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MEMORY PERFORMANCE IN ABSTINENT 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "ECSTASY") USERS[1]

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Summary.—Research with animals and humans has suggested that acute and subacute use of 3,4-methylenedioxymethamphetamine (MDMA "ecstasy") may lead to memory impairment. However, research is limited by (1) low power due to small sample sizes, (2) the possible confound of polydrug use, and (3) the failure to consider intelligence as a covariate. The present study compared the memory performance on the Wechsler Memory Scale–III of 26 abstinent (2-wk. minimum) recreational MDMA users with 26 abstinent (2-wk. minimum) recreational polydrug users. Despite significantly greater polydrug use amongst these MDMA users, no significant group differences in memory were observed. Regression of total lifetime amount of MDMA use also did not predict memory performance after accounting for intelligence. In addition, the length of time since abstinence (at least 2 wk.) was not associated with an increase in memory performance. Greater total lifetime cocaine use, rather than total lifetime MDMA use, was significantly associated with greater decrements in General Memory and Delayed Verbal Memory performance.

Even though MDMA was first synthesized in 1914, it was not until the late 1960s that it first began to be used for recreational and therapeutic purposes (Abbott & Concar, 1992; Parrott, 2001). Such use, however, was minimal until the 1990s when it became increasingly popular as a recreational drug. Towards the late 1990s both dosage (number of tablets) per use, as well as its combination with other drugs also increased (Solowij, Hall, & Lee, 1992; Topp, Hando, Dillon, Roche, & Solowij, 1999). This was accompanied by research investigating possible longer and short-term difficulties related to memory as well as psychiatric problems such as depression, impulsivity, and panic attacks (Solowij, *et al.*, 1992; Curran & Travill, 1997; Morgan, 1998, 2000; Parrott, 2000, 2001).

Research with animals suggests that MDMA is likely to be neurotoxic to serotonin receptors with a resulting reduction in the amount of serotonin in the system (McKenna & Peroutka, 1990; Peroutka, 1990). For example, Taffe, Weed, Davis, Huitron-Resendiz, Schroeder, Parsons, Henriksen, and Gold (2001) found significant reductions in the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) both directly following, as well as three months after, short-term, high dose exposure of MDMA in rhesus monkeys.

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Similar findings have been noted in both rats and humans particularly in the hippocampus, frontal neocortex, caudate nucleus, and many thalamic nuclei (Ricaurte, Martello, Katz, & Martello, 1992; Aguirre, Galbete, Lasheras, & Del Rio, 1995; Sabol, Lew, Richards, Vosmer, & Seiden, 1996; Bolla, McCann, & Ricaurte, 1998; Hatzidimitriou, McCann, & Ricaurte, 1999; Semple, Ebmeier, Glabus, O'Carroll, & Johnstone, 1999). Given both serotonin and the above structures are important for memory and learning (Buhot, Martin, & Segu, 2000), it seems reasonable that MDMA may cause memory impairment in humans.

Formal review of memory and MDMA use supports the conclusion that there is a general decline in memory and learning following MDMA use (see reviews by Morgan, 2000; Parrott, 2001). Two studies have noted a positive correlation between magnitude of memory lowering and reduction in available serotonin among MDMA users (Bolla, *et al.*, 1998; Reneman, Booij, Schmand, van der Brink, & Gunning, 2000). A lowering of memory has been reported following short-term abstinence from MDMA (i.e., 6 wk. in Schifano, Di Furia, Forza, Minicuci, & Bricolo, 1998), and a number of studies have also noted that memory is decreased even despite longer-term abstinence (i.e., 19-wk. mean abstinence for Reneman, *et al.*, 2000, and 46-wk. mean abstinence for Wareing, Fisk, & Murphy, 2000). In addition, Zakzanis and Young (2001) noted progressive decreases in immediate and delayed memory among MDMA users followed over a 12-mo. interval. Morgan (2000) concluded his review by summarizing that for moderate to heavy recreational users, there is a reliable pattern of impaired recall and poor working memory performance.

Despite the above research, the findings are not as clear as might be presumed. The review by Morgan (2000) indicated that in nine of the 14 published studies investigating the relation between MDMA and memory there was no control for other drug use. Thus it might have been either other drugs or a combination of MDMA with other drugs that lowered measures of memory. In particular, cannabis (Croft, Mackay, Mills, & Gruzelier, 2001; Rodney, Mackay, Mills, & Gruzelier, 2001) and amphetamines (McKetin & Mattick, 1997) are likely to be important confounds. Intelligence as a confounding factor was also rarely controlled even though it is likely to be a strong predictor of performance on memory tests. In addition, nearly all the studies included quite small sample sizes with a large number of variables. Despite this, Bonferroni corrections were rarely used in the analyses thereby increasing the chance of Type 1 errors. The research has also been unclear on the pattern of decreases among indices of memory. Some research has indicated decreases in immediate verbal memory, delayed verbal memory, and delayed visual memory but stated that immediate visual memory was left intact (Bolla, *et al.*, 1998; Morgan, 1999). While Klugman, Hardy, Baldeweg, and Gruzelier (1999) similarly stated difficulties in immediate verbal recall, they also observed difficulties with visual memory including facial recognition and learning spatial information. The finding that there are memory impairments has also not been universal as Morgan (1999) recorded no differences in spatial span memory between MDMA and polydrug and nondrug controls. In addition, Bolla, *et al.* (1998) found no significant differences between overall performance on memory between MDMA users and non-MDMA users. No other researchers have found group differences between MDMA and non-MDMA users (Turner, Juby, & Parrott, 1998; Dafters, Duffy, O'Donnell, & Bouquet, 1999; Turner, Godolphin, & Parrott, 1999). Finally, the magnitude of group differences and terms used to describe these differences are unclear but most researchers have indicated that cognitive changes are quite small in magnitude (i.e., Verkes, Gijsman, Pieters, Schoemaker, de Visser, Kuijpers, Pennings, de Bruin, Van de Wijngaart, Van Gerven, & Cohen, 2001). One difficulty is that some researchers (e.g., Rodgers, 2000) have described relatively small decreases in memory (WMS–R Delayed Memory scores of 96.53) as indicating that MDMA users were in the "impaired" range.

The current study was an attempt to replicate and extend previous research by administering the Wecshler Memory Scale–III (Wechsler, 1997) to 26 abstinent MDMA users and 26 polydrug users. In addition, drug use and intelligence were controlled, and Bonferroni corrections were used when indicated. The data were analyzed both between groups as well as for total lifetime use of MDMA.

Method

Participants

Fifty-two volunteers including 26 recreational MDMA users (14 women, 12 men) and 26 non-MDMA polydrug users (13 women, 13 men) participated. They were recruited via either word of mouth or flyers placed in Perth, Australia cafes and clothing and music stores, Perth and Fremantle backpacker hostels, and Western Australian universities. Participants were required to be between 18 and 50 years of age. Participants in the MDMA group were required to have used MDMA on at least 20 occasions and participants in the non-MDMA group were required to have used illicit drugs but never to have used MDMA. Exclusion criteria for both groups included use of an illicit or prescribed psychoactive drug 2 wk. prior to testing, consumption of alcohol 24 hr. prior to testing, current pregnancy, current major psychiatric illness, past or current major medical illness, past or current alcohol dependence, dependence on any drug in the previous six months, and extremely low IQ as estimated by more than 25 incorrect answers on the National Adult Reading Test (Nelson, 1982). However, urine testing was not utilized. Based on these criteria, no participants were excluded. Participants were paid $20.00 for their participation in the study.

Measures

Screening for inclusion and exclusion was conducted via a brief "suitability screening questionnaire," the Severity of Dependence Scale (Gossop, Darke, Griffiths, Hando, Powis, Hall, & Strang, 1995) and the National Adult Reading Test (Nelson, 1982). The suitability screening questionnaire comprised specific inclusion and exclusion questions. The Severity of Depression Scale was used to assess whether a participant had ever been dependent on alcohol or dependent on any other drug in the previous 6 months. This scale is comprised of five items and takes approximately 2 to 3 minutes to complete. Analogous to previous studies, the National Adult Reading Test was employed to provide an estimate of premorbid IQ and to ensure an adequate knowledge of English. The National Adult Reading Test requires the participant to read aloud a set of 50 irregularly spelled words listed in order of increasing difficulty and uses reading skill to provide an estimate of intelligence. Nelson (1982) reported high correlations between the National Adult Reading Test and the Wechsler Adult Intelligence Scale–Revised (WAIS–R) Full Scale IQ and a split-half reliability of .93. The National Adult Reading Test takes about 5 minutes to complete.

Relevant demographic information including sex, age, height, weight, and years of education was obtained via a 'personal details questionnaire'. In eliciting information regarding previous drug use, a 'drug-use questionnaire' adapted from the Opiate Treatment Index (Darke, Ward, Hall, Heather, & Wodak, 1991) was used. In obtaining information about MDMA use, a specific "Ecstasy-use questionnaire" similar to that used by Morgan (1998, 1999) was used to request information on (1) duration of use in years (months), (2) weeks since last used, (3) average session use, (4) maximum session use, and (5) approximate total lifetime use.

The Wechsler Memory Scale–III was administered to test possible effects of MDMA use on memory. Subtests necessary to calculate the following indexes were administered: General Memory, Immediate Verbal Memory, Immediate Visual Memory, Delayed Verbal Memory, Delayed Visual Memory, and Working Memory.

Procedure

Potential participants were advised of the requirements of participation and verbal consent was obtained to screen for inclusion or exclusion. Potential participants were screened for inclusion and exclusion via the suitability screening questionnaire and the Severity of Dependence Scale. Further, they were asked whether they met the inclusion requirements of alcohol or drug abstinence and whether they were willing to adhere to the alcohol or drug abstinence requirements. Testing was only continued as planned if the participant had adhered to the abstinence requirements. If they had not adhered, another testing time and day was organized if they chose.

Results

The means and standard deviations of the demographic variables for participants in the MDMA group and non-MDMA group are presented in Table 1. One-way analysis of variance (using SPSS) of the demographic variables for the MDMA group and non-MDMA group indicated that, using a Bonferroni correction, they were not significantly different in terms of age, sex, height, weight, years of education, and National Adult Reading Test scores.

TABLE 1
Means and Standard Deviations of Demographic Variables (*n*s = 26)

Measure	MDMA Group		Nonecstasy Group	
	M	*SD*	*M*	*SD*
Sex[a]	1.5	0.51	1.5	0.51
Age, yr.	24.0	2.70	21.8	3.92
Height, cm	173.5	12.08	172.8	10.16
Weight, kg	67.5	15.41	70.2	20.27
Education, yr.	14.6	1.86	14.3	1.93
National Adult Reading Test[b]	33.4	4.95	32.4	5.04

[a]Females coded 1, males coded 2. [b]Number correct.

Self-reported recreational MDMA use among the 26 participants in the MDMA groups is summarized in Table 2. Self-reported monthly average licit and illicit drug use and estimated total lifetime illicit drug use for participants in the MDMA group and non-MDMA group are presented in Table 3. One-way analysis of variance of the monthly average drug use data for the two groups indicated that, using a Bonferroni correction, they were

TABLE 2
Means, Standard Deviations, and Ranges of Estimated Self-reported Recreational MDMA Use for the MDMA Group (*n* = 26)

Measure	*M*	*SD*	Range
Duration of use, mo.	51.7	27.3	12.5–113
Period since last use, wk.	33.9	52.5	2–208
Average use per session, no. of tablets	1.8	1.0	0.5–5.0
Maximum use per session, no. of tablets	3.8	2.6	1–11
Average use per month, no. of tablets	2.5	2.2	0.36–9.5
Estimated total lifetime use, no. of tablets	120.0	116.1	20–425

Note.—In individual cases in which frequency of use was inconsistent, frequency of use per month was calculated by dividing the estimated total lifetime use by duration of use in months.

not significantly different in terms of monthly average use of tobacco, cannabis, cocaine, LSD, and heroin. However, the MDMA group reported using significantly more alcohol ($F_{1,50} = 27.33$, $p < .01$) and amphetamines ($F_{1,50} = 14.25$, $p < .01$) per month on average than the non-MDMA group. One-way analysis of variance of the data for estimated total lifetime drug use for the two groups indicated that they were not significantly different in terms of total lifetime use of heroin. However, the MDMA group reported using significantly more amphetamines ($F_{1,50} = 9.49$, $p < .01$) in their lifetime than the non-MDMA group.

TABLE 3
MEANS AND STANDARD DEVIATIONS OF SELF-REPORTED MONTHLY AVERAGE AND ESTIMATED TOTAL LIFETIME RECREATIONAL DRUG USE (*ns* = 26)

Drug Use	MDMA Group		Non-MDMA Group	
	M	*SD*	*M*	*SD*
Alcohol, standard drinks				
Monthly average use	69.3	50.0	16.4	12.8*
Tobacco, pack of 25				
Monthly average use	6.9	8.4	4.0	10.4
Cannabis, cones				
Monthly average use	23.1	44.1	9.6	18.2
Total lifetime use	1616.2	2282.5	424.6	990.5
Amphetamines, occasions				
Monthly average use	1.8	2.3	0.1	0.3*
Total lifetime use	60.3	98.4	0.8	2.9*
Cocaine, occasions				
Monthly average use	2.9	7.9	0.1	0.2
Total lifetime use	25.8	63.1	0.6	2.7
LSD				
Monthly average use	1.3	1.5	0.4	0.9
Total lifetime use	39.9	68.3	3.2	10.9*
Heroin, occasions				
Monthly average use	0.4	1.1	0.1	0.2
Total lifetime use	0.4	1.1	0.4	2.4

Note.—In individual cases in which the frequency of use was inconsistent, the frequency of use per month was calculated by dividing the estimated total lifetime use by the duration of use in months. *$p < .01$ (the more stringent .01 level was used rather than .05 given the Bonferroni correction and given the small sample size and number of comparisons).

The Wechsler Memory Scale–III memory index sums of scaled scores were individually screened for outliers via examination of the standardized scores. With the criteria for exclusion set at 3 *SD* above or below the mean, no outliers were detected. Given the relatively small sample size combined with the large number of variables, the Bonferroni adjustment procedure was applied to the dependent variables (Wechsler Memory Scale–III measures including index scores, General Memory, and Working Memory). Hence differences were considered significant with $p < .025$.

The means and standard deviations of the Wechsler Memory Scale–III memory index scores for participants in the two groups is presented in Table 4. One-way analysis of variance of the memory index sums of scaled scores (rather than index scores) for the two groups indicated that they were not significantly different in their performance on General Memory ($F_{1,50}$ =1.79, ns), Immediate Verbal ($F_{1,50}$=2.64, ns), Immediate Visual ($F_{1,50}$=0.66, ns), Delayed Verbal ($F_{1,50}$=1.96, ns), Delayed Visual ($F_{1,50}$=0.14, ns), and Working Memory ($F_{1,50}$=0.16, ns).

TABLE 4
MEANS AND STANDARD DEVIATIONS OF WECHSLER MEMORY SCALE–III MEMORY INDEX SCORES FOR MDMA USERS AND NON-MDMA POLYDRUG USERS (*n*s = 26)

Wechsler Memory Scale–III	MDMA Group		Non-MDMA Group	
	M	*SD*	*M*	*SD*
General Memory	105.4	11.7	109.5	10.3
Immediate Verbal	107.4	15.2	113.2	11.6
Immediate Visual	97.1	13.6	99.9	10.4
Delayed Verbal	108.4	12.1	112.2	9.0
Delayed Visual	99.2	11.2	100.3	9.2
Working Memory	107.6	14.6	105.5	8.2

Note.—No significant between-group differences were observed (p=.01).

One-way analysis of covariance was computed for group differences in memory performance after statistically controlling for the potential confounding influence of National Adult Reading Test scores. The National Adult Reading Test was considered an extraneous variable given significant positive correlations ranging from .28 to .47 between National Adult Reading Test scores and five of the six Wechsler Memory Scale–III memory indexes, with the exception of Immediate Visual Memory, which did not correlate significantly. Hence, the higher the National Adult Reading Test score, the higher the Wechsler Memory Scale–III memory index sum of scaled scores. Evaluation of the assumptions of normality and homogeneity of variance was unnecessary given equal sample sizes and the absence of outliers (Tabachnick & Fidell, 1996), and the results of evaluation of the assumptions of linearity were satisfactory as indicated above.

One-way analysis of covariance indicated no significant differences between group performance on General Memory ($F_{1,49}$=3.78, ns), Immediate Verbal ($F_{1,49}$=4.50, ns), Delayed Verbal ($F_{1,49}$=4.11, ns), Immediate Visual ($F_{1,49}$=0.87, ns), Delayed Visual ($F_{1,49}$=0.44, ns), and Working Memory ($F_{1,49}$ =0.04, ns) after adjustment for reading scores. However, between-group differences fell just short of significance for General Memory (p=.06), Immediate Verbal (p=.04), and Delayed Verbal Memory (p=.05). As can be seen in Table 4, MDMA users performed slightly but not significantly lower than non-MDMA polydrug users on the aforementioned Wechsler Memory Scale–III memory indexes.

Correlations were computed to estimate whether higher monthly average use of alcohol or higher total lifetime use of MDMA, cannabis, amphetamines, cocaine, or LSD was associated with lower memory performance. Monthly alcohol use data were used, as total lifetime alcohol use data were not available. Further associations between memory performance and tobacco and heroin were not investigated as tobacco is not commonly associated with memory deficits, and only five participants had ever used heroin. Correlations were statistically significant and negative for estimated total lifetime use of MDMA with General Memory ($r = -.40$, $p < .05$), and Delayed Visual Memory ($r = -.44$, $p < .05$) and between estimated total lifetime use of cocaine with General Memory ($r = -.57$, $p < .01$), Immediate Verbal Memory ($r = -.50$, $p < .01$), and Delayed Verbal Memory ($r = -.61$, $p < .01$). No other significant correlations were observed.

Hierarchical multiple regression was employed to evaluate whether estimated total lifetime use of MDMA and cocaine predicted performance on the respective correlated memory indexes beyond that afforded by differences in National Adult Reading Test scores. This was done to judge whether a third variable was contributing to the statistically significant negative correlations reported above. The National Adult Reading Test was considered an extraneous variable given significant positive correlations ranging from .44 to .66 between National Adult Reading Test scores and four of the six Wechsler Memory Scales–III memory index scores for the MDMA group, with the exceptions of Immediate Visual and Delayed Visual Memory which did not correlate significantly. Hence, the higher the National Adult Reading Test score, the higher the Wechlser Memory Scale–III memory index sum of scaled scores. Results of evaluation of the assumptions of multicollinearity and singularity and normality, nonlinearity, and heteroscedasticity were satisfactory.

Table 5 displays Pearson correlations between the variables, the standardised regression coefficient (β), the part correlations (sr^2), plus R^2 and adjusted R^2 after entry of all independent variables for each respective Wechsler Memory Scale–III memory index. As can be seen, the National Adult Reading Test contributes 37% of the variance in scores of General Memory ($p < .01$), 40% of the variance in scores of Immediate Verbal Memory ($p < .01$), and 44% of the variance in scores of Delayed Verbal Memory ($p < .01$), so reading scores are a significant predictor in all the aforementioned Wechsler Memory Scale–III memory indexes. In contrast, the National Adult Reading Test contributes only 9% of the variance in Delayed Visual Memory Index sum of scaled scores ($p > .05$).

After accounting for the variance contributed by the National Adult

TABLE 5

SUMMARY OF HIERARCHICAL REGRESSION ANALYSES OF NATIONAL ADULT READING TEST AND MDMA USE AND COCAINE USE VARIABLES ON RESPECTIVE CORRELATED WECHSLER MEMORY SCALES–III MEMORY INDEX SUM OF SCALED SCORES ($n = 26$)

Dependent Variable	Independent Variable	β	sr^2	R^2	Adj. R^2
General Memory	Step 1			.37	.35
	National Adult Reading Test	.61	.61†		
	Step 2			.42	.36
	National Adult Reading Test	.54	.50†		
	MDMA Use, lifetime	–.22	–.21		
	Step 3			.51	.44
	National Adult Reading Test	.43	.38*		
	MDMA Use, lifetime	–.12	–.11		
	Cocaine Use, lifetime	–.35	–.31*		
Immediate Verbal	Step 1			.40	.38
	National Adult Reading Test	.64	.64†		
	Step 2			.48	.43
	National Adult Reading Test	.52	.47†		
	Cocaine Use, lifetime	–.29	–.27		
Delayed Verbal	Step 1			.44	.42.
	National Adult Reading Test	.66	.66†		
	Step 2			.58	.55
	National Adult Reading Test	.50	.45†		
	Cocaine Use, lifetime	–.41	–.38†		
Delayed Visual	Step 1			.09	.05
	National Adult Reading Test	.30	.30		
	Step 2			.22	.15
	National Adult Reading Test	.17	.16		
	MDMA Use, lifetime	–.38	–.36		

*$p < .05$. †$p < .01$.

Reading Test, total lifetime cocaine use did not add significant proportions of the variance in scores on the Immediate Verbal Memory Index. Further, total lifetime MDMA use did not account for significant proportions of the variance in scores on the General Memory and Delayed Visual Memory indexes. In contrast, total lifetime cocaine use accounted for 14% of the variance in scores on the Delayed Verbal Memory index after accounting for the National Adult Reading Test ($p < .01$) and 8% of the variance in scores on the General Memory index after accounting for both reading scores and total lifetime MDMA use ($p < .05$).

Pearson correlations were computed between MDMA abstinence and the Wechsler Memory Scale–III memory index sums of scaled scores to estimate whether longer MDMA abstinence was associated with better memory performance. The correlations were not statistically significant between the Wechsler Memory Scale–III memory indexes and MDMA abstinence.