Published in final edited form as:

J Psychopharmacol. 2011 April ; 25(4): 465–477. doi:10.1177/0269881110372545.

Procedural and declarative memory performance, and the memory consolidation function of sleep, in recent and abstinent Ecstasy/MDMA users

Mark Blagrove¹, Jennifer Seddon¹, Sophie George², Andrew C. Parrott¹, Robert Stickgold³, Matthew Walker⁴, Katy Jones¹, and Michael J. Morgan²

¹Swansea University

²University of Sussex and SERAF (University of Oslo)

³Harvard Medical School

⁴University of California, Berkeley

Abstract

This study assessed the effects of ecstasy/MDMA on declarative memory (Rivermead Behavioral Memory task - RBMT), on procedural learning (Finger Tapping Task - FTT), and on the memory consolidation function of sleep for these two tasks. Testing occurred in 2 afternoon testing sessions, 24 hours apart so that a full period of sleep was allowed between them. Groups were: Non-drug taking Controls (n=24); Recent Ecstasy/MDMA users, who had taken ecstasy and/or MDMA 2–3 days before the first testing session (n=25), and Abstinent Ecstasy/MDMA users, who had not taken ecstasy/MDMA for at least 8 days before the first session (n=17). The recent ecstasy/MDMA users performed significantly worse than controls on the RBMT (mean recall 76.1% of control group recall), but did not differ from controls on FTT performance.

Correspondingly there was a significant regression between the continuous variable of recency of ecstasy/MDMA use and RBMT performance. However, there was an interaction between ecstasy/MDMA use and subsequent other drug use. Controls had similar RBMT scores to recent ecstasy/MDMA users who did not take other drugs 48 – 24 hours before testing, but scored significantly better than recent ecstasy/MDMA users who took various other drugs (mainly cannabis) 48 – 24 hours before testing. For both tasks the control, recent ecstasy/MDMA and abstinent ecstasy/MDMA users did not differ in their change of performance across 24 hours; there was thus no evidence that ecstasy/MDMA impairs the memory consolidation function of sleep for either declarative or procedural memory. For participants in the two ecstasy/MDMA groups greater lifetime consumption of ecstasy tablets was associated with significantly more deficits in procedural memory. Furthermore, greater lifetime consumption of ecstasy tablets and of cocaine, were also associated with significantly more deficits in declarative memory.

Keywords

MDMA; ecstasy (drug); sleep; learning; memory; declarative memory; procedural learning; memory consolidation

Introduction

Ecstasy is the street name for $[+/-]$ -3,4-methylenedioxymethamphetamine [MDMA]. This study aimed to examine the declarative and procedural memory performance of frequent ecstasy/MDMA users, 2–3 days after recreational use of ecstasy/MDMA, and during abstinence from ecstasy/MDMA, while controlling for various trait and state factors, including sleep length prior to testing. It also aimed to assess the change in memory across a 24 hour period, so as to investigate a hypothesised effect of ecstasy/MDMA on sleep-dependent memory consolidation.

Relative to drug-naïve controls and ecstasy/MDMA -naïve polydrug controls, the most consistent neurocognitive impairment observed in recreational ecstasy/MDMA users has been deficits in memory and learning (Morgan, 1999; Parrott and Lasky, 1998; Zakzanis et al, 2007; Rogers et al, 2009), although there are a few negative findings (e.g. Back-Madruga et al. 2003). These memory deficits can persist after prolonged abstinence from ecstasy/MDMA (Morgan et al. 2002; Thomasius et al. 2005). It has also been reported that the sub-acute effects of ecstasy/MDMA can disrupt mood, cognition and psychobiological well-being 2–4 days after consumption, although many of these sub-acute deficits recover to baseline values after 7 days (Curran and Travill 1997; Parrott and Lasky, 1998, Verheyden et al. 2003; Curran et al. 2004; Jones et al, 2008; Huxster et al. 2006). In order to separate out these sub-acute effects from the longer term chronic psychobiological effects, we included two subgroups of current ecstasy/MDMA users: those *who had* taken Ecstasy/MDMA in the previous 2–3 days, and those who *had not taken* any Ecstasy/MDMA in the 8 or more days prior to testing.

Our second aim was to assess whether ecstasy/MDMA affects the process of sleep-dependent memory consolidation. A period of sleep on the night after a procedural learning task can improve subsequent performance - despite no intervening practice on the task (Stickgold, 2005; Walker, 2005), and is not due to reduced sleepiness (Walker et al., 2002). The sleep effect is also seen for declarative memory tasks (Axmacher et al, 2008; Ellenbogen et al., 2009), but here usually refers to a smaller deficit in delayed recall performance after sleep than after a similar period spent awake (Born and Gais, 2003).

We hypothesised that the sleep-dependent consolidation effect for declarative and procedural memory might be absent in individuals who consume ecstasy/MDMA, because of the disruptive effects of this drug on sleep (Carhart-Harris et al., 2009; Kirilly et al., 2008; Jones et al., 2008; Pirona and Morgan, 2009; Huxster et al., 2006). The hypothesis of a decrement in procedural memory consolidation is further supported by the finding of an enhancement of memory consolidation during sleep for a procedural finger tapping task when SSRI administration occurred in the period between learning and sleep (Rasch et al. 2009). Such SSRI administration augments serotonin activity, whereas serotonin deficiencies are hypothesised to occur in the days after ecstasy/MDMA use (Thomasius et al, 2003; Walker et al, 2007).

Our third aim was to take account of three areas of confound present in naturalistic studies of recreational ecstasy/MDMA use. The first of these is the co-use of other drugs, which may themselves cause memory deficits (Croft et al., 2001; Gouzoulis-Mayfrank & Daumann, 2006; Lamers et al., 2006; Parrott, 2006). The use of illegal drugs within 24 hours of testing was therefore an exclusion criterion for the study. However, as there is evidence for ketamine (Morgan et al., 2004), cocaine (Schierenbeck et al., 2008) and cannabis (Pope et al., 2001) having cognitive effects longer than 24 hours, after the initial analysis we reanalyzed the data having excluded participants who reported any illegal drug use in the 48–24 hour period prior to testing. The second area of confounds is pre-morbid IQ and also

personality differences between ecstasy/MDMA users and non-users. The following traits which may act as confounds of memory performance, either directly or in interaction with drug-use were proposed: Locus of Control (Blagrove and Akehurst, 2001), conscientiousness (Saucier, 1994), and morningness-eveningness, a measure of preference that the individual has to do effortful or intense work in the morning. Self-reported usual time of maximum alertness was also recorded. A third type of confound addressed is pre- and during-test factors, such as length of sleep (Kuypers et al., 2007) and alcohol, caffeine and nicotine use prior to testing, and level of sleepiness during testing.

To summarise, it was hypothesised that:

1. Declarative memory performance (RBMT) will be impaired in recent and abstinent ecstasy/MDMA users compared to non-drug using controls.
2. Procedural memory (FTT) will be impaired in recent and impaired ecstasy/MDMA users compared to non-drug using controls, and more impaired in recent ecstasy/MDMA users than less recent users and, with respect to the memory consolidation function of sleep,
3. Recent and abstinent ecstasy/MDMA users will exhibit a greater decrement in declarative memory performance, after a night's sleep, than non-drug using controls.
4. Recent and abstinent ecstasy/MDMA users will show a reduced improvement in procedural memory performance, after a night's sleep, compared to non-drug using controls.

Method

Participants and Drug Conditions

117 participants were recruited, following telephone screening for exclusion criteria. All 117 participants were tested and paid so as, on ethical grounds, to avoid giving the impression that participation and payment were dependent upon use, or reported non-use, of any drugs, and so that encouragement to use drugs was not implied. 38 participants were excluded due to not meeting the criteria for membership of the 3 experimental groups. A further 8 were excluded due to reporting taking illegal drugs within the 24 hours before either testing session. One participant (control) was excluded because of alcohol use an hour prior to testing, and 3 recent ecstasy/MDMA users and 1 abstinent ecstasy/MDMA user were excluded due to their reported level of alcohol use in the evening/night prior to testing (reported units for these 4 participants = 40, 30, 21, and 30 respectively). Our final sample was thus a total of 66 participants, divided into three groups:

Control group (n=24; mean age=21.88 yrs (SD = 3.51, range 18 – 29 years); 11 males, 13 females). This comprised participants who reported having never taken ecstasy or MDMA nor other illegal drugs, except for minor cannabis use (defined as lifetime consumption 10 joints) that was not within the last year. 9 in this group (37.5%) reported having used cannabis at least once.

Recent ecstasy/MDMA group (n=25; mean age=21.44yrs (2.40, 18 – 28); 10 males, 15 females). This comprised regular ecstasy/MDMA users (defined as taking ecstasy and/or MDMA at least twice per month) who reported taking ecstasy/MDMA 2–3 days before the first performance testing session.

Abstinent ecstasy/MDMA group (n=17; mean age=22.29yrs (3.26, 18 – 29); 8 males, 9 females). This comprised regular (defined as above) ecstasy/MDMA users who reported not

taking ecstasy or MDMA for 8 days or more before the first performance testing session. Period of abstinence from ecstasy/MDMA for this group ranged from 8 – 28 days before the first performance testing session.

Measures

1. Sleep questionnaire: This included questions on usual time of going to sleep and waking up on work and on rest days, and usual sleep quality ('during the last month, how would you rate your sleep quality overall: 1=very good, 2 = fairly good, 3 = fairly bad, 4 = very bad').
2. Drug history questionnaire, combining the General Drug Use History Questionnaire (GDUQ; Huxster et al., 2006) and the UEL Drug History Questionnaire (Parrott et al., 2000). The questionnaire recorded lifetime history of drug use.
3. The previous 24 hour drug use questionnaire. This assessed self-reported drug use, and caffeine, alcohol and nicotine use, in the 24 hours prior to each performance testing session.
4. The 50 word, National Adult Reading Test (NART; Nelson, 1982). This provides an estimate of pre-morbid full IQ.
5. The short mini-markers version of the Big – 5 personality inventory (Saucier, 1994), to assess Conscientiousness.
6. The Composite Morningness Scale (Smith et al., 1989). This assesses preferred times of day for alert effortful activity, and other circadian rhythm variables. Higher scores represent morningness.
7. Locus of Control questionnaire (Levenson, 1981). This assesses level of belief in whether events or aspects of one's life are under one's internal control.
8. Daily diary for recording drug use, sleep times and mood. The diary included for each day items recording any drugs taken during the day, and the quantities of these, time of going to bed, time taken to fall asleep, time of waking, and also items on self-assessment of mood. For mood, participants completed two 10cm visual analogue scales: 1) anchored as Very tense (score = 0) to Very relaxed (score = 100) and 2) anchored as Very happy (score = 0) to Very sad (score = 100).
9. The Rivermead Behavioral Memory Task (RBMT; Wilson et al., 1985). This involves the participant listening to a 65 word newspaper-type story concerning the fighting of a fire. Free recall was assessed immediately, after a delay of 20 minutes, and then 24 hours later, and scored each time for recall of the 21 idea components.
10. The Finger Tapping Task (FTT; Walker et al., 2002). The FTT involves typing the numbers 4-1-3-2-4 on a keypad for 12 trials of 30 seconds each, with a break of 30 seconds between each trial. Speed is calculated as the number of correct sequences typed in 30 seconds. The crucial comparison is between the mean speed of the last 3 trials on the first testing session and the mean speed of the first 3 trials on the second testing session, which was 24 hours later. Error rate was also assessed.
11. The Stanford Sleepiness Scale (Hoddes et al., 1973). This is a state measure of sleepiness, with items from 1 = 'Feeling active, vital, alert, wide awake', to 7 = 'Almost in reverie, cannot stay awake, sleep onset appears imminent'.

Procedure

Institutional ethics approval was obtained. Written informed consent was obtained from all participants and strict confidentiality was guaranteed. Hair assays were not used to confirm self-reports of ecstasy/MDMA use as ethical issues would have resulted from the holding of such objective evidence of illegal activity, and because it may have reduced the number of people willing to take part in the study.

Advertisements were placed for individuals who frequently attend nightclubs: there was no mention of drugs in the advertisements. This ensured that participants had a similar nightclubbing social life, so that factors such as sporadic late nights and intense dancing are controlled for, but also that self-selection on the basis of drug use did not occur. Such controlling for lifestyle, however, did result in difficulty in finding non-drug taking controls who had never taken cannabis. Thus, it was thus decided to include in the control group participants who had occasionally taken cannabis, but who had not taken it within the last year. The exclusion criteria for all participants were: a history of epilepsy, schizophrenia, bipolar disorder, any intravenous drug use, or any serious current medical condition that requires or has required medication. These were assessed by telephone interview. Substance dependence was not assessed.

Participants then attended an initial questionnaire session at which they completed demographic details, the Sleep times and quality questionnaire, the Morningness Questionnaire, the National Adult Reading Test (NART), and the Drug history questionnaire. They then took home the daily diary for recording sleep times, mood and drug use.

The first performance testing session occurred the following week, usually in an afternoon but sometimes in the early evening. The session comprised: the previous 24 hours drug use questionnaire; the Stanford Sleepiness Scale (SSS); RBMT story presentation and immediate recall; Finger Tapping Task; Locus of Control questionnaire; 20 minute delayed RBMT recall, and SSS.

The second testing session occurred exactly 24 hours later. Tests: 24 hour drug usage questionnaire; SSS; 24 hour delayed RBMT recall; FTT; Big-5 mini-markers, and SSS. At this session the completed daily sleep and drug use diary was returned to the experimenters.

Participants were asked not to take illegal drugs in the 24 hours prior to each performance testing session, and not to take alcohol for 12 hours prior to testing. Anyone who did report doing so was tested and paid for their participation, but are not included in any of the analyses.

Design

Participants were assigned to groups based upon their reported drug use prior to and during the study. Performance tests occurred in two late afternoon testing sessions, held exactly 24 hours apart. Effects of ecstasy/MDMA on sleep-dependent memory consolidation were assessed by the comparison of the groups across this day and night period. The study did not use a further control condition where there was only a period of wakefulness between testing times because previous research, as reviewed above, has shown the superiority of performance after a sleep period than after a wake period for declarative and procedural tasks. Furthermore, due to the variability of sleep times for the illicit drug taking participants it would not have been possible to utilise the usual design of 10:00h and 22:00h (i.e., wake condition) versus 22:00h and 10:00h (i.e., sleep condition) testing times, and so a control wake period matching the sleep periods of the illicit drug participants was not feasible.

Statistics

The data were first analysed with SPSS version 13. The groups were compared for sleep, personality and drug use variables using one way ANOVAs and Kruskal Wallis tests. Repeated measures ANOVAs for the RBMT and FTT were performed, with drug group as a between subjects factor. Comparisons in these ANOVAs are between recent ecstasy/MDMA users and controls, and between abstinent ecstasy/MDMA users and controls, and the threshold p value for each of the two comparisons is thus set at .025. Regressions of RBMT and of FTT on the continuous variable recency of ecstasy/MDMA use were then conducted. Recency of ecstasy/MDMA use was not normally distributed and so non-parametric rank regression was performed, using the RREG procedure on Minitab version 15 (Hollander & Wolfe, 1999). These regression analyses are reported immediately after the corresponding between groups repeated measures ANOVAs. As an association was found between recency of ecstasy/MDMA use and RBMT score the potential confounding variables (e.g., NART IQ, gender, mood, personality) were then investigated by being sequentially entered into the regression equation. The repeated measures ANOVAs were then rerun excluding participants who reported having taken illegal drugs in the period 48 – 24 hours before testing, and the interaction between recent ecstasy/MDMA use and recent other drug use investigated further.

The repeated measures analyses were then further rerun using only participants who had obtained at least 7 hours sleep prior to each of the two performance testing days. The group $\times$ test day interaction was computed in order to establish if the groups differed in the change of memory over the 24 hours, i.e. to test whether ecstasy/MDMA use was associated with differences in memory consolidation.

Multiple regressions were then performed to establish associations between lifetime drug use and mean scores on each of the memory tasks. Lifetime drug use variables were not normally distributed and so these regressions were run with the non-parametric rank regression procedure on Minitab version 15. To avoid multicollinearity of drug use variables the control group participants were not used in these lifetime drug use analyses. Lifetime usage of ecstasy tablets and of MDMA (grams) were entered first, other drug usage variables were then entered stepwise with $p > .05$ set as the criterion for removal of standardized betas from the regression, until the most predictive model was established from the Jaeckel-Hettmansperger-McKean test statistic HM (Hollander & Wolfe, 1999).

Results

There were no sex differences on any personality, drug, IQ, sleep or performance (mean RBMT and mean FTT) variable. Table 1 shows the lifetime drug history for the three groups. The two ecstasy/MDMA groups did not differ significantly on reported lifetime use of any of the drugs. Table 2 shows the level of reported current use of illicit drugs, and of alcohol and tobacco, by the two drug-using groups. Frequency and dose refer to the last year, and are calculated only for individuals who reported having taken the drug within the last year. Cannabis frequency and dose for the drug-naïve control group are thus zero. The only significant difference between groups in illicit drugs was in MDMA frequency, which was significantly higher for the recent ecstasy/MDMA than the abstinent group (Mann-Whitney $U = 88.50$, $z = 2.76$, $p = .005$). The three groups did not differ significantly on alcohol frequency, mean alcohol dose, or number of cigarettes per day. For the recent ecstasy/MDMA group, in the 2 – 3 days prior to the first memory performance testing session, mean self-estimate of ecstasy/MDMA tablets consumed = 2.88 (SD=5.25) and mean self-estimates of grams of MDMA consumed = 0.35 (SD=0.42).

Table 3 shows the group mean scores on personality, usual sleep and diary period mood variables. The groups were significantly different on time of going to sleep at weekends and time of going to sleep on work days. The recent ecstasy/MDMA group was significantly lower in morningness than was the control group, but the groups did not differ on self-reported usual time of maximum alertness, which for all groups was in the afternoon. None of the variables that we speculated might be confounds in the study (i.e., Morningness; Conscientiousness, NART IQ and Locus of Control) were significantly related to both group membership and to task performance (the only significant relationship between any of these variables and performance was between internal LOC and mean Rivermead score, $r=.27$, $p=.03$). Nevertheless, these four variables were introduced into the recency of ecstasy/MDMA use regression analyses to assess whether they were confounds.

Table 4 reports alcohol consumption and sleep length on the evening/night before each testing session, sleepiness during the performance testing sessions, and last use of caffeine prior to the first testing session (time since last use of caffeine was not assessed for the second testing session). Mean mood variables for the day of the first testing session (happy/sad and anxious relaxed) are reported, mean mood scores were not collected on the second testing day. The only significant difference between the groups was in sleepiness at the start of the first session. Across the 4 sleepiness ratings there was no significant difference in sleepiness between the groups ($F(2,63)=1.26$), no effect of day ($F(1,63)=3.58$), no change in sleepiness across the testing session ($F(1,63)=0.56$) and no significant interactions between any of these factors. The similarity between the groups in mood before first testing, and, from Table 3, in mood and variation in mood across the diary period, shows that mood was not a confound for the memory performance results. Last use of nicotine over the previous 24 hours was assessed at testing session 1, there was no significant difference in this between the groups (Kruskal Wallis test, Chi square (2) = .942: Controls, Mean = 6.33 hrs (SD=8.39, $n=3$), Recent ecstasy/MDMA users, mean = 6.59 (7.98, $n=11$), Abstinent ecstasy/MDMA users, mean = 5.17 (6.11, $n=6$)).

Table 5 shows the means on the three RBMT recall tests for the control, recent ecstasy/MDMA and abstinent ecstasy/MDMA groups. There was a significant effect of test ($F(2,126)=30.49$, $p<.001$) with significant decreases in recall between the immediate and 20 minutes delayed testing sessions (Sidak pairwise comparison, $p<.001$) and between 20 minutes delayed testing and 24 hours delayed testing (Sidak pairwise comparison, $p<.05$). There was no interaction between group and change in recall across tests ($F(4,126)=1.23$). The 3 groups differed significantly from each other ($F(2,63)=3.22$, $p<.05$), with a post hoc directional Dunnett test showing that recent ecstasy/MDMA users scored significantly lower than controls ($p=.017$). Over the three tests the recent ecstasy/MDMA users recalled 76.1% of the level of Control group recall.

Non parametric rank regressions were performed to investigate the association between memory and recency of ecstasy/MDMA use. A continuous recency variable was computed as the reciprocal of the number of days since last use of ecstasy or MDMA. This varied from a maximum of 0.5 (reciprocal of 2 days) to 0 (meaning ecstasy or MDMA had never been consumed). This recency variable was entered into a regression as a predictor of the mean of the three Rivermead testing sessions, and the mean of the two FTT speed scores.

For all our participants taken together, recency of ecstasy/MDMA use predicts Rivermead memory score with standardised beta = $-.217$, $p=.01$. When gender was entered into the regression the beta for the recency variable = $-.220$, $p<.01$, beta for gender was not significant. When the morningness, mood, variation in mood, and NART IQ variables from Table 3, and the means of the prior sleep length, prior alcohol consumption and mood variables in Table 4 are entered into the regressions the recency of taking ecstasy/MDMA

remains significantly associated with mean RBMT score, with, in all cases, beta being negative and of greater magnitude than .20, and $p < .025$. Negligible decreases in the size of the beta for recency of ecstasy/MDMA consumption occurred after entry of Locus of Control (beta for ecstasy/MDMA recency = $-.17$, $p = .03$), mean sleepiness (beta for recency = $-.19$, $p = .025$) and conscientiousness (beta for recency = $-.20$, $p < .05$). In all cases where a potentially confounding variable was entered into the regression equation the beta for the potential confounding variable was highly non-significant. However, one confound did occur: when participants who reported having taken illicit drugs in the period 24 – 48 hours prior to testing were excluded from the regression the standardised beta became insignificant (beta = $-.01$; drugs reported to have been consumed were cocaine, ketamine, amphetamine and cannabis). Those who had taken illicit drugs in this period were 16 of the recent ecstasy/MDMA users and 2 abstinent ecstasy/MDMA users. The difference between the three groups on the repeated measures ANOVA also became non-significant ($F(2,45) = 0.20$) when these individuals were excluded.

To examine further this confound of other drug use, Table 6 reports the comparison of RBMT scores for the controls and for the recent ecstasy/MDMA users divided into those who did ($n = 16$) versus those who did not ($n = 9$) consume illicit drugs in the period 48 – 24 hours before testing. (As only 2 members of the abstinent ecstasy/MDMA users group had taken other illicit drugs in the 48–24 hour period further analysis is not possible with that group's members.) The controls and recent ecstasy/MDMA sub-groups differed significantly on RBMT scores ($F(2,46) = 3.95$, $p = .026$), with ecstasy/MDMA participants who had taken other drugs in the period 48 – 24 hours before testing scoring significantly worse than controls (directional Dennett test, $p = .007$), and with recent ecstasy/MDMA users who had not taken other drugs scoring below the controls, but not significantly so.

Importantly, comparisons on various drug use variables between ecstasy/MDMA users who used ($n=16$) or did not use ($n = 9$) illicit drugs 48 – 24 hours prior to testing are presented in Table 7 and show that those who had this other drug use reported similar use of ecstasy tablets, albeit significantly less frequently, and non-significantly higher use of MDMA and cannabis. All other drug use was very similar between the groups. Those who took illicit drugs in the 48 – 24 hours prior to testing reported significantly higher use of MDMA in the 2 – 3 days prior to testing, but non-significantly fewer ecstasy tablets (with median ecstasy tablets for those who took illicit drugs = .25, and median ecstasy tablets for those who did not take illicit drugs = 2). That those recent ecstasy/MDMA who took other drugs prior to testing scored significantly worse than controls, whereas those who did not take other drugs did not score worse than controls, may thus be because of an interaction between ecstasy/MDMA and those other illicit drugs, or because of the higher MDMA use of those who also happened to take other illicit drugs. (It was not possible to treat the taking the illicit drugs 48 – 24 hours before testing as a factor in the repeated measures ANOVAs because only 2 participants in the abstinent ecstasy/MDMA group had used illicit drugs during that period.)

Table 8 shows speed on the last 3 trials of FTT1 and on the first three trials of FTT2. There was a significant increase in speed between the two sessions ($F(1,61)=34.11$, $p < .001$) which did not interact with group ($F(2,61)=0.12$). There were no significant differences between the 3 groups on mean FTT speed ($F(2, 61) = 0.44$). A mean FTT score was then calculated as the mean of the last 3 trials of FTT1 and the first three trials of FTT 2. In a regression analysis recency of taking ecstasy/MDMA has a non-significant beta = $-.06$ for predicting FTT speed score.

Table 7 also reports mean error rates on the last 3 trials of FTT session 1 and on the first 3 trials of FTT session 2. There was a significant decrease in errors between the testing sessions ($F(1,61)=7.22$, $p < .01$), which did not interact with group ($F(2,61)=0.05$). There

were no significant differences between the 3 groups on FTT errors ($F(2,61)=0.81$). The same pattern of inferential results for FTT speed and error rates remained when participants who reported having taken illicit drugs in the period 24 – 48 hours prior to testing were excluded, and negligible changes to the means presented in Table 7 occurred.

Analyses across 24 hours that includes participants who had at least 7 hours sleep

In order to address the hypothesised effect of ecstasy/MDMA on sleep-dependent memory consolidation for RBMT performance, between subjects ANOVAs were run with the score on the second (20 minutes delayed memory) and third (24 hours delayed memory) tests as the repeated measure, for individuals who had obtained at least 7 hours sleep on each of the nights before the 2 testing sessions. Included in the analysis are thus controls, $n=11$; recent ecstasy/MDMA users, $n=13$; and abstinent ecstasy/MDMA users, $n=10$. The means obtained are similar to those presented in table 5 and so are not presented. There was no significant decrease in memory across days ($F(1,31)=1.87$) and no interaction of memory change with group ($F(2,31)=1.53$). There was thus no effect of ecstasy/MDMA on the memory consolidation function of sleep for the Rivermead Behavioural Memory task. There was a significant difference between the three groups in RBMT recall ($F(2,31)=5.63$, $p<.01$) and recent ecstasy/MDMA users differed significantly from Controls (directional Dunnett test, $p=.002$). This significant group difference disappeared if individuals who reported having taken illicit drugs in the period 24 – 48 hours prior to testing were excluded ($F(2,23)=2.55$).

Only individuals who had obtained at least 7 hours sleep on each of the nights before the testing sessions were then included in the between subjects repeated measures ANOVA of the FTT variables. (Participants now included for analysis: controls, $n=11$; recent ecstasy/MDMA, $n=12$; abstinent ecstasy/MDMA, $n=9$; ns differ from RBMT analysis because 2 participants were unable to learn the task The means obtained are similar to those in table 7 and so are not presented). There was a significant increase in speed between testing sessions ($F(1,29)=42.85$, $p<.001$) and significant decrease in errors ($F(1,29)=7.29$). The interaction of test day with group remained non-significant for the FTT speed ($F(2,29)=0.09$) and error analyses ($F(2,29)=0.13$). There was thus no effect of ecstasy/MDMA on the memory consolidation function of sleep for the procedural memory task. Such an interaction could have been interpreted as a state-dependent recall effect, given that the recent ecstasy/MDMA users were learning the Rivermead story 2–3 days after taking ecstasy/MDMA and having delayed recall 3–4 days after consuming ecstasy/MDMA. The lack of a day $\times$ group interaction shows that such an effect was not found.

Associations of memory with lifetime ecstasy/MDMA use

Non parametric rank regressions were run to investigate the prediction of each of the mean memory scores by lifetime drug use. Lifetime usage was chosen as the long term measure of total drug use as it had correlations with memory scores that, in general for the drugs used, exceeded other possible total drug use measures, such as current frequency, current dose and the product of frequency and dose. Table 9 shows the nonparametric multiple regression results for lifetime drug use predictors of mean score on RBMT and FTT.

RBMT: Ecstasy lifetime usage and MDMA lifetime usage were first entered into the regression as predictors. As the continuous variable recency of use of ecstasy/MDMA and the dichotomous variable use of other illegal drugs 48 – 24 hours before testing had been found to be related to RBMT score, these were also entered at the same time. Both MDMA lifetime usage and recency of use of ecstasy/MDMA had non-significant betas and were hence removed from the regression. The next best predictor of RBMT score, cocaine lifetime usage, was then entered which resulted in model 2. Addition of any other lifetime

drug variable failed to add to the predictive value of the model, and all these other variables also had insignificant standardised betas when entered into the regression.

FTT: Ecstasy lifetime usage and MDMA lifetime usage were first entered into the regression as predictors of FTT mean speed. Recency of use of ecstasy/MDMA and the dichotomous variable use of illicit drugs 48–24 hours before testing were not predictive of FTT speed and were not entered into this regression. MDMA lifetime usage was found to have a negligible and non-significant beta ($\beta = -.01$) and so was removed. Model 1 thus had ecstasy lifetime usage as the significant predictor of FTT. The next largest predictor, cocaine lifetime usage, was then added, but it did not improve the predictive value of the model. Addition of any other lifetime drug variable failed to add to the predictive value of the model, and all these variables had non-significant betas.

Discussion

In comparison to non-drug using controls, recent ecstasy/MDMA users showed significant impairment of declarative verbal memory as measured by the Rivermead memory test (Table ..). Recency of ecstasy/MDMA use, as a continuous variable, was also significantly associated with a significant deficit in declarative memory (Table ..). This association remained significant when prior alcohol consumption, prior sleep length, sleepiness during the task, NART estimated pre-morbid IQ, gender, mood and specific personality variable were controlled for. The ecstasy/MDMA using participants were heavier smokers than the controls, but given that participants were not required to abstain from smoking, there should be minimal performance effects related to nicotine. Caffeine use prior to testing did not differ between groups, and so it was also believed not to be a confound. Although we did not assess substance dependence, it is doubtful that deficit in recall for the recent ecstasy/MDMA users was due to any abstinence from ecstasy/MDMA, as only 2 participants reported a frequency of taking ecstasy/MDMA more than twice per week.

In a more detailed analysis, however, it was found that this association of recent ecstasy/MDMA use with impaired declarative recall was only significant for participants who also reported using other illicit drugs between 48–24 hours prior to testing, and not for those who had recently taken ecstasy/MDMA, but had not also taken other illicit drugs in the 48–24 hour period. Importantly, those individuals who used other illicit drugs were not heavier in ecstasy or MDMA use than were those who did not take other illicit drugs prior to testing. However, there were a number of differences between these subjects and those that did not take other illicit drugs during the 48 – 24 hours pre-test period. Firstly, there was a significantly higher recent use of MDMA in the group of participants who took other illicit drugs may have contributed to the declarative memory deficiency of this group. Secondly, given that cannabis was the most prevalent illicit drug used in this 48 – 24 hour period, it may be that there was a residual effect of cannabis that lasted until testing. A third possibility follows from the finding that the ecstasy/MDMA using participants who used illicit drugs in this period were heavier cannabis users in general: participants who took illicit drugs in this period may thus have had greater substance dependence for cannabis that might then have impacted performance as a result of the enforced abstinence period in the 24 hours before testing (Solowij & Battisti, 2008). Finally, it is also possible that there was an interaction between the recent ecstasy/MDMA use and some or all of the other illicit drugs taken that resulted in greater performance deficits. The latter possibility is consistent with investigators who have attributed memory deficits in ecstasy/MDMA users to the concurrent recent use of cannabis and other drugs (Gouzoulis-Mayfrank & Daumann, 2006; Croft et al., 2001; Lamers et al., 2006). It is also consistent with our most recent study (Pirone & Morgan, 2009) in which we observed no sub-acute effects of ecstasy/MDMA on

objective verbal recall performance after systematically controlling for sleep deprivation and concurrent use of all other substances.

The procedural memory performance of recent and abstinent ecstasy/MDMA users did not differ from controls. This is consonant with Zakzanis et al (2007), who noted that ecstasy/MDMA does not cause motor skill deficits. However, whereas the finding that the abstinent ecstasy/MDMA group did not show declarative memory deficits may be partly due to our use of a night-clubbing control group, and there may have been an effect on the types of illicit drug users who were recruited by this not ostensibly being a drug study, this result for declarative memory does appear to contradict Zakzanis et al (2007) and many other reports (e.g. Reneman 2001a, 2001b, 2006; Thomasius et al. 2005, Zakzanis and Young, 2001; Zakzanis and Campbell 2006). The latter findings, though, have not been completely consistent: for example, Reneman et al (2001) reported that ecstasy/MDMA users recalled significantly fewer words than controls on delayed, but not immediate recall, and Thomasius et al (2005) reported that only ex-ecstasy/MDMA users, and not current users, were significantly impaired on verbal recall. Furthermore, although Reneman et al (2006) reported that heavy and ex-ecstasy/MDMA users performed significantly worse on memory tasks than controls, there was no evidence of memory impairment in moderate ecstasy/MDMA users. We acknowledge, however, that there are numerous studies which have shown significant memory effects of chronic ecstasy/MDMA use (review: Parrott, 2006; Rendell et al, 2007).

Nevertheless, the present study did provide some other evidence that ecstasy/MDMA consumption is implicated in impaired declarative and procedural memory. Multiple regression indicated that lifetime usage of ecstasy tablets and of cocaine were (negative) predictors of declarative memory. The association of impaired declarative memory with lifetime ecstasy use is consistent with Schilt et al (2008), de Sola Llopiis et al (2008) and Thomasius et al (2005), and with the view that MDMA-induces neurotoxicity (e.g. Gouzoulis-Mayfrank et al. 2003). The more unexpected association with extent of lifetime cocaine use may be consistent with evidence that cocaine disrupts the HPA axis as a result of its action on 5-HT_{1A}-autoreceptors. There is evidence of down-regulation of 5-HT_{1A} receptors in rat hypothalamus and dentate gyrus after “binge” pattern cocaine administration (e.g. Perrett et al. 1998). It has also been suggested that since psychostimulants are neurotoxic upon both serotonergic and dopaminergic neurons they may act synergistically with MDMA and enhance its long-term adverse effects (Gouzoulis-Mayfrank and Daumann, 2006). The present study also found a significant association between lifetime ecstasy tablet consumption and Finger Tapping Task procedural learning. It is unclear why reported lifetime number of ecstasy tablets consumed was associated with declarative memory and procedural learning, whereas the associations with reported lifetime grams of MDMA consumed were negligible. This may indicate that estimations of powder MDMA use are less accurate than number of tablets consumed, either because powder mass may be difficult to assess, or because powders have more instances where they can be subject to adulteration than do tablets.

On both the declarative and procedural memory tasks there was no support for the third and fourth hypotheses, of a deficit in the memory consolidation effect of sleep for the ecstasy/MDMA users on the two tasks used here. Whether this holds for all forms of sleep-dependent consolidation remains to be determined. Tucker and Fishbein (2009) have recently demonstrate that postsleep performance gains on a declarative paired associates task and on the procedural finger tapping task are very similar regardless of whether subjects obtain a half night or a full night of sleep. It may thus be that the mild effects of ecstasy/MDMA on sleep length and quality are not sufficient to disrupt sleep-dependent memory consolidation for the task used in their and our studies.

Recent and abstinent ecstasy/MDMA users were found to have significantly lower morningness than controls. Future research should assess whether this is a result of extreme evening preference types choosing to take ecstasy/MDMA, or whether this increased eveningness is a result of ecstasy/MDMA use. The latter is a possibility as circadian rhythms are affected by MDMA in hamsters (Colbron et al., 2002) and rats (Balogh et al., 2004). However, it should be noted that morningness scales in general, including the one used here, do confound individual differences in alertness across the day with habitual bed and wake times. Future work should thus address whether, relative to one's normal wake up time, ecstasy/MDMA users and non-users differ in their pattern of alertness across the day. From the results here, all groups had their maximum alertness approximately 5.5 – 6 hours after waking: Frequent ecstasy/MDMA use does not therefore seem to be altering the pattern of alertness across the day.

The present study suffered from a number of potential methodological limitations. One was that we decided not to undertake assays to confirm substance use. Our rationale for this was that we considered it an unnecessary burden on participants since we (Pirone & Morgan, 2009) have recently observed that oral serum assays confirmed that all ecstasy/MDMA users accurately reported using ecstasy/MDMA and all non-users accurately reported abstinence. Furthermore, Thomasius et al. (2003) reported very high concordance between self-reported ecstasy/MDMA use and the results of hair analyses. Parrott (2004) also noted the high purity of ecstasy tablets, so that taking 'ecstasy' tablets typically results in MDMA ingestion. There were other methodological limitations that are generic to naturalistic studies of ecstasy/MDMA users including: difficulties recruiting polydrug users who had never consumed ecstasy/MDMA and, as a consequence, difficulties statistically controlling for the possible influence of other illicit drugs. There was also the fundamental limitation inherent to all cross-sectional studies of being unable to infer causality.

In summary, recent ecstasy/MDMA use only resulted in declarative memory deficits when associated with use of other illicit drugs, in particular cannabis 48 – 24 hours prior to testing. Procedural memory was not affected by recent ecstasy/MDMA use. However, declarative memory deficits, and procedural memory deficits, were both associated with significantly higher levels of lifetime ecstasy tablet usage. Finally, the recreational use of Ecstasy/MDMA did not affect the memory consolidation function of sleep for the declarative or procedural tasks used in the study.

Acknowledgments

this study was funded by UK Economic and Social Research Council award RES-000-22-2426.

References

- Axmacher N, Haupt S, Fernández G, Elger CE, Fell J. The Role of Sleep in Declarative Memory Consolidation—Direct Evidence by Intracranial EEG. *Cerebral Cortex*. 2008; 18:500–507. [PubMed: 17573370]
- Back-Madruga C, Boone KB, Chang L, Grob CS, Lee A, Nations H, Poland RE. Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. *The Clinical Neuropsychologist*. 2003; 17:446–459. [PubMed: 15168910]
- Balogh B, Molnar E, Jakus R, Quate L, Olverman HJ, Kelly PAT, Kantor S, Bagdy G. Effects of a single dose of 3,4-methylenedioxymeth-amphetamine on circadian patterns, motor activity and sleep in drug-naïve rats and rats previously exposed to MDMA. *Psychopharmacology*. 2004; 173:296–309. [PubMed: 15083265]
- Blagrove M, Akehurst L. Personality and the modulation of effects of sleep loss on mood and cognition. *Personality and Individual Differences*. 2001; 30:819–828.

- Born, J.; Gais, S. Roles of early and late nocturnal sleep for the consolidation of human memories. In: Maquet, P.; Smith, C.; Stickgold, R., editors. *Sleep and brain plasticity*. Oxford University Press; 2003.
- Carhart-Harris RL, Nutt DJ, Munafo M, Wilson SJ. Current and former ecstasy users report different sleep to matched controls: a web-based questionnaire study. *Journal of Psychopharmacology*. 2009; 23:249–257. [PubMed: 18562419]
- Colbron S, Jones M, Biello SM. MDMA alters the response of the circadian clock to a photic and non-photic stimulus. *Brain Research*. 2002; 956:45–52. [PubMed: 12426045]
- Croft RJ, Mackay AJ, Mills AT, Gruzelier JG. The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology*. 2001; 153:373–379. [PubMed: 11271410]
- Curran HV, Travill RA. Mood and cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”): Weekend “high” followed by mid-week “low”. *Addiction*. 1997; 92:821–831. [PubMed: 9293041]
- Curran HV, Rees H, Hoare T, Hoshi R, Bond AJ. Empathy and aggression: two faces of ecstasy? A study of interpretative bias and mood change in ecstasy users. *Psychopharmacology*. 2004; 173:425–433. [PubMed: 14735288]
- Ellenbogen JM, Hulbert JC, Jiang Y, Stickgold R. The Sleeping Brain's Influence on Verbal Memory: Boosting Resistance to Interference. *PLoS ONE*. 2009; 4(1):e4117. [PubMed: 19127287]
- Gouzoulis-Mayfrank E, Daumann J. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *Journal of Psychopharmacology*. 2006; 20:188–193. [PubMed: 16510477]
- Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; 27:819–827. [PubMed: 12921915]
- Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. *Psychophysiology*. 1973; 10:431–436. [PubMed: 4719486]
- Hollander, M.; Wolfe, DA. *Nonparametric statistical methods*. 2nd edition. New York: Wiley-Interscience; 1999.
- Huxster JK, Pirone A, Morgan MJ. The sub-acute effects of recreational Ecstasy (MDMA) use: A controlled study in humans. *Journal of Psychopharmacology*. 2006; 20:281–290. [PubMed: 16510486]
- Jones KA, Callen F, Blagrove M, Parrott AC. Sleep, energy and self rated cognition across 7 nights following recreational ecstasy/MDMA use. *Sleep and Hypnosis*. 2008; 10:16–28.
- Kirilly E, Molnar E, Balogh B, Kantor S, Hansson SR, Palkovits M, Bagdy G. Decrease in REM latency and changes in sleep quality parallel serotonergic damage and recovery after MDMA: a longitudinal study over 180 days. *International Journal of Neuropsychopharmacology*. 2008; 11:795–809. [PubMed: 18261250]
- Lamers CT, Bechara A, Rizzo M, Ramaekers JG. Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. *J Psychopharmacol*. 2006; 20:302–311. [PubMed: 16510488]
- Levenson, H. Differentiating among internality, powerful others, and chance. In: Lefcourt, HM., editor. *Research with the locus of control construct, vol.1: assessment methods*. New York: Academic Press; 1981.
- Montgomery C, Fisk JE, Wareing M, Murphy P. Self reported sleep quality and cognitive performance in ecstasy users. *Hum Psychopharmacol*. 2007; 22:537–548. [PubMed: 17960556]
- Morgan CJ, Riccelli M, Maitland CH, Curran HV. Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug Alcohol Depend*. 2004; 75:301–308. [PubMed: 15283951]
- Morgan MJ. Memory deficits associated with recreational use of “ecstasy” (MDMA). *Psychopharmacology*. 1999; 141:30–36. [PubMed: 9952062]
- Morgan MJ, McFie L, Fleetwood H, Robinson JA. Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology*. 2002; 159:294–303. [PubMed: 11862362]
- Nelson, HE. *National Adult Reading Test (NART): Test manual*. Windsor, UK: NFER-Nelson; 1982.

- Parrott AC. Is Ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology*. 2004; 173:234–241. [PubMed: 15007594]
- Parrott AC. MDMA in humans: factors which influence the neuropsychobiological profiles of recreational Ecstasy users: the integrative role of bioenergetic stress. *Journal of Psychopharmacology*. 2006; 20:147–163. [PubMed: 16510474]
- Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology*. 1998; 139:261–268. [PubMed: 9784083]
- Parrott AC, Sisk E, Turner JJD. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug Alcohol Depend*. 2000; 60:105–110. [PubMed: 10821995]
- Perrett G, Schluger JH, Unterwald EM, Kreuter J, Ho A, Kreek MJ. Down-regulation of 5-HT1A receptors in rat hypothalamus and dentate gyrus after "binge" pattern cocaine administration. *Synapse*. 1998; 30:166–171. [PubMed: 9723786]
- Pirone A, Morgan MJ. An investigation of the sub-acute effects of ecstasy on neuropsychological performance, sleep and mood in regular ecstasy users. *Journal of Psychopharmacology*. 2009 (in press).
- Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*. 2001; 58:909–915. [PubMed: 11576028]
- Rasch B, Pommer J, Diekelmann S, Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nat Neurosci*. 2009; 12:396–397. [PubMed: 18836440]
- Rendell PG. Prospective memory impairment in "ecstasy" (MDMA) users. *Psychopharmacology (Berl)*. 2007; 194:497–504. [PubMed: 17619860]
- Reneman L, Booij J, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, den Heeten GJ, van den Brink W. Effects of dose, sex, and long-term abstinence from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet*. 2001; 358:1864–1869. [PubMed: 11741626]
- Reneman L, Schilt T, de Win MM, Booij J, Schmand B, van den Brink W, Bakker O. Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users. *J Psychopharmacol*. 2006; 20:389–399. [PubMed: 16574713]
- Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, Zawada A, Somerville M. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technol Assess*. 2009; 13(6):iii–iv. ix–xii, 1–315. [PubMed: 19195429]
- Saucier G. Mini-Markers: A Brief Version of Goldberg's Unipolar Big-Five Markers. *Journal of Personality Assessment*. 1994; 63:506–516. [PubMed: 7844738]
- Schierenbeck T, Riemann D, Berger M, Horny M. Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana. *Sleep Medicine Reviews*. 2008; 12:381–389. [PubMed: 18313952]
- Schilt T, de Win MM, Jager G, Koeter MW, Ramsey NF, Schmand B, van den Brink W. Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users. *Psychol Med*. 2008; 38(9):1309–1317. [PubMed: 17988417]
- Smith CS, Reilly C, Midkiff K. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *Journal of Applied Psychology*. 1989; 74:728–738. [PubMed: 2793773]
- de Sola Llopis S, Miguelez-Pan M, Peña-Casanova J, Poudevida S, Farré M, Pacifici R, Böhm P, Abanades S, Verdejo García A, Langohr K, Zuccaro P, de la Torre R. Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. *Journal of Psychopharmacology*. 2008; 22:498–510. [PubMed: 18208910]
- Solowij N, Battisti R. The Chronic Effects of Cannabis on Memory in Humans: A Review. *Current Drug Abuse Reviews*. 2008; 1:81–98. 2008, 81. [PubMed: 19630708]
- Stickgold R. Sleep-dependent memory consolidation. *Nature*. 2005; 437:1272–1278. [PubMed: 16251952]
- Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoltdt A. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology*. 2003; 167:85–96. [PubMed: 12632248]

- Thomasius R, Petersen KU, Zapletalova P, Wartberg L, Zeichner D, Schmoldt A. Mental disorders in current and former heavy ecstasy (MDMA) users. *Addiction*. 2005; 100:1310–1319. [PubMed: 16128720]
- Tucker M, Fishbein W. The impact of sleep duration and subject intelligence on declarative and motor memory performance: how much is enough? *Journal of Sleep Research*. 2009; 18:304–312. [PubMed: 19702788]
- Verheyden SL, Henry JA, Curran HV. Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. *Hum Psychopharmacol*. 2003; 18:507–517. [PubMed: 14533132]
- Walker M. A refined model of sleep and the time course of memory formation. *Behavioral and Brain Sciences*. 2005; 28:51–64. [PubMed: 16047457]
- Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002; 35:205–211. 2002. [PubMed: 12123620]
- Walker QD, Williams CN, Jotwani RP, Waller ST, Francis R, Kuhn CM. Sex differences in the neurochemical and functional effects of MDMA in Sprague-Dawley rats. *Psychopharmacology (Berl)*. 2007; 189:435–445. [PubMed: 17019566]
- Wilson, BA.; Cockburn, J.; Baddeley, A. *Rivermead Behavioral Memory Test (RBMT)*. Oxford, UK: Pearson; 1985.
- Zakzanis KK, Campbell Z, Jovanovski D. The neuropsychology of ecstasy (MDMA) use: a quantitative review. *Hum Psychopharmacol*. 2007; 22:427–435. [PubMed: 17896346]

Table 1

Lifetime drug consumption for the control and ecstasy groups

	Controls	Recent Ecstasy/MDMA	Abstinent Ecstasy/MDMA
	n=24	n=25	n=17
Alcohol ever n =	24	25	17
Tobacco ever n =	12	25	16
Cannabis ever n=	9	25	16
Cannabis lifetime consumption (joints)	3.6 (2.9)	3771.1 (8057.1)	2969.3 (4764.0)
Ecstasy ever n=	0	25	17
Ecstasy lifetime consumption (tablets)		268.8 (274.9)	422.1 (511.6)
MDMA ever n=	0	23	17
MDMA lifetime consumption (g)		43.5 (49.0)	48.9 (102.4)
Cocaine ever n=	0	24	15
Cocaine lifetime consumption (g)		47.6 (68.7)	55.6 (63.3)
Amphetamine ever n=	0	14	12
Amphetamine lifetime consumption (g)		18.2 (19.3)	47.4 (101.8)
Ketamine ever n=	0	23	11
Ketamine lifetime consumption (g)		25.9 (73.8)	70.0 (151.0)
Mushrooms n=	0	16	10
Mushrooms lifetime consumption (hits)		7.4 (6.4)	12.2 (7.0)
LSD n=	0	10	7
LSD lifetime consumption (tabs)		7.2 (9.4)	20.1 (30.0)
Heroin (non-IV) n=	0	1	1
Heroin lifetime consumption (g)		2.0	0.1
Poppers n =	0	19	12
Poppers lifetime consumption (hits)		90.8 (150.3)	140.5 (276.1)

Table 2

Current alcohol, tobacco and illicit drug use by the three drug using groups over the previous year. n = Number of participants reporting use of each substance during the previous year. Frequency = number of days on which consumption occurred in the past year.

	Recent Ecstasy/MDMA	Abstinent Ecstasy/MDMA
	n=25	n=17
^a Alcohol	25	17
^a Alcohol usual dose (units)	12.48 (11.17)	10.24 (5.61)
^a Alcohol frequency (per year)	183.04 (82.23)	208.47 (110.78)
^b Tobacco	24	15
^b Tobacco, cigarettes per day	9.79 (7.56)	7.30 (4.90)
Cannabis	22	11
Cannabis usual dose (joints)	2.93 (2.65)	2.15 (1.29)
Cannabis frequency (per year)	155.77 (149.65)	79.36 (101.09)
Ecstasy	23	16
Ecstasy usual dose (tablets)	3.48 (2.29)	3.31 (1.29)
^c Ecstasy frequency	40.22 (36.27)	39.25 (29.22)
MDMA	23	17
MDMA usual dose (g)	0.68 (0.30)	0.66 (0.45)
^d MDMA frequency *	57.09 (57.53)	23.69 (26.51)
Cocaine	24	14
Cocaine usual dose (g)	0.86 (0.40)	0.98 (0.82)
Cocaine frequency	31.42 (35.32)	40.79 (40.39)
Amphetamine	11	4
Amphetamine usual dose (g)	0.98 (0.57)	1.00 (0.71)
Amphetamine frequency	23.64 (32.59)	53.75 (58.04)
Ketamine	22	10
Ketamine usual dose (g)	0.70 (0.66)	0.86 (0.69)
Ketamine frequency	16.52 (17.92)	21.10 (19.87)
Mushrooms	8	4
Mushrooms frequency	2.75 (2.12)	2.25 (1.89)
LSD	5	4
LSD usual dose (tabs)	1.40 (0.55)	1.75 (0.50)
LSD frequency	2.60 (1.34)	3.00 (2.00)
Poppers	13	7
Poppers usual dose (hits)	8.38 (8.53)	8.86 (8.09)
Poppers frequency	9.92 (11.52)	13.29 (14.36)

Notes:

^aNon-drug controls: alcohol use in previous year (n = 24), usual dose = 8.42 units (SD= 5.24), frequency = 138.71 per year (SD = 74.07). Usual dose has non-significant difference between groups, Kruskal Wallis test, chi sq (2) = 4.95. Frequency has non-significant difference between groups, Kruskal Wallis test, chi sq (2) = 3.01.

^bNon-drug controls: tobacco use in previous year (n=11), mean = 2.00 cigarettes per day (SD=1.55). Cigarettes per day differs between groups, Kruskal Wallis test, chi sq (2) = 13.91, p=.001. Significant difference between controls and recent ecstasy users, Mann Whitney U = 38.00, z=3.41, p=.001, and between controls and abstinent ecstasy users, Mann Whitney U = 22.00, z=3.23, p=.001.

^cNo frequency of using ecstasy exceeded twice per week

^dOnly 2 participants, both in the recent ecstasy/MDMA group, reported a frequency of taking MDMA > twice per week (these were 156 and 260 times per year)

* Ecstasy groups differ at p=.005, Mann Whitney

Table 3

Mean of IQ, Personality, habitual sleep variables, and diary mood variables for the Controls, Recent Ecstasy/MDMA and Abstinent Ecstasy/MDMA groups.

	Controls (n=24)		Recent E/MDMA (n=25)		Abstinent E/MDMA (n=17)		F(2,63)	p
	Mean	SD	Mean	SD	Mean	SD		
NART Full IQ	114.25	5.39	113.04 ^a	4.60	117.24 ^a	3.90	4.04	.022
Conscientiousness	39.83	2.97	39.44	4.41	40.88	3.92	0.74	n.s.
Internal locus of control	34.38	5.75	30.68	3.79	31.74	8.04	2.56	n.s.
Usual sleep quality ¹	2.21	0.51	2.56	0.77	2.35	0.61	1.85	n.s.
Time of going to sleep on work days	0:16	1:16	0:58	1:24	0:00	1:05	3.39	.040
Time of going to sleep on weekends ²	1:32 ^{bc}	1:23	3:23 ^c	2:02	3:18 ^b	1:28	8.76	<.001
Time of waking on work days	8:42	1:17	9:22	1:36	8:51	1:14	1.52	n.s.
Time of waking on weekends ²	10:13	1:59	11:18	1:35	10:50	1:19	2.46	.04
Morningness	31.46 ^b	6.02	26.12 ^b	5.40	27.47	6.03	5.49	.006
Time of maximum alertness	14:47	3:43	15:27	2:57	14:14	4:15	0.60	n.s.
Mood across diary: happy / sad ³	36.59	9.49	35.37	15.38	39.33	10.06	0.54	n.s.
Mood across diary: tense / relaxed ⁴	59.80	11.86	62.05	12.59	57.23	10.40	0.85	n.s.
Variation in happy/sad across diary	17.38	5.99	17.33	7.91	17.31	7.10	0.00	n.s.
Variation in tense/relaxed across diary	18.18	4.09	19.95	8.68	18.89	6.68	0.42	n.s.

Notes:

¹ Scale ranged: 1=very good, to 4 = very bad.

² Recent Ecstasy/MDMA n = 24, Abstinent Ecstasy/MDMA n=16; F has dfs (2,61)

³ Visual analogue scale scored as Very happy (score = 0) to Very sad (score = 100).

⁴ Visual analogue scale scored as Very tense (score = 0) to Very relaxed (score = 100)

aa between groups comparison p<.025, Dunnett test

bb between groups p<.01, Dunnett test

Table 4

Means of alcohol consumption and sleep length on the evening/night prior to each testing session, and sleepiness at the start and at the end of each testing session, for the Controls (n=24), recent ecstasy users (n=25) and abstinent ecstasy users (n=17).

	Controls		Recent Ecstasy/MDMA		Abstinent Ecstasy/MDMA		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F(2,63)	P
Session 1								
Alcohol on evening/night before session	0.92	1.86	2.14	3.68	3.47	4.52	2.82	n.s.
Sleep length on night before session	8:03	1:38	7:47	2:32	7:30	2:27	0.30	n.s.
Last use of caffeine (hrs before testing) ¹	5:80	6:84	4:20	3:05	2:00	1:55	1.21	n.s.
Sleepiness at start of session ²	2.21 [*]	0.83	3.00 [*]	0.87	2.65	1.32	3.92	.025
Sleepiness at end of session ²	2.38	1.24	3.04	1.06	2.88	1.45	1.89	n.s.
Happy / sad on day of session ^{1,3}	31.75	19.53	36.89	21.92	37.35	20.82	0.48	n.s.
Anxious / relaxed on day of session ^{1,4}	61.92	20.83	64.17	20.16	55.29	20.14	0.90	n.s.
Session 2								
Alcohol on evening/night before session	2.94	4.74	1.74	3.43	3.29	5.16	0.76	n.s.
Sleep length on night before session	7:26	1:12	7:46	3:02	7:34	1:32	0.15	n.s.
Last use of caffeine (hrs before testing) ⁵	3.13	1.46	4.39	4.40	5.94	6.21	0.80	n.s.
Sleepiness at start of session ²	2.42	1.35	2.52	1.12	2.29	0.77	0.20	n.s.
Sleepiness at end of session ²	2.42	1.32	2.36	0.95	2.41	0.94	0.02	n.s.

* and * groups differ p<.025 (Dunnett test)

¹Numbers taking coffee in previous 24 hours: controls, n=10, recent E, n=10, abstinent E, n=6, dfs for ANOVA = 2,23.

²₁= Feeling active, vital, alert, wide awake to 7 = Almost in reverie, cannot stay awake, sleep onset appears imminent.

³happy (0) to sad (100)

⁴anxious (0) to relaxed (100)

⁵Numbers taking coffee in previous 24 hours: controls, n=8, recent E, n=17, abstinent E, n=8, dfs for ANOVA = 2,30.

Scores on Rivermead Behavioral Memory Task for Control, recent ecstasy users and abstinent ecstasy users. All participants reported no drug use in the 24 hours before testing.

Table 5

	n	Immediate recall		20 mins delayed recall		24 hours delayed recall		Between-group comparisons (Dunnett test, 1 tail)
		Mean	SD	Mean	SD	Mean	SD	
All Ps	66							
Controls	24	9.56 *	3.73	8.60 *	3.47	8.19 **	3.67	] p=0.17]
Recent Ecstasy users	25	7.48 *	2.78	6.66 *	3.05	5.90 **	2.99	
Abstinent ecstasy users	17	8.91	2.72	8.03	2.67	8.09	2.37	

* and * groups differ p < .025 (1-tail)

** and ** groups differ p = .01 (1-tail)

Score on Rivermead Behavioural Memory Task for controls, recent ecstasy users who reported no use of other illicit drugs 48 – 24 hours before testing, and recent ecstasy users who reported illicit drug use 48 – 24 hours before testing.

Table 6

	n	Immediate recall		20 minutes delayed recall		24 hours delayed recall		Dunnett test (directional) comparison of main effect
		Mean	SD	Mean	SD	Mean	SD	
Controls	24	9.56*	3.73	8.60*	3.47	8.19**	3.67	] p=.007]
Recent Ecstasy users without other illicit drug use	9	8.72	3.15	8.00	4.01	7.28	3.80	
Recent ecstasy users with other illicit drug use	16	6.78*	2.37	5.91*	2.16	5.13**	2.19	

Between groups directional Dennett test comparisons:

* and * p<.025

** and ** p<.01

Comparison of ecstasy/MDMA variables for recent ecstasy/MDMA users who took versus did not take illicit drugs 48 – 24 hours prior to testing

Table 7

	Ecstasy/MDMA users who did not take illicit drugs 24 – 48 hours prior to testing (n=9)		Ecstasy/MDMA users who took illicit drugs 24 – 48 hours prior to testing (n=16)		Comparison between groups (Mann Whitney test)
	Mean	SD	Mean	SD	
Ecstasy lifetime usage (tablets)	252.78	155.76	277.75	328.27	n.s.
Ecstasy frequency (per year)	66.44	37.06	20.44	24.14	p<.001 U = 14.00, z = 3.38
Ecstasy usual dose (tablets)	2.94	2.70	3.34	2.29	n.s.
MDMA lifetime usage (g)	35.11	45.39	42.81	51.28	n.s.
MDMA frequency (per year)	43.33	39.04	57.69	66.05	n.s.
MDMA usual dose (g)	0.48	0.36	0.70	0.32	n.s.
Cannabis lifetime usage (joints)	1318	2799	4998	9583	n.s.
Cannabis frequency (per year)	63.00	71.41	178.75	166.61	n.s.
Cannabis usual dose (joints)	1.72	1.48	3.07	3.10	n.s.
Ecstasy tablets consumed in 2 – 3 days prior to testing	2.94	2.96	2.84	6.28	n.s.
MDMA consumed in 2 – 3 days prior to testing	0.11	0.22	0.48	0.46	p<.05 U = 29.50 Z = 2.50

Notes:

Participants excluded for drug use 48 – 24 hours prior to testing had consumed only amphetamine (n=1), only ketamine (n=1), only cocaine (n=1), cocaine & cannabis (n=3) and only cannabis (n=8).

For all other drugs assessed there were no significant differences between the two conditions (included versus excluded for 24 – 48 hr drug use) on any lifetime usage, frequency of use or usual dose variable. There were also no significant differences in nicotine or alcohol use.

Mean speed and error rates on the Finger Tapping Task for Control, recent ecstasy users and abstinent ecstasy users for all participants (n=64^a). Means refer to the last 3 FTT trials of the first performance testing session and the first 3 trials of the second testing session, which is 24 hours later.

Table 8

	n	Day 1		Day 2	
		Mean	SD	Mean	SD
Speed					
Controls	24	17.68	5.09	20.04	5.22
Recent Ecstasy users	24	17.40	5.86	20.12	5.32
Abstinent ecstasy users	16	19.10	5.65	21.35	6.12
Error rate					
Controls	24	0.22	0.23	0.12	0.09
Recent ecstasy users	24	0.24	0.34	0.13	0.11
Abstinent ecstasy users	16	0.29	0.30	0.21	0.28

Note:

^aData are missing for two participants who were unable to learn the task, one from the recent ecstasy and one from the abstinent ecstasy groups.

Table 9

Nonparametric rank regression results, including standardised beta and Jaekel-Hettmansperger-McKean test statistic HM, for predictors of mean scores on Rivermead Behavioral Memory Test and Finger Tapping Task for ecstasy users (n=42).

Dependent variable, model, and rejected predictors	Significant predictors	B	SE	Beta	HM statistic	P
RBMT						
Enter: Ecstasy lifetime usage; MDMA lifetime usage; recency of taking ecstasy/MDMA; use of illicit drugs 48–24 hours before testing						
Model 1						
	Ecstasy lifetime usage	–0.00227	0.00115	–.20	4.96	.026
	Use of illicit drugs 48–24 hr before testing	2.32520	0.89210	.64	8.58	.003
Rejected (p>.05): MDMA lifetime usage Recency of taking ecstasy/MDMA					10.73 (df=2)	.0047
Enter: Cocaine lifetime usage						
Model 2						
	Ecstasy lifetime usage	–.00176	0.00097	–.15	4.23	.040
	Use of illicit drugs 48 – 24 hours before testing	2.52020	0.75090	.69	11.37	.0007
	Cocaine lifetime usage	–0.01541	0.00580	–.16	7.69	.006
					19.25 (df=3)	.0002
FTT speed						
Enter: Ecstasy lifetime usage; MDMA lifetime usage ^a						
Model 1						
Rejected (p>.05): MDMA lifetime usage	Ecstasy lifetime usage	–0.00515	0.00260	–.17	4.99	.026

Note: HM statistic is converted to p by reference to Chi Square distribution (Hollander & Wolfe, 1999). HM has df = 1 unless otherwise stated. RBMT Model 1, F(2,39) = 4.68; Model 2, F(3,38) = 6.18; FTT Model 1, F(1,40) = 4.55.

Recency of taking ecstasy/MDMA and use of illicit drugs 48 hours before testing were both highly non-significant as predictors of FTT speed, and hence were not entered.