

# Ecstasy (MDMA) and memory function: a meta-analytic update

Keith R. Laws\* and Joy Kokkalis

*School of Psychology, University of Hertfordshire, UK*

A meta-analysis was conducted to examine the impact of recreational ecstasy use on short-term memory (STM), long-term memory (LTM), verbal and visual memory. We located 26 studies containing memory data for ecstasy and non-ecstasy users from which effect sizes could be derived. The analyses provided measures of STM and LTM in 610 and 439 ecstasy users and revealed moderate-to-large effect sizes (Cohen's  $d$ ) of  $d = -0.63$  and  $d = -0.87$ , respectively. The difference between STM versus LTM was non-significant. The effect size for verbal memory was large ( $d = -1.00$ ) and significantly larger than the small effect size for visual memory ( $d = -0.27$ ). Indeed, our analyses indicate that visual memory may be affected more by concurrent cannabis use. Finally, we found that the total lifetime number of ecstasy tablets consumed did not significantly predict memory performance. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — ecstasy; MDMA; methylenedioxymethamphetamine; memory; meta-analysis; neurotoxicity

## INTRODUCTION

Ecstasy (MDMA or 3,4-methylenedioxymethamphetamine) is an increasingly popular recreational drug that has provoked much public concern regarding the health consequences. MDMA is a potent, indirect monoaminergic agonist that elicits pharmacological effects which both inhibits the reuptake and promotes the acute release of serotonin (5-HT) among other neurotransmitters, for example dopamine (McDowell and Kleber, 1994; Liechti and Vollenweider, 2001).

Animal studies point to the neurotoxic potential of MDMA on serotonergic terminals (Ricaurte and McCann, 1992; Ricaurte *et al.*, 2000), with repeated administration resulting in low serotonin levels and low densities of serotonin reuptake sites especially in the frontal lobes and hippocampus, where 5-HT terminals and axons are abundant (review in Green *et al.*, 2003). Growing evidence suggests that these toxic effects can be long lasting or even permanent in experimental animals (Fischer *et al.*, 1995; Hatzidi-

mitriou *et al.*, 1999). While ecstasy may be neurotoxic in humans (review in Green *et al.*, 2003), the evidence must, however, be indirect. Nevertheless, if the reported memory problems in ecstasy users do reflect the neurotoxic impact on 5-HT neurons, then we would expect the functional consequences to increase with continued use in humans. Despite increasing research interest, a clear picture of long-term effects of ecstasy (MDMA) on human cognitive function has yet to be determined (see Kalechstein *et al.*, 2007).

The ability to determine the contribution of MDMA-induced serotonergic neurotoxicity to memory deficit is difficult in human studies. Open trial studies of recreational drug users and controls suffer from confounding variables including polydrug use, problems associated with uncertain dosage, drug purity and the chemical composition of illegally purchased drugs (reviewed in Curran, 2000). Although cross-sectional studies with user populations suffer from substantive methodological problems, it has been argued that the evidence for neurotoxicity-related memory decline in ecstasy users is strong (Back-Madruga *et al.*, 2003; Bhattachary and Powell, 2001; Bolla *et al.*, 1998; Gouzoulis-Mayfrank *et al.*, 2000, 2003; Hanson and Luciana, 2004; Krystal *et al.*, 1992; McCardle *et al.*, 2004; Morgan, 1999; Parrott

\*Correspondence to: Prof. K. R. Laws, School of Psychology, University of Hertfordshire, College Lane, Hatfield, AL10 9AB, UK. Tel: +44-(0)1707-281137. E-mail: k.laws@herts.ac.uk

and Lasky, 1998; Reneman *et al.*, 2000; Rodgers *et al.*, 2001; Zakzanis and Young, 2001). Many studies have indeed reported dose-related impairments of learning and memory performance in *currently abstinent* ecstasy users (Bhattachary and Powell, 2001; Bolla *et al.*, 1998; Gouzoulis-Mayfrank *et al.*, 2000, 2003; Hanson and Luciana, 2004; Krystal *et al.*, 1992; McCardle *et al.*, 2004; Morgan, 1999; Parrott and Lasky, 1998; Reneman *et al.*, 2000; Rodgers, 2001; Rodgers *et al.*, 2003; Zakzanis and Young, 2001).

Nonetheless, a minority of studies have reported no memory differences between ecstasy users and controls (Dafters *et al.*, 1999; Wareing *et al.*, 2000); and a recent study reported an association between low-memory performance and the extent of the concurrent use of cannabis rather than the use of ecstasy *per se* (Dafters *et al.*, 2003).

A previous meta-analysis by Verbaten (2003) comparing memory performance in healthy controls and ecstasy users reported very large effect sizes both for short-term memory (STM:  $d = 1.55$ ) and for long-term memory (LTM:  $d = 1.88$ ). Verbaten's meta-analysis reviewed 10 early STM and LTM studies that were available prior to August 2002; however, the recent surge in relevant studies should help provide a more reliable estimate of memory ability in recreational ecstasy users. The present meta-analytic review updates the current picture concerning the impact of recreational ecstasy use on memory. The current meta-analysis extends the previous meta-analysis by including the large number of recent studies. As well as assessing the impact of ecstasy on STM and LTM, recent studies allow us to compare the relative impact on verbal and visual memory domains. Finally, further analyses also throw new light on the role of confounding/moderator variables that might mediate the relationship between memory and ecstasy consumption (including lifetime dose of ecstasy, concurrent use of cannabis and size of ecstasy sample).

## METHOD

An electronic search for all articles (until the end of 2006) which compared recall memory performance in current users of ecstasy and healthy non-using controls. The relevant studies were traced by using Medline, Google Scholar, PsyInfo, National Institute on Drug Abuse official site and Erowid. The keywords were: *MDMA*, *memory*; *ecstasy*, *cogniti\**; *neuropsych\** and combinations of these keywords. We also performed supplementary searches through a number

of core online journals using the same key words and a search through the reference sections of retrieved papers. The main journals that were searched were: *Addiction*, *Archives of General Psychiatry*, *Biological Psychiatry*, *The Clinical Neuropsychologist*, *Cognitive Neuropsychiatry*, *Drug and Alcohol Dependence*, *Human Psychopharmacology*, *Journal of Psychopharmacology*, *Journal of Neurology Neurosurgery and Psychiatry*, *Psychopharmacology*, *Psychological Medicine*, *Neurology*, *Neuropsychobiology* and *Neuropsychopharmacology*.

The main search revealed more than 300 hits for the keywords. From the initial sample of studies, we removed those that focussed on Neuroimaging/Brain imaging, animal behaviour, neurobiological or physiological measures. After filtering, 28 relevant studies remained comparing memory test performance in ecstasy users and non-ecstasy using controls. Studies were included when they contained relevant memory subtest data (such as those described below) for an appropriate non-MDMA using control group that could be used to derive an effect size. In only eight studies could the controls be described as drug naïve (Bhattachary and Powell, 2001; Croft *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2000; Morgan, 1998; Rodgers, 2000; Roiser *et al.*, 2007; Thomasius *et al.*, 2006; Verkes *et al.*, 2001).

The memory tasks<sup>1</sup> included standardised recall memory measures such as digit span (forward), spatial span (forward), visual reproduction, logical memory, visual and verbal paired associates, the Rivermead behavioural memory test battery, the Rey Auditory Verbal Learning Test, the Coughlan list, California Verbal Learning Test, Rey-Osterreith Complex Figure Test. Long-term measures typically involved the use of delayed administrations of the tasks. Most studies included more than one measure of STM, LTM, verbal and/or visual memory. In studies with more than one measure of the same memory function, for example STM (using the same memory patients and controls), we aggregated individual test effect sizes to produce an average effect size (rather than arbitrarily select one memory measure to calculate the effect size: cf. previous meta-analysis by Verbaten). Studies sometimes included more than one ecstasy subgroup (e.g. heavy, medium and low users; report problems vs. do not report problems; former vs. current users). In these situations we compared controls with the heaviest user group (as per the previous meta-analysis by Verbaten); where ecstasy groups included those who did and did

<sup>1</sup>This excluded studies that used self-ratings of memory performance rather than actual measures (e.g. Heffernan *et al.*, 2001).

not report problems, we included the former; and finally, when studies contained former and current users, only the latter were included.

Data obtained from each study were converted into the effect size 'Cohen's  $d$ ', which is the difference between the patient and control group means divided by their pooled standard deviation. When means and standard deviations were not provided,  $d$ -values were computed from exact  $p$ -values,  $t$ -values or  $F$ -values. Hedges' (Hedges and Olkin, 1985)  $d$  correction was used to correct for the tendency of studies with small sample sizes to overestimate the population effect size. All effect sizes were extracted independently by both authors and all differences resolved.

The meta-analysis was conducted using *MetaWin 2.1* (Rosenberg *et al.*, 2000). All analyses initially used the fixed effects model, but where studies significantly deviated from homogeneity, we also used a random effects model (which assumes random variation in the effect of interest among the studies). Homogeneity was calculated using the  $Q_{wi}$  statistic (Hedges and Olkin, 1985), which tests whether the studies can be taken to share a common population effect size. A significant  $Q_{wi}$  statistic indicates heterogeneity of the individual study effect sizes, that is whether the variability of ES is larger than would be expected from sampling error (Lipsey and Wilson, 2001). To test for the significance of the mean effect, bias-corrected confidence intervals were calculated using bootstrapping with 999 replications run in *MetaWin 2.1* (Rosenberg *et al.*, 2000). This approach does not require that effect sizes be parametrically distributed. Effect sizes are considered significantly different from zero when the confidence interval does not include zero. After computing effect sizes for each study, meta-analytic methods were applied in order to obtain a combined effect size, which indicated the magnitude of the association across all studies. Effect sizes were calculated both weighted for variance (to correct for upwardly biased estimation of the effect in small sample sizes) and unweighted. The nomenclature of Cohen (1988) suggests the following classification of effect sizes (small  $d = 0.20$ – $0.49$ ; medium  $d = 0.50$ – $0.79$ ; and large  $d = 0.80$ +). To examine for publication bias, we used Rosenthal's (1979) fail-safe calculations (with a probability of  $p = 0.05$ ), that is to estimate the number of null (unpublished) studies required to overturn a significant effect size.

The  $Q_B$  statistic was used to test for significant differences in mean effect sizes, for example STM versus LTM, visual versus verbal.  $Q_B$  has a chi-square distribution and is analogous to an  $F$ -test.

## RESULTS

Weighted and unweighted effect sizes (Cohen's  $d$ ) were calculated for STM, LTM, verbal and visual memory by comparing ecstasy users and controls. For each effect size, 95% confidence intervals were derived from 999 bootstrap samples.

### STM

A fixed effects model was used to analyse STM in 25 studies and revealed a large effect size ( $d = -0.61$ ; 95%CI  $-0.90$  to  $-0.32$ ; unweighted  $d = -0.66$ ). The studies showed heterogeneity ( $Q_{wi} = 108.44$ ,  $df = 26$ ,  $p < 0.0001$ ). A random effects model analysis revealed a moderate effect size ( $d = -0.63$ ; 95%CI  $-0.91$  to  $-0.41$ ; unweighted  $d = -0.66$ ) and the studies showed homogeneity ( $Q_{wi} = 23.38$ ,  $df = 24$ ,  $p = 0.50$ ). All except 3 out of 25 STM studies (Back-Madruga *et al.*, 2003; Morgan, 1998; Roiser *et al.*, 2007) reported worse performance in ecstasy users; and in 9 out of 25 studies, the effect size was large, that is ( $d > 0.79$ ). Rosenthal's (1979) fail-safe statistic indicates that 170 null studies would be required to overturn this effect size.

### LTM

A fixed effects model was used to analyse STM in 19 studies. The weighted mean effect size was also large ( $d = -0.86$ ; 95%CI  $-1.02$  to  $-0.70$ ; unweighted  $d = -0.88$ ); and the studies were heterogeneous ( $Q_{wi} = 212.28$ ,  $df = 20$ ,  $p < 0.0001$ ). A random effects model analysis revealed a large effect size ( $d = -0.87$ ; 95%CI  $-1.38$  to  $-0.45$ ; unweighted  $d = -0.92$ ) and the studies were homogenous ( $Q_{wi} = 15.28$ ,  $df = 18$ ,  $p = 0.64$ ). All except 2 out of 19 LTM studies reported worse performance by ecstasy users (Fox *et al.*, 2002; Zakzanis *et al.*, 2003) and in 8 out of 19 studies, a large effect ( $d > 0.79$ ) size was found. Rosenthal's (1979) fail-safe statistic indicates that 54 null studies would be required to overturn this effect size.

### STM versus LTM

A fixed effects model was used to compare weighted STM ( $n = 25$ ) and LTM ( $n = 19$ ) effect sizes. This revealed a non-significant difference ( $Q_B = 6.41$ ,  $df = 1,43$ ,  $p = 0.48$ ); the studies were heterogeneous ( $Q_{wi} = 331$ ,  $df = 43$ ,  $p < 0.0001$ ). A random effects model also revealed no significant difference ( $Q_B = 0.67$ ,  $df = 1,43$ ,  $p = 0.41$ ) with LTM effect size being larger;

and the studies were homogenous ( $Q_{wi} = 39.54$ ,  $df = 43$ ,  $p = 0.62$ ).

#### Verbal memory

A fixed effects model was used to analyse verbal memory in 22 studies. The weighted mean effect size was large ( $d = -0.92$ ; 95%CI  $-1.51$  to  $-0.48$ ; unweighted  $d = -1.02$ ); and the studies were heterogeneous ( $Q_{wi} = 222.29$ ,  $df = 21$ ,  $p < 0.0001$ ). A random effects model analysis revealed a large effect size ( $d = -1.00$ ; 95%CI  $-1.45$  to  $-0.59$ ; unweighted  $d = -1.02$ ) and the studies were heterogeneous ( $Q_{wi} = 19.36.51$ ,  $df = 21$ ,  $p = 0.56$ ). Rosenthal's (1979) fail-safe statistic indicates that 125 null studies would be required to overturn this effect size.

#### Visual memory

A fixed effects model was used to analyse verbal memory in 14 studies. The weighted mean effect size was small ( $d = -0.42$ ; 95%CI  $-0.79$  to  $-0.02$ ; unweighted  $d = -0.25$ ); and the studies were heterogeneous ( $Q_{wi} = 57.10$ ,  $df = 14$ ,  $p < 0.0001$ ). A random effects model analysis revealed a moderate effect size ( $d = -0.27$ ; 95%CI  $-0.55$  to  $-0.03$ ; unweighted  $d = -0.25$ ) and the studies were heterogeneous ( $Q_{wi} = 9.75$ ,  $df = 14$ ,  $p = 0.77$ ). Since the confidence intervals pass through zero, the effect of ecstasy on visual memory is non-significant. Rosenthal's (1979) fail-safe statistic indicates that no null studies would be required to overturn this effect size.

#### Verbal versus visual memory

A fixed effects model was used to compare weighted verbal and visual memory effect sizes. This revealed difference that approached significance ( $Q_B = 23.23$ ,  $df = 1.35$ ,  $p = 0.1$ ); the studies were heterogeneous

( $Q_{wi} = 302.54$ ,  $df = 36$ ,  $p < 0.0001$ ). A random effects model revealed that effect sizes are significantly larger for verbal than visual memory ( $Q_B = 5.75$ ,  $df = 1.35$ ,  $p = 0.013$ ); and the studies were homogenous ( $Q_{wi} = 38.22$ ,  $df = 36$ ,  $p = 0.31$ ).

#### Drug naïve controls

Eight studies used controls who could clearly be identified as drug naïve, that is never having taken any recreation drugs (Bhattachary and Powell, 2001; Croft *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2000; Morgan, 1998; Rodgers, 2000; Roiser *et al.*, 2007; Thomasius *et al.*, 2006; Verkes *et al.*, 2001). We compared memory performance in ecstasy users with controls classified as either drug naïve or those with no such classification (i.e. either taking other recreational drugs or simply not stated in the study). No significant difference emerged in the effect sizes calculated using naïve and 'non-naïve' controls for STM ( $d = -0.69$  [ $k = 8$ ] vs.  $-0.60$  [ $k = 17$ ]); for LTM ( $d = -0.61$  [ $k = 5$ ] vs.  $-1.00$  [ $k = 12$ ]); verbal memory ( $d = -1.06$  [ $k = 6$ ] vs.  $-0.99$  [ $k = 16$ ]); or visual memory ( $d = -0.07$  [ $k = 6$ ] vs.  $-0.41$  [ $k = 9$ ]). Nonetheless, if anything, the effect sizes tend to be slightly smaller for studies using drug naïve controls.

#### Moderator variables: Lifetime dose of ecstasy and size of ecstasy sample

Additional analyses were conducted using lifetime consumption of ecstasy and size of ecstasy sample as predictor variables for effect size in regression analyses. Information regarding lifetime number of tablets was available in 22 out of 26 studies. The mean number of tablets was 327 ( $SD = 296$ ) with a range of 16–902. Table 1 shows that the lifetime dose of ecstasy and size of ecstasy sample failed to significantly predict the effect sizes for any memory measure.

Table 1. Descriptive variables for studies included in meta-analyses

	Number of studies	Ecstasy sample size	Control sample size	Total sample size
	<i>K</i>	<i>M (SD)</i>	<i>M (SD)</i>	Range
STM	25	24.40 (17.77)	23.96 (17.44)	15–200
LTM	19	24.52 (19.74)	25.19 (19.69)	15–200
Verbal	22	24.13 (18.31)	24.22 (18.02)	26–200
Visual	14	26.50 (22.41)	26.60 (22.94)	26–200
Lifetime ecstasy consumption (tablets)	22	327 (296) Median = 50	—	16–902

*Use of cannabis by ecstasy users*

Several recent studies did address the polydrug issue by covarying cannabis use in analyses (Bhattachary and Powell, 2001; Croft *et al.*, 2001; Lamers, 2006; McCardle *et al.*, 2004; Morgan, 1999; Reneman, 2006; Wareing *et al.*, 2004a, 2004b, 2005).

A random effects model was used to compare weighted STM studies in which cannabis was covaried ( $d = -0.62$ ;  $k = 9$ ) and not covaried ( $d = -0.62$ ;  $k = 16$ ). This revealed no significant difference ( $Q_B = 0.01$ ,  $df = 1.23$ ,  $p = 0.95$ ); the studies were homogenous ( $Q_{wi} = 22.90$ ,  $df = 24$ ,  $p = 0.52$ ). A random effects model was also used to compare weighted LTM studies in which cannabis was covaried ( $d = -0.66$ ;  $k = 6$ ) and not covaried ( $d = -0.97$ ;  $k = 13$ ). This revealed no significant difference ( $Q_B = 0.26$ ,  $df = 1.18$ ,  $p = 0.67$ ); the studies were homogenous ( $Q_{wi} = 14.58$ ,  $df = 18$ ,  $p = 0.69$ ).

A random effects model was used to compare weighted verbal memory studies in which cannabis was covaried ( $d = -0.91$ ;  $k = 7$ ) and not covaried ( $d = -1.05$ ;  $k = 15$ ). This revealed no significant difference ( $Q_B = 0.07$ ,  $df = 1.21$ ,  $p = 0.82$ ); the studies were homogenous ( $Q_{wi} = 18.53$ ,  $df = 21$ ,  $p = 0.61$ ). A random effects model was also used to compare weighted visual memory effect sizes in which cannabis was covaried ( $d = 0.02$ ;  $k = 6$ ) and not covaried ( $d = -0.54$ ;  $k = 8$ ). This revealed a significant difference ( $Q_B = 4.28$ ,  $df = 1.14$ ,  $p = 0.04$ ); the studies were homogenous ( $Q_{wi} = 14.08$ ,  $df = 14$ ,  $p = 0.44$ ).

## DISCUSSION

This meta-analysis corroborates the notion that the recreational use of ecstasy is associated with considerable memory impairment, significantly affecting both short-term and long-term memory. Although the effect size was larger for LTM than STM, this difference did not reach significance. In practical terms, the STM and LTM memory performance in 72 and 81% of ecstasy users (respectively) is exceeded by the mean of the non-ecstasy using controls<sup>2</sup>. The effect size for verbal memory was large and significantly larger than the small effect size observed for visual memory. Our findings accord with the notion that the recreational use of ecstasy produces

<sup>2</sup>Cohen (1988) provides a measure associated with  $d$  and this is termed  $U_3$  (it tells us what proportion of the memory scores in ecstasy users are exceeded by the mean of the control group). The value of  $U_3$  for verbal and visual memory was 84 and 60%, respectively.

Table 2. Results from regression analyses

	Lifetime dose	Number of ecstasy users in sample <sup>a</sup>
STM	$Q_{1,20} = 0.40$ , $p = 0.52$	$Q_{1,23} = 1.14$ , $p = 0.29$
LTM	$Q_{1,14} = 0.58$ , $p = 0.45$	$Q_{1,16} = 0.16$ , $p = 0.81$
Verbal	$Q_{1,17} = 2.13$ , $p = 0.14$	$Q_{1,20} = 0.01$ , $p = 0.96$
Visual	$Q_{1,12} = 0.31$ , $p = 0.57$	$Q_{1,13} = 0.49$ , $p = 0.48$

<sup>a</sup>Yip and Lee (2005) represented an outlier in terms of sample size ( $n = 100$  ecstasy users and  $n = 100$  controls) and had undue influence on the regression analyses. We therefore removed it for the sample size regression analyses.

a moderate to large effect on STM, LTM and verbal memory, but not on visual memory (Table 2).

Our findings accord with Verbaten's (2003) earlier meta-analysis, although the STM and LTM effect sizes documented here are smaller (STM  $-0.63$  vs.  $-1.15$  and LTM  $-0.87$  vs.  $-1.36$ ). The quantitative differences could be attributed to several factors. First, the current meta-analysis has the advantage of including twice as many new studies and much larger aggregated samples of ecstasy users (STM:  $n = 439$  vs. 180; LTM:  $n = 610$  vs. 181) and this would provide a more reliable estimate of the effect sizes. It should be noted that the sample sizes of ecstasy users are often quite small, with the modal number being just 11 (controls = 15) in the current meta-analysis. Nevertheless, our regression analyses showed that number of ecstasy users did not significantly predict the effects size for any memory measure. Second, our aggregating approach (as described in the Section 'Method') contrasts with Verbaten's (2003), which examined single effect sizes from each study. The problem with the latter approach is that many studies included multiple memory measures and choosing any one will be less representative than the aggregate of several related measures. Finally, Verbaten (2003) did not examine measures of visual (e.g. spatial, non-verbal) and the current meta-analysis reveals that ecstasy use is associated with little visual memory decrement. Hence, focussing on verbal memory (and excluding visual memory) is likely to inflate effect sizes.

An important consideration is whether the memory effects resulting from ecstasy use are clinically significant. It is interesting to note the apparently inconsistent reports concerning self-perceived cognitive problems associated with ecstasy use. Fox *et al.* (2002) found no differences in self-reported problems for low (<100 tablets), medium (100–500) and high (500+) users on a cognitive failures questionnaire, suggesting that self-reported problems are not dose related. In a similar vein, both Rodgers (2000) and

Halpern *et al.* (2004) found that ecstasy users did not perceive their cognitive performance to be any worse than that of drug-free or cannabis using control subjects. Nevertheless, more specific examination of memory function does uncover self-reported memory problems by ecstasy users. In two separate samples, Heffernan *et al.* (2001) found that ecstasy users perceived their memory ability to be impaired on the Prospective Memory Questionnaire (with *d* values between 1.00 and 1.34). In a large web-based study, Parrott *et al.* (2002) also found self-reported memory problems in 73% of heavy (100+ tablets), 52% of moderate (10–100) and 19% of novice (1–9) ecstasy users. This latter study suggests that awareness of memory problems in ecstasy users; and that the problems are related to amount of ecstasy use (even though the number of tablets is much lower than, e.g. in the Fox *et al.* study). Future work is required to address the specificity of self-reported cognitive problems, that is whether ecstasy users are aware of true memory problems or have possibly become more sensitised to memory issues by media reports.

The issue of polydrug use has dogged human ecstasy research. It is well documented that ecstasy users are often polydrug users (Schifano *et al.*, 1998) and this confounds the precise role of ecstasy in memory disturbances (e.g. Rodgers *et al.*, 2001; Solowij *et al.*, 2002). Experimental studies using, for example a dose-related double-blind placebo paradigm are, of course, impossible. Conversely, it could also be cogently argued that sampling *pure* groups of ecstasy users would create groups that are atypical of most ecstasy users. In particular, some ecstasy users also regularly use cannabis and the latter could impact on a range of cognitive functions (including memory: Croft *et al.*, 2001; Simon and Mattick, 2002; Solowij *et al.*, 2002). Indeed, studies have reported no memory differences between ecstasy users and cannabis using controls (Croft *et al.*, 2001; Dafters *et al.*, 1999, 2003; Gouzoulis-Mayfrank *et al.*, 2000; Roiser *et al.*, 2007). Nevertheless, a recent meta-analysis indicates that cannabis may have small effects on memory and learning (effect sizes of 0.24 and 0.21, respectively: Grant *et al.*, 2003) even in chronic heavy cannabis users. These effect sizes contrast starkly with the large effect sizes documented here for ecstasy users. Critically, several ecstasy studies have tried to control for cannabis effects by covarying usage (Bhattachary and Powell, 2001; Croft *et al.*, 2001; Lamers, 2006; McCardle *et al.*, 2004; Morgan, 1999; Reneman, 2006; Wareing *et al.*, 2004a, 2004b, 2005). Our comparison of effect sizes in those studies with the remaining studies revealed no significant differences

for STM, LTM or verbal memory, that is the areas of memory most commonly associated problems following ecstasy use. A comparison of the above controlled studies versus the rest for visual memory, however, did reveal a significant difference. In particular, the covaried studies revealed no visual memory difference at all (with an effect size of zero) between ecstasy users and controls; however, the remainder of the studies revealed a significantly larger effect size ( $d=0.5$ ). This suggests that the use of cannabis in conjunction with ecstasy may produce visual memory problems that do not emerge with ecstasy use alone. The issue of visual memory problems has produced conflicting and uncertain reports in the ecstasy literature and our meta-analysis may throw some light in this. When combined, these findings suggest that ecstasy is adding a substantial degree of impairment over that which may be attributable to the cannabis use (except in the case of visual memory). This may go some way to explaining the varied results obtained for visual memory in ecstasy users.

Although individual studies have provided evidence in favour of dose-related impairments of learning and memory in abstinent ecstasy users (Bhattachary and Powell, 2001; Bolla *et al.*, 1998; Gouzoulis-Mayfrank *et al.*, 2000; Krystal *et al.*, 1992; Morgan, 1999; Parrott and Lasky, 1998; Rodgers, 2001; Zakzanis and Young, 2001), the meta-analysis failed to uncover any significant dose-related relationship in current users. The failure to find a continuous relationship between lifetime consumption of ecstasy and any of four measures of memory raises questions about the possible causal neurotoxic effects of ecstasy use. One possibility is that any relationship between ecstasy use and memory deterioration is more stepwise than linear. For example, it is possible that a one-off recreational dose of MDMA may produce the negative effect and so, further consumption is less important (see Verbaten, 2003). Nonetheless, it should be noted that illicit recreational drugs such as ecstasy will show large variability in actual MDMA content (e.g. Sherlock *et al.*, 1999). The range of lifetime ecstasy use reported in the studies included here was between 19 and over 900 tablets. Attempting to estimate the lifetime ecstasy dose, however, is problematic because of the potentially high unknown and uncontrolled degree of measurement error. This may well contribute to the lack of an obvious dose–memory relationship.

To summarise, this meta-analysis confirms that ecstasy users show significantly impaired STM and LTM when compared with non-ecstasy users. The ecstasy users also displayed significantly worse verbal

than visual memory. Indeed, their visual memory was relatively normal and seems to be affected more by concurrent cannabis use. Finally, we found no relationship between lifetime number of ecstasy tablets consumed and any of the memory measures; however, estimating lifetime dosage of illegal recreational drugs is fraught with difficulties.

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