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Neurocognitive function in users of MDMA: the importance of clinically significant patterns of use

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ABSTRACT

Background. Use of MDMA (ecstasy), a serotonin neurotoxin, has been associated with memory impairment and psychological dysfunction. This study examined cognitive functioning in abstinent MDMA users and MDMA-naïve controls.

Method. Participants completed measures of intelligence, motor function, attention, memory span, verbal fluency, immediate and delayed verbal memory, and working memory. They were also assessed for the presence of psychopathology. In addition to comparing cognitive function in MDMA users relative to controls, the possibility that clinically dysfunctional MDMA use increases the risk of cognitive impairment was examined.

Results. MDMA users exhibited relative deficits in mnemonic and executive functions. Additionally, users that met DSM-IV substance use disorder criteria for lifetime MDMA abuse or dependence exhibited a number of additional deficits relative to those who did not meet these criteria.

Conclusion. These findings suggest that clinically dysfunctional, rather than purely recreational, MDMA use is associated with cognitive impairment. Future research studies of diverse samples of users may shed light on the mechanisms that underlie these differences.

INTRODUCTION

The drug 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'), a synthetic amphetamine derivative, is commonly used at all-night dance parties ('raves'). Use of MDMA has risen significantly in recent years and is a source of considerable public health concern (Strote *et al.* 2002). MDMA is a potent and relatively selective serotonin (5-HT) releasing agent and reuptake inhibitor (Battaglia *et al.* 1987; Schmidt, 1987; O'Hearn *et al.* 1988). It has acute subjective effects of enhanced mood, increased energy, openness and heightened sensory perception, which are evident 30–60 min after intake and persist for up to 24 h (Vollenweider *et al.* 1998; Liechti *et al.* 2001). Adverse reactions in the acute phase of use include anxiety, difficulty concentrating, paranoia, tachycardia, hypertension and hyperthermia (Peroutka *et al.* 1988; Cohen, 1995; Davidson & Parrott, 1997; Schifano *et al.* 1998; Vollenweider *et al.* 1998). Long-term consequences have also been reported.

To assess the drug's long-term effects, neuropsychological performance prior to the first-time use of MDMA would ideally be compared to performance after various levels of use. Because ethical and pragmatic limitations prohibit this type of study, MDMA users are typically compared with various control groups, including people without prior use of illicit drugs, MDMA-naïve individuals (i.e. no prior use of MDMA, but other mild drugs may have been used), MDMA-naïve alcohol or cannabis users, or MDMA-naïve polydrug users (i.e. no prior use of MDMA, but otherwise similar levels of previous illicit drug use) (Morgan, 1998, 1999; Gouzoulis-Mayfrank *et al.* 2000; Parrott *et al.*

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2000; Croft *et al*. 2001; Morgan *et al*. 2002). Relative to these various groups, the most consistent neuropsychological finding in MDMA users is a deficit in verbal memory under immediate- and delayed-recall conditions. Paragraph- or prose-recall tasks from the Wechsler Memory Scale – Revised Edition (WMS-R) (Wechsler, 1987), the Rivermead Behavioural Memory Test (RMBT) (Wilson *et al*. 1985), or word recall tasks (Rey Auditory Verbal Learning Test: RAVLT) (Rey, 1964) have been used to assess verbal memory. MDMA users demonstrate deficits relative to alcohol users, non-drug controls, and MDMA-naïve polydrug controls, including cannabis users (Curran & Travill, 1997; Bolla *et al*. 1998; Parrott & Lasky, 1998; Parrott *et al*. 1998; Morgan, 1999; Rodgers, 2000; Bhattachary & Powell, 2001; Fox *et al*. 2001*a*; Reneman *et al*. 2001*a*, *b*; Morgan *et al*. 2002). A 1-year follow-up study of MDMA users revealed a significant decline in immediate and delayed verbal memory, as well as the total RBMT score (Zakzanis & Young, 2001). Collectively, these findings provide persuasive evidence that MDMA use is associated with verbal memory impairment. Only a few studies have failed to replicate this association (Dafters *et al*. 1999; Fox *et al*. 2001*b*).

In addition to impaired verbal recall, MDMA users have less consistently demonstrated impairments in visual recognition and working memory (Curran & Travill, 1997; Fox *et al*. 2002), short-term memory (McCann *et al*. 1999) and scores on composite memory batteries (Wilson *et al*. 1990). However, Morgan (1998) reported similar spatial memory spans in MDMA users, MDMA-naïve polydrug users and a non-drug control group. Thus, while MDMA might impact multiple aspects of memory function, more research is needed to describe the extent of this impairment.

Whether memory impairment is associated with changes in 5-HT activity has also been examined. Bolla *et al*. (1998) tested MDMA users and MDMA-naïve controls and found that lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) was associated with poorer memory performance. Reduced CSF 5-HIAA concentrations and poorer memory function were associated with increased monthly doses of MDMA. Another lab reported that regular MDMA users exhibited significantly lower levels of CSF 5-HIAA, but not homovanillic acid (a dopamine metabolite), relative to MDMA-naïve control subjects (McCann *et al*. 1999). However, 5-HIAA levels were unrelated to cognitive performance. Pharmacological and amino acid challenge studies provide additional evidence of 5-HT system dysregulation. Under intravenous infusion of the 5-HT precursor tryptophan, MDMA users exhibited mild-to-moderate impairment in immediate and delayed prose recall relative to age-matched norms (Krystal *et al*. 1992). After administration of the 5-HT agonist dexfenfluramine, MDMA users exhibited poorer memory span, poorer recognition for words and figures, and altered 5-HT neuroendocrine function compared with non-using controls (Verkes *et al*. 2001). These studies suggest that MDMA users are differentially sensitive, on a neurocognitive level, to alterations in 5-HT activity.

Mnemonic deficits in MDMA users may be dose-related, since heavier lifetime use, increasing monthly dose, and longer duration of use are associated with more significant impairment (Bolla *et al*. 1998; McCann *et al*. 1999; Gouzoulis-Mayfrank *et al*. 2000; Bhattachary & Powell, 2001; Fox *et al*. 2001*b*; Reneman *et al*. 2001*a*; Verkes *et al*. 2001; Zakzanis & Young, 2001; Morgan *et al*. 2002). In addition, evidence suggests that memory impairment in MDMA users is long-lasting (Morgan, 1999) and potentially irreversible (Wareing *et al*. 2000; Morgan *et al*. 2002).

Deficits in other areas of cognitive function, such as verbal fluency, executive function, impulse control, reaction time and processing speed have been reported (see, for example, Morgan, 1998; Schifano *et al*. 1998; Dafters *et al*. 1999; Wareing *et al*. 2000; Bhattachary & Powell, 2001; Heffernan *et al*. 2001; Morgan *et al*. 2002). Evidence for attentional deficits varies depending on the task employed (McCann *et al*. 1999; Gouzoulis-Mayfrank *et al*. 2000). Other studies have not found evidence for impaired attention (Parrott *et al*. 1998; Vollenweider *et al*. 1998; Rodgers, 2000). Some research suggests that MDMA use is associated with longer visual scanning times, reaction times, or planning times (Parrott & Lasky, 1998; Gouzoulis-Mayfrank *et al*. 2000; Fox *et al*. 2001*b*, 2002). Others have found no differences in reaction times or processing

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speeds (Parrott *et al.* 1998; Rodgers, 2000; Wareing *et al.* 2000).

Interpretation of this literature is complicated by the fact that MDMA users typically abuse other drugs, which may exert independent or interactive effects on cognitive performance (Gouzoulis-Mayfrank *et al.* 2000; Croft *et al.* 2001). Another difficulty is that because most studies rely on retrospective reporting, it is possible that cognitive impairments pre-date MDMA use. Cause–effect relationships have not been definitively established.

The current study provides a comprehensive assessment of psychological functioning in MDMA users. One limitation of previous research is an inadequate assessment of psychopathology. Many studies did not report the method of assessment for psychiatric disorders; others evidently did not perform a comprehensive assessment for Axis I disorders. A recent report suggests that many users meet diagnostic criteria for substance abuse and/or dependence on MDMA and that the presence of this diagnosis should be further evaluated (Cottler *et al.* 2001). In the current study, participants underwent a full assessment of DSM-IV Axis I adult mental disorders. In addition, many studies report on only one or two areas of cognitive functioning and use only rough estimates of IQ (e.g. the National Adult Reading Test: Nelson, 1982). Participants in the present study completed tests of general intelligence (Wechsler, 1997), verbal memory span, immediate and delayed verbal memory, verbal working memory, spatial working memory, affective working memory, motor function, verbal fluency, and attention and vigilance. As data accumulate to suggest that there are pronounced individual differences in vulnerability to MDMA-induced cognitive damage, rigorous assessments of MDMA users are needed in order to better characterize those who suffer adverse consequences of use.

METHOD

Participants

Fifty-two individuals, aged 18–32, were invited to participate in a study of personality, emotion, and cognitive processes. Two samples were recruited: (*a*) MDMA users ($N=26$); and (*b*) individuals without a history of MDMA use, psychiatric illness, or substance abuse ($N=26$), as determined by DSM-IV criteria. Researchers recruited all control participants and 11 MDMA users from undergraduate psychology courses at the University of Minnesota. These individuals received extra credit points for their study participation. Fifteen MDMA users were recruited through the use of posted advertisements throughout the university and within a local newspaper. These individuals received monetary payment for their participation. All dependent variables were compared between those MDMA users who received monetary *versus* extra credit point compensation, and the two samples did not significantly vary in their neurocognitive performance. Thus, the groups were combined into a single sample of MDMA users.

Researchers conducted brief telephone interviews to screen respondents for study eligibility. Requirements included being a native English speaker, having normal or corrected-to-normal vision and hearing, and no reported history of neurological problems, current pregnancy, or physical disease. Participants were medication-free with the exception of birth control pills. Intended control participants were excluded from further participation if they were found after study enrolment to meet DSM-IV (*Diagnostic and Statistical Manual for Mental Disorders, 4th edn., Revised*) (APA, 2000) criteria for any psychiatric disorder, including substance abuse or dependence. This exclusion applied to 14 individuals (10 alcohol abusers, one with bipolar disorder, one with anxiety disorder and two with eating disorders). All participants agreed to abstain from using recreational drugs for at least 1 week and to refrain from drinking alcohol for at least 48 h prior to testing. Compliance was measured by self-report. Participants were permitted to use their typical amounts of tobacco and caffeine in order to avoid confounds associated with nicotine or caffeine withdrawal. All participants provided informed consent prior to participation. The study was approved by the University of Minnesota's Institutional Review Board.

Procedure

During individual testing sessions, participants completed a medical screening questionnaire, a semi-structured clinical interview to assess for

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the presence of psychopathology (SCID-P) (First *et al*. 1997), and an estimate of global cognitive ability (selected subtests from the WAIS-III) (Wechsler, 1997). The Beck Depression Inventory (BDI) (Beck *et al*. 1961), a 21-item self-report measure of depression, was administered. Participants completed a neuropsychological testing battery as well as several self-report measures of personality traits. They also answered questions regarding their prior use of illicit drugs when the SCID was administered. MDMA users were interviewed in extensive detail regarding their patterns of MDMA use. They answered questions regarding the total number of occasions of MDMA use, the number of occasions used in the past year, the total duration of use (in months), the time elapsed since their last use (in weeks), the average number of pills ingested per occasion of use, the maximum number of pills ever taken on a single occasion. An estimate of the average number of occasions that MDMA was used per month was derived (total number of occasions of use divided by total number of months of use).

Neuropsychological testing

General intellectual function

A pro-rated IQ estimate was obtained from scores on selected subtests from the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) (Wechsler, 1997): Vocabulary, Similarities, Digit Span, Digit Symbol-Coding and Block Design. The first three tests were pro-rated to provide an estimate of Verbal IQ. The latter two tests were prorated to provide an estimate of Performance IQ (Sattler, 2001). The number of digits correctly recalled in forward order on the digit span task was interpreted as a measure of short-term attention and verbal memory span. The number of digits correctly recalled in backward order was interpreted as an index of verbal working memory.

Motor function

Psychomotor speed was measured through use of the Finger Tapping Test. On each of three trials per hand, participants were instructed to tap a key as rapidly as possible for 10 s using the index finger. The average number of taps per hand was calculated. Participants also completed the Grooved Pegboard Task. They were instructed to place 25 small, grooved, metal pegs into a pegboard under timed conditions. A single trial was conducted for each hand. Time-to-completion (in seconds) and the number of dropped pegs per hand were recorded.

Attention and Vigilance: *Letter Cancellation Task* (Lezak, 1995)

Participants were given a sheet of paper with printed rows of capital letters. They were instructed to work row-by-row, placing a slash through all occurrences of the letters ‘E’ and ‘C’ as quickly as possible. Time to completion (in seconds) and errors of omission and commission were recorded.

Verbal Fluency: *Controlled Oral Word Association Test* (*COWAT*) (Lezak, 1995)

Participants were instructed to generate as many words as possible that began with a given letter during a time period of 1 min. They were instructed not to use proper names and not to repeat the same word with a different suffix. Three trials were performed using the letters ‘F’, ‘A’ and ‘S’. The number of words generated per letter, rule-breaking errors (e.g. proper names, non-words), perseverations (e.g. saying the same word repeatedly or using the same word with different endings) and inappropriate words (e.g. words with profane themes) were tabulated.

Verbal Paragraph Recall: *Wechsler Memory Scale – Revised*, *Logical Memory subtest* (*WMS-R*) (Wechsler, 1987)

This task was administered only to MDMA users. The experimenter read aloud a short paragraph that contained 25 items of information. Participants were asked to immediately recite the paragraph word for word. This process was repeated for a second paragraph. Recall was assessed again after a delay of 30 min. The number of items correctly recalled was recorded, and age-corrected percentile scores for Immediate and Delayed recall were computed based on normative data (Wechsler, 1987).

Spatial Delayed Response Task

This task measured working memory for the locations of spatial targets. In a prior study, task performance was impaired by the 5-HT agonist,

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fenfluramine (Luciana & Collins, 1997; Luciana *et al*. 1992, 1998). Given MDMA's structural similarity to fenfluramine, it was hypothesized that altered spatial working memory skills might be evident in MDMA users due to 5-HT neurotoxicity. During each of 48 trials, subjects observed a central fixation point on a computer monitor for 3 s. Next, a visual cue (a black asterisk) appeared in peripheral vision for 200 ms. After the occurrence of this visual cue, the cue and fixation point disappeared, and the screen blackened for randomly interspersed delay intervals of 500 ms, 4000 ms, or 8000 ms. After the delay interval, the screen instantly lit, and the subject indicated the remembered location of the cue with a touch-pen device (FastPoint Technologies, Inc.). A block of 16 'no delay' trials was administered to measure basic perceptual and visuomotor processes. The average error scores for each delay condition (0, 500, 4000 and 8000 ms) and response latencies (in milliseconds) were recorded.

Affective Working Memory (Luciana *et al*. 2001)

This task was recently developed in our laboratory and is a modification of the delayed paired associates paradigm, which has been described by Milner (1995) as an index of frontal lobe function. The goal in developing the task was to devise a non-spatial measure of working memory that would include affective content and would maximize the demand for recall *versus* recognition memory. In a recent study, we reported that variations in 5-HT levels, achieved through precursor depletion and augmentation, influenced healthy subjects' working memory for stimuli with sad affective content (Luciana *et al*. 2001). We hypothesized a similar association in MDMA users. On each of 96 trials, participants viewed a central '+' in the centre of a computer monitor. After 3 s, a face appeared. The face, presented in black and white, was a stimulus taken from the Ekman Pictures of Facial Affect and displayed one of seven affective states (neutral, happy, surprised, disgusted, fearful, angry, or sad). Type of affect and gender of the individual displayed were varied and unpredictable across trials. No stimulus was presented twice. Following stimulus presentation, the screen darkened for a delay interval of either 500 or 8000 ms. Afterwards, a second-part of a face appeared that was the eyes, nose or mouth of one of the faces. Individuals had to decide whether or not this second facial feature was an identical match (in terms of facial identity and affect) to what had just been seen as the target stimulus. To indicate response selections, participants pressed 'yes' or 'no' buttons. Stimulus presentation and response time measurements were controlled through the use of the PsyScope software package (Cohen *et al*. 1993) and button box. Accuracy and response latency for each stimulus type were recorded.

Table 1. *Demographic characteristics of control participants and MDMA users*

	Control ($N=26$)	MDMA ($N=26$)	F or χ^2
Age	20·7 (3·4)	21·3 (3·6)	0·35
Gender ratio (male : female)	14 : 12	14 : 12	$\chi^2=0{\cdot}00$
Right-handed, %	84·6%	96·2%	$\chi^2=1{\cdot}99$
Depression score†	3·6 (3·3)	8·7 (8·3)	8·16**
Years of education	14·2 (1·0)	13·9 (1·1)	1·46
Verbal IQ‡	114·3 (14·3)	114·6 (15·1)	0·00
Performance IQ‡	117·0 (16·2)	114·9 (15·8)	0·24
Full Scale IQ‡	116·8 (15·0)	115·8 (14·3)	0·06
Vocabulary	12·7 (2·7)	12·9 (2·9)	0·12
Similarities	12·1 (2·6)	12·0 (2·6)	0·01
Digit Span	12·0 (3·2)	12·0 (3·0)	0·00
Digit Symbol Coding	12·1 (2·7)	11·8 (2·7)	0·22
Block Design	12·5 (2·8)	12·3 (3·1)	0·06

Values are means (and standard deviations) unless stated otherwise.

† Beck Depression Inventory, maximum possible range = 0–63.

‡ Using selected subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III), pro-rated IQ: Verbal subtests, Vocabulary, Similarities and Digit Span; Performance subtests, Digit Symbol Coding and Block Design. WAIS-III subtest scores are expressed in standard score units (mean = 10·0, S.D. = 3·0).

MDMA, Methylenedioxymethamphetamine.

** $P<0{\cdot}01$.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS, Inc, Chicago, IL, USA), version 10.0 for Windows. Distributions of all variables were examined prior to analysis, and those that did not meet the assumptions for parametric analysis were log-10 transformed. These variables included grooved pegboard drops, letter cancellation errors of omission and commission, and verbal fluency perseverative responses, rule-breaking errors, and 'inappropriate' responses. MDMA-use characteristics were compared between subsamples of the MDMA group using the

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Table 2. *MDMA use characteristics*

	Total group		MDMA No diagnosis	MDMA diagnosis	
	Mean (S.D.)	Range	Mean (S.D.)	Mean (S.D.)	*U*
Occasions of MDMA use, *N*	64·9 (122·9)	11–650	29·3 (25·5)	95·4 (162·2)	45·0*
Duration of use (months)	27·0 (22·9)	7–77	24·2 (23·5)	29·4 (22·9)	65·5
Time since last use (weeks)	10·9 (10·5)	1–40	6·4 (5·2)	14·7 (12·4)	48·5
Occasions of use in past month, *N*	0·5 (0·9)	0–4	0·7 (0·7)	0·4 (1·1)	50·0*
Occasions of use in past year, *N*	18·3 (15·8)	2–73	10·8 (5·8)	24·9 (18·8)	35·5*
Average pills per session, *N*	1·9 (0·8)	1–4	1·6 (0·6)	2·1 (0·9)	48·0
Maximum pills ever taken in one session, *N*	4·4 (5·5)	1–30	2·6 (1·3)	6·0 (7·1)	32·5**
Estimated average occasions used per month, *N*†	2·3 (2·0)	0·5–9	1·4 (0·5)	3·0 (2·5)	52·5

† Total number of occasions of use ÷ total number of months of use.
MDMA, Methylenedioxymethamphetamine.
* $P<0·05$; ** $P<0·01$.

Mann–Whitney procedure. Chi-square analyses were used to compare dichotomous variables (i.e. gender and handedness distribution). Unless otherwise indicated, one-way analysis of variance (ANOVA) was used to test group differences. When significant group differences were found in comparisons involving more than two independent variables, a Bonferroni test was conducted *post hoc* to determine the nature of the differences. Alpha levels below 0·05 were considered statistically significant.

RESULTS

Demographics

Demographic information and other participant characteristics are presented in Table 1. MDMA and control groups were similar in age, their years of education, their relative proportions of males and females, and in their proportions of right-handed *versus* non-right-handed individuals. MDMA users' mean BDI depression score was significantly higher than that of controls. Scores on the BDI can range from 0 to 63, and according to recommended interpretive cut-offs (Kendall *et al.* 1987), MDMA users and controls fall within the non-clinical or normal range. In terms of general intellectual function, controls and MDMA users performed similarly on all WAIS-III subtests. On average, both groups performed overall in the high average range of intellectual ability.

MDMA characteristics and other illicit drug use

The characteristics of MDMA use within the MDMA sample are presented in Table 2.

Table 3. *Abuse or dependence upon other illicit drugs in the MDMA sample*

	Current abuse	Current dependence	Past abuse	Past dependence	No diagnosis
Alcohol	2	0	11	11	2
Marijuana	1	4	6	8	7
Cocaine	1	0	1	5	19
Other psychostimulants	1	1	0	4	20
Hallucinogens	0	0	5	0	19
Opioids	1	0	5	2	18
Sedatives	0	0	2	3	21

Total sample size = 26. Values represent number of individuals diagnosed.

Consistent with previous studies, MDMA users reported prior use of several other drugs (Bolla *et al.* 1998; McCann *et al.* 1999; Morgan, 1999) and many met past (or rarely current) diagnostic criteria for other types of substance abuse or dependence. These data are summarized in Table 3. In addition to MDMA, the most commonly abused substances in this cohort were alcohol and marijuana.

Co-morbid psychopathology

In addition, based on the SCID-P, some users met criteria for psychological disorders, consistent with what has been reported by others (Krystal *et al.* 1992; Parrott *et al.* 2001). Other than substance-related disorders, the most common clinical condition observed in our sample of MDMA users was unipolar depression ($N=8$). Of these, all episodes were past episodes. Four of these eight individuals carried an additional diagnosis of current anxiety disorder

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Table 4. *Cognitive task performance in controls and MDMA users*

	Control ($N=26$)	MDMA ($N=26$)	F†
Finger Tapping Test‡			
Dominant hand	50·5 (6·9)	46·0 (6·8)	7·29**
Non-dominant hand	46·5 (7·2)	41·7 (6·2)	
Grooved Pegboard: time§			
Dominant hand	67·7 (8·4)	64·6 (8·1)	2·61
Non-dominant hand	74·5 (13·2)	70·0 (10·3)	
Grooved Pegboard: drops¶			
Dominant hand	0·2 (0·4)	0·3 (0·5)	0·15
Non-dominant hand	0·4 (0·8)	0·2 (0·5)	
Letter Cancellation			
Time§	105·0 (15·8)	102·3 (15·9)	0·36
Omission errors	1·5 (1·9)	2·5 (1·5)	3·68*
Commission errors	0·1 (0·3)	0·2 (0·6)	
Verbal Fluency			
Total words, *N*	45·0 (7·8)	43·9 (9·0)	0·20
Perseverative errors	2·3 (2·0)	1·6 (1·8)	1·66
Errors	0·6 (0·9)	1·1 (1·3)	4·25*
Inappropriate words	0·8 (1·1)	1·4 (1·3)	3·57
Digit Span‖			
Digits forward	7·5 (1·2)	7·2 (1·2)	0·47
Digits backward	6·0 (1·5)	5·8 (1·5)	0·21
Verbal Paragraph Recall+			
Immediate recall	—	58·5 (32·2)	$t=-3·72$***
30-min Delayed recall	—	56·5 (30·4)	$t=-4·28$***
Spatial Working Memory			
Accuracy (500 ms delay)	7·4 (3·6)	6·9 (1·5)	0·53
Accuracy (4000 ms delay)	9·0 (2·6)	9·4 (2·0)	0·53
Accuracy (8000 ms delay)	10·6 (3·2)	11·6 (2·5)	1·40
4000 ms–500 ms difference	1·5 (2·1)	2·5 (1·6)	4·02*
8000 ms–500 ms difference	3·2 (3·0)	4·7 (2·3)	4·15*
Latency (500 ms delay)	1500·2 (475·4)	1484·2 (372·1)	0·02
Latency (4000 ms delay)	1426·4 (395·6)	1528·1 (399·3)	0·85
Latency (8000 ms delay)	1472·6 (434·1)	1593·4 (435·6)	1·00
4000 ms–500 ms difference	−73·9 (252·1)	43·9 (299·5)	2·35
8000 ms–500 ms difference	−27·7 (289·3)	109·3 (315·2)	2·66
Affective Working Memory			
Correct (500 ms delay), %	74·2 (6·9)	72·4 (7·0)	0·79
Correct (8000 ms delay), %	68·1 (7·4)	67·1 (8·2)	
Latency (500 ms delay)	1551·1 (416·1)	1520·0 (438·1)	0·04
Latency (8000 ms delay)	1923·9 (644·5)	2012·3 (572·4)	

Unless otherwise indicated, values are raw score means (and standard deviations).
† F statistics reflect main effects of Group (MDMA *v.* Control).
‡ Average number of taps across three 10 s trials.
§ Time to completion (s).
¶ Number of dropped pegs.
‖ Number of digits correctly recalled in forward and backward sequence.
+ Wechsler Memory Scale – Revised (WMS-R): Logical Memory I (Immediate recall) and Logical Memory II (30-min Delayed recall) age-corrected percentile equivalent scores. Values from a one-sample t test are presented (value of comparison = 82).
MDMA, Methylenedioxymethamphetamine.
* $P<0·05$; ** $P<0·01$; *** $P<0·001$.

(two generalized anxiety disorder and two specific phobia).

Cognitive testing

Means, standard deviations, tests statistics, and P values for main effects on cognitive task performance are shown in Table 4.

Motor function

To examine performance on the Finger Tapping Test, the average number of finger taps across three 10 s trials for each hand was entered into a repeated measures ANOVA with Hand (dominant and non-dominant) as the within-subjects factor and Group (control *v.* MDMA) as the

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between-subjects factor. This analysis revealed a significant main effect of Hand ($F(1,50) = 31{\cdot}40$, $P < 0{\cdot}000$), a significant main effect of Group ($F(1,50) = 7{\cdot}29$, $P < 0{\cdot}01$), but no significant Group × Hand interaction ($F(1,50) = 0{\cdot}02$, NS). Participants were faster when they used their dominant hands, and MDMA users were slower than controls.

On the Grooved Pegboard task, the amount of time to complete the task was similarly compared between groups. There was a significant main effect of Hand ($F(1,50) = 15{\cdot}58$, $P < 0{\cdot}000$). Performance was faster with the dominant hand. However, there was no significant main effect of Group ($F(1,50) = 2{\cdot}61$, NS) and no significant Group × Hand interaction ($F(1,50) = 0{\cdot}23$, NS). Analysis of the number of dropped pegs revealed no significant main effect of Hand ($F(1,50) = 0{\cdot}03$, NS), no significant main effect of Group ($F(1,50) = 0{\cdot}15$, NS) and no significant Group × Hand interaction ($F(1,50) = 1{\cdot}64$, NS).

Thus, MDMA users were slower in their gross motor speeds but equivalent to controls in their fine-motor dexterity.

Attention and vigilance

For the Letter Cancellation task, the time to task completion and errors of omission and commission were recorded. Controls and MDMA users did not differ in their completion times ($F(1,49) = 0{\cdot}36$, NS). However, when error scores were examined in a multivariate analysis of variance, there was a significant main effect of Group ($F(2,49) = 3{\cdot}68$, $P < 0{\cdot}05$). MDMA users made significantly more omission errors than controls, suggesting a normal rate of information processing but poor vigilance.

Verbal Fluency

The groups were equivalent in the average number of words generated on the task ($F(1,50) = 0{\cdot}20$, NS) and in the number of perseverative errors ($F(1,49) = 1{\cdot}66$, NS). However, MDMA users made more rule-breaking errors ($F(1,49) = 4{\cdot}25$, $P < 0{\cdot}05$) and generated a marginally greater number of 'inappropriate' responses ($F(1,49) = 3{\cdot}57$, $P < 0{\cdot}10$).

Verbal Memory

Digit Span

One-way ANOVAs indicated no group differences in the number of digits correctly recalled in forward ($F(1,50) = 0{\cdot}47$, NS) or backward ($F(1,50) = 0{\cdot}21$, NS) order.

Verbal Paragraph Recall

MDMA users' age-corrected percentile scores for Immediate recall (mean percentile = 58·5, S.D. = 32·2, range = 2 to 97%) and 30-min Delayed recall (mean percentile = 56·5, S.D. = 30·4, range = 1 to 97%) were compared with the percentile equivalent of each participant's Vocabulary scaled score. The rationale for this method of analysis is as follows. In clinical neuropsychology, the concept of deficit measurement is central to the interpretation of findings within a given test battery (Lezak, 1995). Because individuals often present for neuropsychological evaluation in the absence of any reliable baseline representation of their performance, the clinician derives an estimate of the individual's pre-morbid level of function based on available information. There are a number of acceptable options for making such an estimate (Lezak, 1995; Vanderploeg, 2000), one of which is to use test scores that are least likely to be compromised with brain injury as representative of an individual's pre-morbid level of ability. Certain subtests of the Wechsler Adult Intelligence Scales fit this general requirement. Vocabulary, for example, is highly correlated with full-scale IQ and is generally impervious to cerebral damage except in cases of left-hemisphere injury or advanced dementia (Lezak, 1995). MDMA users in our sample achieved an average Vocabulary scaled score of 12·7, which represents the 82nd percentile of functioning (Kaufman & Lichtenberger, 1999). Therefore, a one-sample *t* test was conducted on Logical Memory percentile scores with the value of comparison set to 82. MDMA users differed significantly from expected levels of performance on both Immediate recall ($t(25) = -3{\cdot}72$, $P < 0{\cdot}000$) and 30-min Delayed recall ($t(25) = -4{\cdot}28$, $P < 0{\cdot}000$). Immediate recall was not significantly different from Delayed recall performance ($t(25) = 1{\cdot}16$, NS).

Working Memory

Spatial Working Memory

Two processes are of interest in evaluating data from this task. The first concerns error scores obtained at each delay level (0, 500, 4000 and 8000 ms). The second concerns the relative

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impact of increasing delay (memory load) on performance. The impact of memory load is examined by computing the difference between error scores or reaction times on 8000 ms *v.* 500 ms trials and on 4000 ms *v.* 500 ms trials. When these difference scores are examined between groups, they represent the Delay × Group interaction effect. Groups differed significantly in their performance on no-delay trials ($F(1,51) = 5{\cdot}63$, $P < 0{\cdot}05$). Contrary to expectation, MDMA users were more accurate than control subjects. The groups did not significantly differ in their accuracy scores on 500, 4000, or 8000 ms trials. However, they varied on the difference between 8000 and 500 ms ($F(1,51) = 4{\cdot}15$, $P < 0{\cdot}05$) and 4000 *v.* 500 ms trials ($F(1,51) = 4{\cdot}02$, $P < 0{\cdot}05$). MDMA users were more negatively impacted by increasing delay intervals than were control subjects. Response latencies were similarly examined but did not vary by group.

Affective Working Memory

The average percentage correct for 500 ms and 8000 ms trials for each type of affective stimulus was compared in a repeated measures ANOVA with two levels of Delay and seven levels of Emotion as within-subjects factors. Group was entered as a between-subjects factor. This analysis revealed a significant main effect of Delay ($F(1,43) = 17{\cdot}97$, $P < 0{\cdot}000$), a main effect of Emotion ($F(6,38) = 10{\cdot}60$, $P < 0{\cdot}01$), but no significant main effect of Group ($F(1,43) = 1{\cdot}31$, NS). The only interactions to approach significance were between Delay and Emotion ($F(6,38) = 7{\cdot}25$, $P < 0{\cdot}01$) and between Delay, Emotion and Group ($F(6,38) = 1{\cdot}96$, $P < 0{\cdot}10$). Performance was generally worse on long *versus* short delay trials, except when the emotion of 'fear' was processed, in which case performance was more accurate with longer delays. To investigate the nature of the three-way interaction, the processing of individual affects was examined in a series of *post hoc* exploratory analyses. For each of the seven affective states displayed on trials of this task (neutral, disgust, happy, sad, angry, fearful, surprised), a repeated measures ANOVA was conducted on the percentage of correct responses with Delay interval (500 ms *v.* 8000 ms) as the within-subjects factor and Group as a between-subjects factor. Main effects of Delay were observed for the processing of neutral, angry, sad and fearful faces. Consistent with our hypothesis, a main effect of Group was observed only for the processing of sad faces ($F(1,46) = 3{\cdot}95$, $P < 0{\cdot}05$) with MDMA users performing worse than controls. The interaction between Delay and Group was significant at a trend level for angry faces ($F(1,45) = 2{\cdot}80$, $P < 0{\cdot}10$).

The average response latencies were similarly compared in a repeated measures ANOVA with Delay and Emotion as within-subjects factors, revealing a significant main effect of Delay ($F(1,47) = 94{\cdot}33$, $P < 0{\cdot}000$) but no significant main effect of Group or Delay × Group interaction. The main effect of Delay was due to relatively slow responses on 8000 ms *v.* 500 ms trials. When the specific affective presentations were individually evaluated, there was consistently a significant main effect of Delay, but there were no significant Group or Delay × Group effects.

Summary

MDMA users differed from expected levels of performance in their motor speed, attention and vigilance, rule-breaking errors and impulsivity of speech on the Verbal Fluency task, spatial working memory (sensitivity to increments in memory load), working memory for sad affective stimuli and verbal recall. In combination, these findings suggest the possibility of temporal and frontostriatal dysfunction.

However, MDMA users present a complex picture in terms of their clinical states and drug use histories, so these deficits are difficult to attribute to MDMA. As mentioned previously, the MDMA users differed significantly from the control group in their BDI scores. When the above analyses were repeated, covarying for BDI scores, significant differences in finger-tapping rate, spatial working memory load, accuracy of working memory for sad affective content and verbal fluency errors decreased to a trend level. The differences in Letter Cancellation omission errors and inappropriate words generated on the Verbal Fluency test remained significant. Logical Memory scores were not significantly correlated with depression levels.

These findings reinforce the notion that there is a substantial degree of heterogeneity in individuals who use MDMA. This heterogeneity is reflected in patterns of use, in levels of

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concomitant psychopathology, and in the extent of previous drug use. In examining characteristics of our sample, we were intrigued to find that approximately half of our MDMA users attained a DSM-IV MDMA abuse or dependence ($N=14$) diagnosis and that half were without such diagnoses ($N=12$). Of those who received an MDMA-related diagnosis, two reported at least four symptoms consistent with past MDMA dependence, 11 reported past MDMA abuse, and two reported current MDMA abuse. Of those diagnosed with past or current MDMA abuse, 46% reported one abuse symptom, 46% reported two abuse symptoms, and 8% reported three abuse symptoms. The most commonly reported symptom was using the drug in a situation where it might have been dangerous to do so. Method of recruitment (university *versus* community sample) did not vary between those users with and without a diagnosis ($\chi^2(1)=0{\cdot}54$, NS). Whether the diagnostic groups were differentially prone to cognitive dysfunction was next considered.

Exploratory analysis: MDMA users with *versus* without DSM-IV MDMA abuse or dependence

The demographic characteristics of these groups were compared. The groups were similar in age, IQ scores, average years of education, Beck depression scores, male *versus* female representation, and in their proportions of right and non-right handed individuals.

The MDMA use characteristics of the two groups are presented in Table 2. On average, MDMA users with an MDMA-related diagnosis reported significantly more lifetime occasions of MDMA use ($U=45{\cdot}0$, $P<0{\cdot}05$), more occasions of use within the past year ($U=35{\cdot}5$, $P<0{\cdot}05$), and a higher maximum number of pills ever taken in one session ($U=32{\cdot}5$, $P<0{\cdot}01$). Surprisingly, MDMA users without an MDMA diagnosis reported significantly more occasions of use in the past month ($U=50{\cdot}0$, $P<0{\cdot}05$) and had used MDMA marginally more recently than those with this diagnosis ($U=48{\cdot}5$, $P<0{\cdot}10$). However, users with an MDMA-related diagnosis had a marginally higher average number of pills ingested per session ($U=48{\cdot}0$, $P<0{\cdot}10$). No significant differences were found between the groups in the total duration of use or in the estimated average monthly use of MDMA.

Cognitive testing

Table 5 presents details regarding cognitive performance between the two groups.

Motor function

Analysis of the Finger Tapping Task revealed no significant group differences. On the Grooved Pegboard task, the groups were equivalent in their times to complete the task, but varied when the number of dropped pegs was examined ($F(1,24)=9{\cdot}53$, $P<0{\cdot}01$). Users with an MDMA diagnosis dropped more pegs, regardless of which hand was used.

Attention and vigilance

For the Letter Cancellation task, the completion time for individuals with an MDMA diagnosis was significantly greater than the completion time for those without this diagnosis ($F(1,23)=4{\cdot}98$, $P<0{\cdot}05$). Error rates were equivalent.

Verbal Fluency

The groups differed in the total number of words generated ($F(1,23)=6{\cdot}04$, $P<0{\cdot}05$). Users with an MDMA diagnosis produced fewer words than those without an MDMA diagnosis. However, no significant group differences were found for perseverative errors ($F(1,23)=0{\cdot}63$, NS) or for the number of inappropriate words ($F(1,23)=1{\cdot}18$, NS). Users with an MDMA-related diagnosis made marginally significantly more rule-breaking errors than those without this diagnosis ($F(1,23)=3{\cdot}88$, $P<0{\cdot}10$).

Verbal Memory

Digit Span

Recall of digits in forward and backward sequence did not differ between individuals with *versus* without an MDMA-related diagnosis.

Verbal Paragraph Recall

Individuals with an MDMA diagnosis recalled significantly less information from the paragraphs than individuals without an MDMA diagnosis on both Immediate recall ($F(1,24)=7{\cdot}84$, $P=0{\cdot}01$) and 30-min Delayed recall ($F(1,24)=9{\cdot}46$, $P<0{\cdot}01$).

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Table 5. *Cognitive performance in MDMA users with and without an MDMA-related substance use diagnosis*

	Without diagnosis	With diagnosis	*F*†
Finger Tapping Test‡			
Dominant hand	47·6 (7·5)	44·6 (6·0)	1·35
Non-dominant hand	43·1 (7·3)	40·5 (5·0)	
Grooved Pegboard: time§			
Dominant hand	63·7 (9·2)	65·4 (7·4)	0·74
Non-dominant hand	68·1 (8·5)	71·6 (11·8)	
Grooved Pegboard: drops¶			
Dominant hand	0·1 (0·3)	0·5 (0·5)	9·53**
Non-dominant hand	0·0 (0·0)	0·4 (0·6)	
Letter Cancellation			
Time§	94·9 (12·5)	108·1 (16·2)	4·98*
Omission errors	2·6 (1·6)	2·4 (1·4)	1·25
Commission errors	0·0 (0·0)	0·4 (0·8)	
Verbal Fluency			
Total words, *N*	48·1 (8·7)	40·1 (7·6)	6·04*
Perseverative errors	1·8 (1·9)	1·4 (1·9)	0·63
Errors	0·7 (0·8)	1·5 (1·6)	3·88
Inappropriate words	1·8 (1·4)	1·2 (1·2)	1·18
Digit Span‖			
Digits forward	7·6 (1·3)	6·9 (1·1)	1·96
Digits backward	5·8 (1·5)	5·8 (1·5)	0·00
Verbal Paragraph Recall+			
Immediate recall	75·4 (22·7)	44·0 (32·7)	7·84**
30-min Delayed recall	73·6 (22·5)	41·8 (29·1)	9·46**
Spatial Working Memory			
Accuracy (500 ms delay)	7·1 (1·8)	6·7 (1·2)	0·51
Accuracy (4000 ms delay)	9·3 (2·0)	9·6 (2·1)	0·13
Accuracy (8000 ms delay)	11·2 (3·1)	11·9 (2·0)	0·55
4000 ms–500 ms difference	2·2 (1·3)	2·9 (1·7)	1·36
8000 ms–500 ms difference	4·0 (2·5)	5·2 (2·1)	1·65
Latency (500 ms delay)	1397·3 (337·3)	1558·6 (396·3)	1·23
Latency (4000 ms delay)	1512·6 (527·4)	1541·3 (266·1)	0·03
Latency (8000 ms delay)	1524·9 (556·2)	1652·1 (308·5)	0·54
4000 ms–500 ms difference	115·3 (315·3)	−17·3 (282·1)	1·28
8000 ms–500 ms difference	127·6 (348·3)	93·5 (296·5)	0·07
Affective Working Memory			
Correct (500 ms delay), %	74·5 (5·9)	70·6 (7·6)	0·95
Correct (8000 ms delay), %	67·4 (9·3)	66·8 (7·5)	
Latency (500 ms delay)	1389·7 (415·1)	1630·2 (442·2)	2·42
Latency (8000 ms delay)	1813·6 (527·1)	2180·3 (527·1)	

Values are means (and standard deviations).
† *F* statistics reflect main effects of Group (MDMA users without diagnosis *v*. MDMA users with diagnosis).
‡ Average number of taps across three 10 s trials.
§ Time to completion (s).
¶ Number of dropped pegs.
‖ Number of digits correctly recalled in forward and backward sequence.
+ Wechsler Memory Scale – Revised (WMS-R): Logical Memory I (Immediate recall) and Logical Memory II (30-min Delayed recall) age-corrected percentile equivalent scores.
MDMA, Methylenedioxymethamphetamine.
* $P<0{\cdot}05$; ** $P<0{\cdot}01$.

Working Memory

Spatial Working Memory

Performance was indistinguishable between groups on all variables of the task.

Affective Working Memory

Accuracy scores representing targets with neutral, happy, surprised, fearful, sad, angry and disgusted faces across two delay intervals

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Table 6. *Associations between MDMA sample characteristics and cognition*

	MDMA use						
	Number of occasions of use	Time since last use (weeks)	In past month	In past year	Average pills per session	Maximum pills ever taken in one session	BDI score
Grooved Pegboard							
Dominant hand drops	−0·039	0·390*	−0·477*	−0·006	0·000	0·034	0·223
Non-dominant hand drops	0·382*	−0·099	−0·028	0·389*	0·088	0·056	−0·237
Letter Cancellation, time	0·050	0·190	−0·296	0·511**	0·511**	0·426*	0·221
Verbal Fluency							
Total words, *N*	−0·277	0·002	0·071	−0·221	−0·141	−0·178	−0·106
Rule-breaking errors	0·141	0·153	−0·048	0·411*	0·297	0·112	0·024
Verbal Paragraph Recall							
Immediate recall	−0·336	−0·108	0·322	−0·392*	−0·188	−0·286	−0·144
30-min Delayed recall	−0·477*	−0·137	0·300	−0·343	−0·321	−0·418*	−0·154

Values are Spearman's rho non-parametric correlations between task performance and MDMA-use characteristics that differed significantly between users with *versus* without an MDMA-related diagnosis.
MDMA, Methylenedioxymethamphetamine; BDI, Beck Depression Inventory.
* $P<0·05$; ** $P<0·01$.

(500 ms and 8000 ms) were compared between groups, revealing a significant effect of Delay ($F(1,21)=6·47$, $P<0·05$), a significant Delay × Emotion interaction ($F(6,126)=3·97$, $P<0·01$) and a significant three-way interaction among Group, Emotion and Delay ($F(6,126)=2·78$, $P<0·05$). Follow-up MANOVAs were conducted to investigate the nature of the three-way interaction. Significant Delay × Group interactions were observed for fear ($F(1,22)=4·40$, $P<0·05$) and marginally for anger ($F(1,21)=3·27$, $P<0·10$). MDMA users with an MDMA diagnosis were more accurate at remembering faces with fearful expressions at short (500 ms) delays, but less accurate at long (8000 ms) delays. Users without an MDMA-related diagnosis showed the opposite pattern.

Analysis of response latencies revealed a significant main effect of Delay ($F(1,22)=77·87$, $P<0·001$) but otherwise, there were no significant main effects or interactions. Responses were slower for long delay trials.

To summarize, individuals whose pattern of MDMA use is dysfunctional to the point of meriting a clinical diagnosis exhibit deficits in verbal memory (immediate and delayed paragraph recall), verbal fluency (total number of words generated and marginally, rule-breaking errors), fine motor dexterity (Grooved Pegboard) and time to complete a letter cancellation task. To examine the association of MDMA-use patterns and BDI scores with these deficits, Spearman's rho non-parametric correlations were computed between task performance and MDMA-use characteristics that differed significantly between users with *versus* without an MDMA-related diagnosis (see Table 6). The variable most closely associated with the observed cognitive deficits was the number of occasions of MDMA-use within the past year. That is, more use of MDMA within the past year was associated with poorer cognitive performance (i.e. more dropped pegs on the Grooved Pegboard task when using the non-dominant hand, slower completion time for Letter Cancellation, more Verbal Fluency rule-breaking errors and poorer Logical Memory performance). Other MDMA-use characteristics that were significantly associated with poorer performance included a higher maximum number of pills ever taken in one session (Letter Cancellation – slower time; Logical Memory –poorer delayed recall), higher total number of occasions of use (Grooved Pegboard – more non-dominant hand peg drops; Logical Memory – poorer delayed recall), and a greater average number of pills ingested per session (slower completion time for Letter Cancellation). Surprisingly, a longer duration since the most recent use of MDMA and fewer occasions of use in the past month were associated with poorer performance on the Grooved Pegboard when using the dominant hand.

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Other illicit drug use

MDMA users reported using a variety of other illicit drugs, as well as alcohol, in substantial quantities. Based on our diagnostic interviews, the presence or absence of substance abuse/dependence was quantified for the following substance categories: alcohol, marijuana, cocaine, other psychostimulants, hallucinogens, sedatives, MDMA, and opioids (see Table 3). In terms of current substance abuse or dependence, 17 individuals (65%) had no current substance use diagnoses, six (23%) had one substance use diagnosis and three (12%) individuals met criteria for two current substance use diagnoses. Co-morbidity was more variable in terms of past substance use diagnoses. The number of past abused substances ranged from 0 to 7. The total (lifetime) number of substances for which this sample reported either abuse or dependence, including MDMA, ranged from 1 to 8. The total number of abused substances was correlated with cognitive performance variables using the Spearman rank-order procedure. Very few correlations were significant. A greater degree of substance-related impairment was associated with slower responses on the Grooved Pegboard task (dominant hand: $r = 0{\cdot}38$, $P = 0{\cdot}05$) and higher error scores on the spatial working memory task under the long (8 s) delay condition ($r = 0{\cdot}39$, $P < 0{\cdot}05$). Thus, it appears unlikely that the more extensive array of cognitive impairments observed in this sample of MDMA users is readily attributed to the influence of other drugs of abuse. Moreover, MDMA users with and without MDMA-related substance use diagnoses did not differ in their lifetime use/dependence on other substances ($F(1,25) = 1{\cdot}85$, NS).

DISCUSSION

In this study, the psychological and neurocognitive characteristics of MDMA users and MDMA-naïve controls were examined in a comprehensive assessment protocol. The groups were matched on age, IQ and years of education. Indeed, this was a relatively high functioning sample, as both groups demonstrated general levels of intellectual ability in the high average range, similar to other samples of MDMA users (e.g. Krystal *et al.* 1992; Morgan, 1998; Croft *et al.* 2001; Morgan *et al.* 2002). The first major finding of this study is that MDMA users, as a group, showed reductions in psychomotor speed, attention and vigilance, more rule-breaking errors and more impulsive speech (i.e. inappropriate words) on the Verbal Fluency Test and deficits in spatial working memory. These findings collectively suggest the possibility of frontostriatal dysfunction. Additionally, MDMA users demonstrate lower than expected levels of verbal memory performance. Their scores on immediate and delayed paragraph recall were at average levels, relative to normative data, but still significantly lower than would be expected based on their higher than average levels of general intellectual ability.

This manner of interpreting the data requires some explanation. The fact that we did not obtain Logical Memory scores on our control subjects is an admitted weakness of this study. We opted, instead, to interpret MDMA users' Logical Memory scores against their levels of general verbal ability, as measured by the WAIS-III. This method of interpretation rests on the assumption that there is a single estimate (typically based on general intelligence or ***g***) of a person's cognitive abilities. It has a strong foundation in clinical neuropsychology where the concept of deficit measurement is central to the interpretation of findings within a given test battery (Lezak, 1995; Vanderploeg, 2000). Once an estimate of pre-morbid function is decided upon, interpretation proceeds using this level of function as a baseline against which all other obtained test scores are compared. While it could be argued that Logical Memory performance in our sample of MDMA users is not objectively 'below average', we maintain that the 25 percentile point discrepancy in performance between it and robust measures of verbal function is significant from a clinical perspective. Others have similarly suggested that a discrepancy between IQ indices and memory scores may be indicative of acquired memory impairment (Quadfasel & Pruyser, 1955; Prigatano, 1974; Milner, 1975). Bornstein *et al.* (1989, cited by the Psychological Corporation, 1997) compared the base rates of IQ-memory score discrepancies in the WMS-R standardization sample *versus* a clinical sample diagnosed with memory impairment. An IQ/delayed memory score discrepancy of 15 points was obtained by 33% of the clinical sample but only 10% of the

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normative sample. MDMA users in our sample obtained performance discrepancies that were, on average, quite a bit larger. Moreover, this pattern is consistent with other researchers who have reported deficits in verbal memory and executive functions in MDMA users (Krystal *et al.* 1992; Bolla *et al.* 1998; Dafters *et al.* 1999; Morgan, 1999; Rodgers, 2000; Bhattachary & Powell, 2001; Morgan *et al.* 2002).

More than half of our MDMA users met diagnostic criteria for abuse or dependence of MDMA, while the others did not. The second major finding of this study is that groups based on the presence or absence of this diagnosis differed in several ways, including performance in verbal memory (immediate and delayed paragraph recall), verbal fluency (total number of words generated and marginally, rule-breaking errors), fine motor dexterity (Grooved Pegboard) and the time to complete a letter cancellation task. In all cases, individuals with an MDMA-related diagnosis displayed relative impairment as compared to those users whose pattern of use was recreational but not necessarily clinically dysfunctional. In light of the relatively small groups, we regard these findings as preliminary in nature.

The reasons for these distinctions are unclear. It may be that users with an MDMA-related substance use diagnosis exhibit pre-morbid characteristics that contribute to their cognitive vulnerabilities. Yet, they were not distinct from recreational users in overall IQ or in other demographic variables, such as years of education, that might impact cognitive functioning. They also did not differ in their histories of non-MDMA drug use and abuse. Several characteristics related to MDMA use or its consequences, did distinguish the groups. In terms of MDMA-use patterns, participants with a history of MDMA abuse or dependence had more lifetime occasions of MDMA use, including more use within the past year, a higher maximum number of pills ever ingested in one session, and a marginally, but non-significantly, higher average number of pills consumed per session. However, the groups did not differ significantly in the estimated average number of occasions of use per month or in the total duration of use, from first use to most recent use. Surprisingly, MDMA users without this diagnosis had used more recently (mean = 6·4 weeks *versus* 14·7 weeks since last use) and more often in the past month.

When these differences were examined in relation to differences in cognitive performance, a greater number of occasions of use within the past year (but not within the past month) was consistently associated with poorer performance. Additionally, although the average dosage of MDMA among users with and without an MDMA-related diagnosis did not differ significantly (2·1 *versus* 1·6 pills per occasion of use, respectively), it is possible that occasional higher doses may be detrimental to cognitive function. This was suggested by the finding that users with an MDMA-related diagnosis reported a higher maximum number of pills consumed on a single occasion and that this was significantly correlated with slower processing time (Letter Cancellation) and poorer delayed verbal paragraph recall (Logical Memory-II). This finding is interesting given evidence that MDMA blood plasma concentrations increase disproportionately with increasing doses of MDMA (de la Torre *et al.* 2000).

It may be that more frequent use, higher dosage, more total uses (especially within the past year), and, in particular, clinically dysfunctional use of MDMA increase the risk of 5-HT neurotoxicity and, hence, greater cognitive deficits. That more recent use of MDMA was not associated with poorer cognitive performance suggests that the risk variables just described are more important than recency of use and that the resulting cognitive deficits may be relatively long lasting. Our findings add a compelling component to the literature, suggesting that a pattern of clinically dysfunctional use of MDMA may increase the risk for developing cognitive impairment. Impairment was not limited in this study to verbal recall but also extended to aspects of executive function, a finding that is consistent with others' findings (Morgan, 1998; Schifano *et al.* 1998; Dafters *et al.* 1999; Wareing *et al.* 2000; Bhattachary & Powell, 2001; Heffernan *et al.* 2001; Fox *et al.* 2002; Morgan *et al.* 2002).

These findings contrast with previous research in that the total lifetime use of MDMA was not as strongly associated with cognitive deficits as has been previously reported (e.g. McCann *et al.* 1999; Bhattachary & Powell, 2001; Fox *et al.* 2001*b*). In agreement with

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previous research (e.g. Bolla *et al.* 1998; McCann *et al.* 1999; Gouzoulis-Mayfrank *et al.* 2000; Bhattachary & Powell, 2001; Fox *et al.* 2001*b*; Verkes *et al.* 2001; Zakzanis & Young, 2001), cognitive deficits were correlated with dosage and frequency of MDMA use, particularly, more use in the past year, more total lifetime uses, a higher maximum number of pills ingested in one session, and a higher average number of pills per session.

The findings of the present study are in apparent contrast to the findings of Fox *et al.* (2001*b*), where 'problem users' were compared to 'non-problem' users. The main finding was that MDMA users showed selective cognitive deficits whether or not they reported problems secondary to MDMA-use. Furthermore, the impairments were dose-related, rather than related to self-reported problems from use. Several methodological distinctions may explain the discrepancies between the Fox *et al.* (2001*b*) study and the current study. First, the criteria for inclusion in the 'problem' *versus* 'non-problem' group was determined by each participant's response to one of three statements administered prior to testing: (*i*) 'I have never used the drug Ecstasy'; (*ii*) 'I have used the drug Ecstasy and experienced no problems as a result of taking the drug'; and (*iii*) 'I have used the drug Ecstasy and experienced problems attributable to the use of the drug' (p. 274). Participants answering affirmatively to the third question above were then asked to describe the nature of their problems. These criteria, based on the participant's subjective response, are substantially different than the objective criteria used in the current study, which included the assessment of DSM-IV abuse or dependence of MDMA. Thus, participants in Fox *et al.*'s 'non-problem' group may have endorsed criteria for abuse or dependence of MDMA when presented with specific symptoms. Although Fox *et al.* (2001*b*) used a questionnaire to assess 'Uplifts, hassels, stresses and cognitive failures' (Parrott & Kaye, 1999) of Ecstasy users, there was apparently no formal assessment of DSM-IV criteria for any psychological disorder, as there was in the current study. We regard the thorough assessment of DSM-IV Axis I psychological disorders as an important strength of the current study, and some important information may have been overlooked due to the omission of a psychological interview in Fox *et al.* (2001*b*). Finally, Fox *et al.* (2001*b*) included a Logical Memory prose recall task, but there were substantial differences in the administration and scoring of the task. The current study followed the guidelines of the WMS-R manual, as described above in the methods section. The version in Fox *et al.* (2001*b*) included 40 total 'ideas' in one story in contrast to the 25 'ideas' per story in the WMS-R version. In addition, the Fox *et al.* (2001*b*) participants were not informed of the delayed recall portion of the task, which was administered 1 h and 30 min following immediate recall, while the current study did inform participants of the delayed recall, administered 30 min after immediate recall. The scoring criteria also differed. Collectively, these disparities may explain the contrast in the findings.

Some general methodological and interpretive difficulties frequently arise in studies of MDMA users (see Morgan, 2000, for a thorough review). For example, most MDMA users have used several other drugs in addition to MDMA (e.g. Bolla *et al.* 1998; McCann *et al.* 1999; Morgan, 1999), so the possibility of interacting effects of other drugs remains a viable one. We found no association between the extent of additional drug abuse and cognitive dysfunction in our sample of users. Similarly, to address the problem of co-morbidity, some researchers include MDMA-naïve poly-drug control groups (e.g. Morgan, 1998, 1999; Gouzoulis-Mayfrank *et al.* 2000; Parrott *et al.* 2000; Croft *et al.* 2001; Morgan *et al.* 2002), a strategy that we plan to explore in future studies.

The assessment of drug history depended on participant self-report, and abstinence was not confirmed via biological measures. While we acknowledge that biological verification of abstinence is desirable, a number of reputable studies that have reported cognitive deficits in MDMA users have apparently failed to verify abstinence status (e.g. Krystal *et al.* 1992; Curran & Travill, 1997; Morgan, 1998, 1999; Parrott *et al.* 1998; Dafters *et al.* 1999; Rodgers, 2000; Bhattachary & Powell, 2001; Fox *et al.* 2001*a*, *b*, 2002; Heffernan *et al.* 2001), although this level of experimental control has been recommended (McCann *et al.* 1999; Gouzoulis-Mayfrank *et al.* 2000). In the current study, participants were encouraged to recollect carefully and

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accurately report their drug use through individual interviews. Notably, a recent study suggests a high concordance (88%) between self-report and biological analysis of recent MDMA use among individuals at club raves with an oral fluid test (Yacoubian & Wish, 2004). Furthermore, Schifano *et al*. (1998) found that urine analysis generally corresponded with self-report.

In generalizing these findings, one must consider how representative this sample is relative to MDMA users within the general population (e.g. in terms of MDMA and other drug use, demographic characteristics, presence of psychopathology) (Morgan, 2000), as well as the sample size. In addition, participants were self-referred and an unknown bias may have occurred with this recruitment technique (Morgan, 2000). Furthermore, the present study used multiple statistical comparisons to analyse the data, and for that reason, we recognize that our results await replication.

Finally, to the extent that they can be achieved given ethical concerns, follow-up studies that include thorough psychological assessments and comprehensive neuropsychological testing are necessary to examine the progression of cognitive deficits. The findings from Zakzanis & Young (2001) suggested a decline in memory functioning over a 1-year period that was related to the frequency, duration and total number of times that MDMA was used (Zakzanis & Young, 2001). Additional follow-up studies incorporating other cognitive measures are needed to supplement this research.

In conclusion, these findings emphasize the importance of assessing for substance abuse and dependence in studies of MDMA and suggest that individual differences may be important in predicting the nature and extent of cognitive impairment associated with use of this drug.

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