pharmacological reaction (Parrott, 2005). The development of tolerance would lead to progressively larger doses and many users may resort to periodic binging (i.e., 'stacking' or 'boosting') to maintain the intensity of the subjective experience.

If drug use continues unabated, long term, then the increasing individual doses associated with growing tolerance will necessarily give rise to increased lifetime exposure and thus long term average dose and lifetime use will be co-related. However, the relationship is not necessarily isomorphic. For example, in Verheyden, Henry and Curran's (2003) sample, a significant number had cut back their use of the drug for various reasons (e.g., financial, adverse physical effects, adverse effects on work or education or because of the reduced subjective effects). Furthermore, in Scholey et al's (2004) sample while 24% of heavy users (more than 100 occasions of use) reported normal doses of between 3-4 tablets and 14% doses of 4+ tablets, the majority were normally consuming between 1-2 tablets per session, the same as the majority of moderate and novice users. Thus long term trends in the

typical dose per session may not always show a straight forward relationship with total lifetime use.

The exact mechanisms through which MDMA causes neurotoxicity remain unclear. Recent investigations have suggested a role for cortisol in the process. Parrott (2009) notes that, in laboratory studies, administration of MDMA stimulates the hypothalamo-pituitary-adrenal (HPA) axis resulting in increased plasma concentrations of cortisol. In a study examining salivary cortisol levels in ecstasy users, increases of up to 800% were observed in participants who were clubbing and on drug compared with baseline and compared with dancing while drug free (Parrott, Lock, Conner, Kissling & Thome, 2008). In another recent study, Wolff et al. (2012) evaluated cortisol levels pre and post clubbing. Interestingly, at baseline, cortisol levels were elevated in their sample compared with normal population and diurnal norms. Post clubbing, increases in cortisol levels were again more pronounced in clubbers who had consumed ecstasy relative to those who had not. Furthermore, genetically based differences in the efficiency of drug metabolism moderated this effect. Specifically, post clubbing increases in cortisol among the ecstasy users were largely limited to those with the two CYP2D6 phenotypes characterised by poor or intermediate metabolism. A second genetic influence was apparent, linked to the COMT genotype (Met/Met) that is associated with low activity drug metabolism. Those associated with this particular phenotype registered larger increases in cortisol post clubbing irrespective of whether they had taken MDMA. Wolff et al (2012) observe that regular use of MDMA may lead to chronic HPA axis dysregulation particularly in those with a genetic makeup characterised by poor xenobiotic metabolism.

In turn, it is possible that MDMA induced, cortisol mediated, HPA axis dysregulation may be responsible for some of the cognitive deficits associated with ecstasy use. Cortisol is known to directly affect learning and memory as well as attentional processes in an inverted

U shaped manner with too much or too little resulting in cognitive impairment. It is directly involved in regulating the activity of a number of neurotransmitters that are crucial in supporting prefrontal executive processes including dopamine. Furthermore, chronically elevated levels have been associated with atrophy in the striatum, hippocampus and prefrontal cortex (Erickson, Drevets & Schulkin, 2003).

Whether ecstasy's neurotoxic effects are directly associated with MDMA, its metabolites, or produced indirectly via the effects on cortisol, it is of interest to consider which of the neural areas associated with PM performance may be susceptible to the drug. Over the previous several years much has been learned as to the neural basis of PM performance. In early neuroimaging research it was demonstrated that increased activity in the lateral frontopolar region, Brodmann area (BA) 10, was associated with retaining the PM intention, while, when the cue was detected, activity in medial BA 10 appeared to decline as attention was diverted away from the external ongoing task and the focus was switched to the internal representation of the PM intention (Burgess, Quayle & Frith, 2001; Burgess et al. 2003). Later research has demonstrated the involvement of other cortical and subcortical areas. During the storage phase, in addition to lateral BA10, activity is also higher in the bilateral medial frontal gyrus (BA 8/32), the left precuneus and left parietal cortex (BA7) (Benoit, Gilbert, Frith, & Burgess, 2012), as well as a region in BA46 extending to the insular cortex and the anterior cingulate (Gilbert, 2011). Responding to the cue and retrieving the intention also results in increased activity in the VLPFC and lateral parietal cortex, the anterior cingulate, more superior regions of the DLPFC, as well as the orbitofrontal cortex (OFC) (Simons, Schölvinck, Gilbert, Frith & Burgess, 2006). Findings reported by Gilbert (2011) suggest that the specific content of the PM intention and the characteristics of the PM cue are not actually stored in BA10 but rather are reflected in differential activation

elsewhere in both cortical (e.g., the medial rostral prefrontal and right superior parietal cortices, the medial occipital cortex) and subcortical structures (e.g., thalamus, putamen).

It is known that ecstasy damages axonal tissue though out much of the neocortex and it may be that one or more of the above mentioned neural areas may be particularly sensitive to ecstasy-related effects. The acute effects of ecstasy on PM were investigated in Ramaekers Kuypers, Wingen, Heinecke and Formisano's (2009) study in which participants, who were regular ecstasy users, performed an event based PM task. While performing the ongoing task and retaining the PM intention, fMRI revealed that relative to placebo, the BOLD response was reduced following the administration of MDMA in the left thalamus, left putamen, left precuneus (BA7), the left inferior /superior parietal lobule (BA40/7) and right inferior parietal lobule (BA40). When retrieving the PM intention administration of MDMA reduced the BOLD response in the inferior parietal lobe (bilateral BA40). Clearly many of the regions demonstrating acute MDMA sensitivity are the same as those supporting event based PM processing, e.g., the parietal cortex, the thalamus and putamen, and it may be that the same regions are implicated with respect to PM deficits in currently abstinent ecstasy/polydrug users.

Since the ecstasy/polydrug users in the present study were also impaired in time based PM, it is of interest to consider which neural areas might be implicated in this regard. Okuda et al. (2007) demonstrated that the lateral frontopolar cortex is also active in storing the intention in time based PM, although there were slight differences, with the left superior frontal gyrus (BA9/10) more active in time based PM. Relative to event based PM, using a clock, instead of subjective time estimation, was associated with greater activation in the right superior frontal gyrus (BA10), the medial frontal lobe (BA10) and the adjoining anterior cingulate gyrus (BA32/10). In a later study, Momennejad and Haynes (2012) focussed on the specific content of the PM intention showing that, during retention, this was encoded in a

range of medial PFC regions including BA 9/ 10, as well as left lateral BA 6, and the occipital lobe (BA17, right inferior BA19) . Differences in the specific timing of the PM intention appeared to be encoded in the lateral PFC including bilateral BA10, right BA46, and BA6, as well as right medial BA10, right posterior parietal lobe, right superior parietal cortex, and the anterior cingulate. At the point of retrieval different delays were associated with differential activation in additional regions including the right precuneus, the inferior right PFC (BA45) and orbitofrontal cortex (BA47).

The neuroimaging results have been augmented by clinical and lesion studies. For example, in a study of patients with focal brain lesions, following appropriate controls, right polar prefrontal (BA10) lesions were associated with a deficit in time-based PM while event-based PM performance was unrelated to lesion status. Interestingly, patients with frontopolar lesions were also significantly impaired in time estimation ability compared to other patients (Volle, Gonen-Yaacovi, de Lacy Costello, Gilbert, & Burgess, 2011). In another study, the relationship between PM performance and grey matter volumes in the medial temporal, prefrontal and parietal regions was examined in a sample of normal and mildly demented older adults. A significant positive association was apparent between medial temporal and more specifically hippocampal grey matter and performance on a focal PM task (Gordon, Shelton, Bugg, McDaniel, & Head, 2011). Lastly, Kondo et al. (2010) administered diffusion tensor imaging (DTI) on subjects with diffuse axonal injury, revealing a significant association emerged between PM performance and the degree of fractional anisotropy (an indication of axonal damage) , in the left parahippocampal gyrus, left inferior parietal lobe, and left anterior cingulate.

Given the range of neural areas which appear to support time based PM processes, it is of interest to consider which of these may feature in the ecstasy-related deficits that have been observed here. Cowan et al. (2003) assessed regional brain grey and white matter

concentration in ecstasy users and controls. The former had decreased grey matter in several brain regions, which were localised to the neocortex in bilateral occipital cortex (BA 18), left middle temporal gyrus (BA 21) and left inferior frontal gyrus (BA 45). Kish et al. (2010) investigated differences between ecstasy users and controls in serotonin transporter densities, the regional volume of grey and white matter and cortical thickness in particular ROIs. Consistent with the outcomes of previous studies (e.g., Buchert et al. 2004; Thomasius et al. 2006) the results revealed that SERT densities were significantly reduced in all cortical areas with the occipital and temporal cortices most affected. No significant differences in SERT binding emerged in the basal ganglia structures or the thalamus. Cortical thinning was evident especially in left hemisphere locations including the superior (BA6) middle (BA10 and BA9) and inferior (BA47) frontal gyri, inferior parietal (BA40), middle temporal gyrus (BA22), occipital cortex (BA17) and right inferior parietal. Furthermore the neural deficits evident in ecstasy/polydrug users were associated with aspects of prior ecstasy consumption (Kish et al. 2010).

Combining, the evidence set out above concerning the neural basis of PM performance and what is known regarding neural damage in ecstasy users, one clear area that is implicated is the frontopolar cortex (lateral BA10) which plays a crucial role in both time and event based PM (e.g., Gilbert, 2011; Okuda et al. 2007) and which has been to shown to exhibit reduced SERT densities and cortical thinning in ecstasy/polydrug users (e.g., Kish et al, 2010). Indeed as noted above patients with right polar prefrontal BA10 lesions were shown to be impaired in time based PM (Volle et al. 2011). It is also possible that the DLPFC more generally (including BA6 BA9) may similarly be implicated. Also the parietal cortex cannot be excluded since it has been identified as playing a role in time and event based PM and also exhibited reduced SERT densities and cortical thinning in Kish et al's (2010) study. Furthermore, reduced activity in areas of the parietal cortex, following acute MDMA

administration, was shown to be directly associated with impaired PM performance (Ramaekers et al. 2009).

A number of limitations need to be acknowledged in relation to the present study. In common with much of the existing literature, this study has relied on self-report data in relation to drug use. However, while objective measures would have been desirable, research suggests a high degree of concordance between self-report and objective measures of recent drug use from saliva (Yacoubian & Wish, 2006) and of longer term use from hair (Scholey et al. 2011; Vignali, Stramesi, Vecchio, Groppi, 2012). Furthermore, concordance between self-reports and objective measures of drug use has been demonstrated for multiple illicit drugs (Vignali et al. 2012), cannabis and cocaine (Vignali et al. 2012; Zaldívar et al. 2009) and ecstasy (Scholey et al. 2011; Yacoubian & Wish, 2006). Obviously it neither ethical nor feasible to administer MDMA to humans for prolonged periods so we have used an opportunity sample. Clearly we cannot exclude the possibility that our groups differed on some other pre-existing condition predating their drug use or in terms of some other lifestyle variable. While we have attempted to control for a number of potential confounds, there may be others perhaps as yet unknown which may have had an impact on the results reported here.

In conclusion, the present study has identified clear long-term **dose**-related effects of ecstasy use on PM performance and in doing so has furthered the current understanding of the basis of PM deficits among ecstasy users. Outside the laboratory, the results obtained may also have utility in informing the development of harm reduction interventions by highlighting the potential risks associated with taking large number of tablets in a single session.

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Table 1: Demographic Variables, Prospective Memory Outcomes and Drug Use Indicators: Study 1

	Ecstasy/Polydrug Users			Non-ecstasy Users			p
	Mean	SD	n	Mean	SD	n	
Age	21.91	2.40	64	20.89	2.38	85	.012
Ravens progressive matrices (maximum 60)	43.95	7.80	62	45.26	8.13	82	ns
Years of education	16.15	1.67	56	15.82	1.90	78	ns
Alcohol (units per week)	13.85	10.47	62	12.49	11.85	75	ns
Cigarettes per day	3.61	4.58	65	1.15	3.44	85	<.001
Fatigue: Short-term time based PM (%)							
Total	54.33	28.39	65	71.40	25.30	82	<.001
First Half	70.26	30.96	65	79.82	29.07	82	(.056)
Second Half	38.87	34.27	65	62.99	35.21	82	<.001
Mail: Long-term time based PM	0.89	1.23	65	1.39	1.35	84	.021
F1: Event based PM							
Total	1.77	2.83	64	0.71	1.48	85	.004
Trial 1	0.78	1.19	64	0.46	0.96	85	(.069)
Trial 2	0.53	1.11	64	0.12	0.45	85	.002
Trial 3	0.45	0.97	64	0.13	0.57	85	.012
Total Prior Consumption							
Cannabis (joints)	1658.02	3162.11	52	485.65	1423.81	30	.024
Cocaine (lines)	616.90	994.41	43	54.28	81.97	4	
Ecstasy (tablets)	316.51	654.56	60	-	-	-	
Current Frequency of Use (times per week)							
Cannabis	2.46	8.60	55	0.43	1.25	35	ns
Cocaine	0.43	0.80	47	0.16	0.28	7	
Ecstasy	0.16	0.25	64	-	-	-	
Weeks since last use[a]							
Cannabis	31.05	56.87	57	78.47	106.37	37	.016
Cocaine	31.61	58.93	49	31.14	40.40	9	
Ecstasy	52.43	72.72	65	-	-	-	

a. The *median* period of abstinence from cannabis was 8 and 16 weeks for ecstasy/polydrug users and non-ecstasy users respectively. The equivalent figures for cocaine were 8 and 20 weeks. The median period of abstinence for ecstasy was 12 weeks.

Table 2: Demographic Variables, Current Consumption of Alcohol and Cigarettes and Prospective Memory Outcomes: Study 2

	Ecstasy/Polydrug Users			Cannabis only users			Nonusers			p value (two-tailed) for oneway ANOVA and Tukey's HSD			
										Overall	E/P vs Non	Cannvs Non	E/P vsCann
	Mean	SD	n	Mean	SD	n	Mean	SD	n				
Age	21.85	2.98	102	21.47	3.00	38	20.64	2.23	65	.024	.018		
Ravens progressive matrices (maximum 60)	44.00	8.99	99	45.71	7.04	38	44.78	8.31	63	ns			
Years of education	15.25	3.20	93	15.55	2.32	33	15.30	2.22	63	ns			
Alcohol (units per week)	14.44	10.32	99	13.66	11.48	35	8.19	10.20	59	.001	.001	.041	
Cigarettes per day	4.17	6.16	103	1.53	3.17	38	0.98	3.63	65	<.001	<.001		.016
Fatigue: Short-term time based PM (%)													
Total	47.37	28.47	103	61.07	23.44	36	77.15	22.05	64	<.001	<.001	.009	.018
First Half	63.41	34.15	103	72.13	30.88	36	84.63	22.88	64	<.001	<.001		
Second Half	28.40	32.08	103	44.31	37.80	36	69.80	32.40	64	<.001	<.001	.001	.038
Mail: Long-term time based PM	0.86	1.21	103	1.18	1.23	38	1.58	1.32	64	.002	.001		
F1: Event based PM													
Total	1.75	2.74	102	0.74	1.11	38	0.60	1.48	65	.001	.003		.037
Trial 1	0.82	1.20	102	0.61	1.00	38	0.38	0.91	65	.038	.030		
Trial 2	0.50	1.09	102	0.05	0.23	38	0.08	0.41	65	.001	.003		.011
Trial 3	0.43	0.96	102	0.08	0.27	38	0.14	0.63	65	.015	.048		.046

Table 3: Measures of Illicit Drug Use for Ecstasy/Polydrug and Cannabis-Only Users: Study 2

	Ecstasy/Polydrug User				Cannabis Only User				p
	Median	Mean	SD	n	Median	Mean	SD	n	
Long-Term Average Dose Per Session									
Cannabis (joints)	2.20	2.71	1.89	85	1.00	1.36	0.88	31	<.001
Cocaine (lines)	4.83	6.49	6.53	64	-	-	-	-	
Ecstasy (tablets)	2.00	2.95	3.80	97	-	-	-	-	
Long-Term Average Frequency (times per week)									
Cannabis	1.00	1.74	2.07	85	0.23	1.02	1.69	31	.084
Cocaine	0.23	0.52	0.66	64	-	-	-	-	
Ecstasy	0.23	0.54	0.91	97	-	-	-	-	
Total Prior Consumption									
Cannabis (joints)	442.00	2110.56	3646.62	85	23.92	473.10	1404.83	31	.001
Cocaine (lines)	247.52	695.78	1113.89	64	-	-	-	-	
Ecstasy (tablets)	63.44	420.28	887.38	97	-	-	-	-	
Average weekly consumption									
Cannabis (joints)	2.04	7.98	11.69	87	0.68	2.47	4.71	30	<.001
Cocaine (lines)	2.17	28.99	164.11	63	-	-	-	-	
Ecstasy (tablets)	1.16	2.55	3.67	95	-	-	-	-	
Duration of use (weeks)									
Cannabis	264.00	297.06	192.80	91	108.00	180.35	199.27	37	.003
Cocaine	127.57	159.96	124.93	75	-	-	-	-	
Ecstasy	133.50	160.48	139.92	102	-	-	-	-	
Current Frequency of Use (times per week)									
Cannabis	0.24	1.86	6.81	90	0.01	0.53	1.45	36	.249
Cocaine	0.14	0.43	0.72	70	-	-	-	-	
Ecstasy	0.04	0.17	0.26	102	-	-	-	-	
Weeks since last use									
Cannabis	4.00	32.07	63.72	92	24.00	77.35	92.57	37	.009
Cocaine	8.00	29.86	59.21	77	-	-	-	-	
Ecstasy	12.00	45.93	70.59	103	-	-	-	-	

Table 4: Association between Long Term Average Dose and Frequency of Use of Major Illicit Drugs and Prospective Memory Outcomes

	n	Zero-Order Correlation with:							
		Fatigue: Short-term Time-based PM			Mail: Long-term time-based PM	F1: Event-based PM			
		Total	First Half	Second Half		Total	Trial 1	Trial 2	Trial 3
Long-Term Average Dose Per Session									
Cannabis (joints)	123	-.141	-.131	-.121	-.066	.120	.074	.139	.086
Cocaine (lines)	70	-.260**	-.195	-.229*	.092	.006	.225*	-.115	-.112
Ecstasy (tablets)	96	-.300***†	-.320***†	-.183*	-.158	.295***†	.249**†	.232**	.268***†
Long-Term Average Frequency (times per week)									
Cannabis	123	-.246***†	-.256***†	-.141	-.151*	.109	.071	.115	.085
Cocaine	70	-.089	-.141	-.074	.029	.163	.149	.148	.119
Ecstasy	96	-.117	-.140	-.034	-.008	.096	.139	.054	.039

*p<.10; **p<.05; *** p< .01121 and FWE <.05 ; †FDR<.10 with m=48; all two tailed

Table 5: Association between More Commonly Used Measures of Illicit Drug Use and Prospective Memory Outcomes

	n	Zero-Order Correlation with:							
		Fatigue: Short-term Time-based PM			Mail: Long-term time-based PM	F1: Event-based PM			
		Total	First Half	Second Half		Total	Trial 1	Trial 2	Trial 3
Total Prior Consumption									
Cannabis (joints)	123	-.128	-.104	-.126	-.079	.038	.008	.041	.051
Cocaine (lines)	70	-.072	-.045	-.129	.120	.083	**.330*** **	-.073	-.066
Ecstasy (tablets)	96	-.182	-.213**	-.075	-.090	.206	.189*	.166	.166
Average weekly consumption									
Cannabis (joints)	125	-.191	-.171*	-.123	-.160*	.032	.000	.069	.012
Cocaine (lines)	69	-.063	-.092	.005	-.076	-.087	-.082	-.069	-.071
Ecstasy (tablets)	94	-.234	**-.278*** **	-.101	-.065	.195	.176*	.151	.172*
Duration of use (weeks)									
Cannabis	136	-.097	-.036	-.145*	-.029	.069	.040	.087	.043
Cocaine	85	-.062	-.073	-.105	-.059	.161	.232**	.152	.014
Ecstasy	101	-.014	-.015	-.018	-.006	.019	.026	.050	-.036
Current Frequency of Use (times per week)									
Cannabis	133	.125	.064	.154(*)	.105	.046	-.033	.047	.128
Cocaine	78	.081	-.012	.144	-.067	.033	.196*	-.061	-.071
Ecstasy	101	-.192	-.170*	-.152	-.049	.149	.065	.182*	.139
Weeks since last use									
Cannabis	137	.155	.128	.084	-.058	-.184	-.137	-.170**	-.142*
Cocaine	88	.150	.225**	.073	.024	-.131	-.092	-.116	-.132
Ecstasy	102	.120	.130	.076	-.178(*)	.093	.151	.030	.042

*p<.10; **p<.05; *** p< .00879 and FWE<.05; †FDR<.10 with m=120; all two tailed;

(*) indicates that although p<.10, the effect was not in the predicted direction