Psychopharmacology (1999) 143 : 417–425

ORIGINAL INVESTIGATION

Una D. McCann · Melissa Mertl
Victoria Eligulashvili · George A. Ricaurte

Cognitive performance in (±) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study

Received: 4 August 1998 / Final version: 12 November 1998

Abstract *Rationale:* (±) 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is an amphetamine analog and drug of abuse. In animals, MDMA damages brain serotonin (5-HT) neurons at doses that overlap with those used recreationally by some humans. To date, few functional sequelae of MDMA-induced 5-HT damage have been identified. *Objective:* Since serotonin is thought to be involved in cognitive processes, and since previous studies have reported verbal and visual memory deficits in MDMA users, the present study sought to determine whether other cognitive processes are influenced by previous exposure to MDMA. *Methods:* Twenty-two MDMA users who had not used MDMA for at least 3 weeks and 23 control subjects were tested repeatedly with a computerized cognitive performance assessment battery while participating in a 5-day controlled inpatient study. Cerebrospinal fluid (CSF) measures of monoamine metabolites were also collected as an index of brain monoaminergic function. *Results:* MDMA users and controls were found to perform similarly on several cognitive tasks. However, MDMA subjects had significant performance deficits on a sustained attention task requiring arithmetic calculations, a task requiring complex attention and incidental learning, a task requiring short term memory and a task of semantic recognition and verbal reasoning. MDMA users also had significant selective decreases in CSF 5-HIAA. *Conclusions:* The present CSF data provide further evidence that MDMA is neurotoxic to brain 5-HT neurons in humans, and the behavioral data suggest that brain 5-HT injury is associated with subtle, but significant, cognitive deficits.

Key words Serotonin · Neurotoxicity · Memory · Attention · Amphetamine

U.D. McCann (✉) · M. Mertl · V. Eligulashvili
Unit on Anxiety, Biological Psychiatry Branch, NIMH, Bethesda, MD 20892-1272, USA

G.A. Ricaurte
Department of Neurology, Johns Hopkins Medical Institutions, Baltimore, MD 21224, USA
e-mail: umccann@helix.nih.gov

Introduction

(±) 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a potent and selective serotonin (5-HT) neurotoxin in a variety of animal species, including non-human primates (Stone et al. 1986; Schmidt et al. 1986; Commins et al. 1987; O'Hearn et al. 1988; Ricaurte et al. 1988a,b). Animals treated with MDMA develop long-lasting decrements in regional brain 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) (Schmidt et al. 1986; Stone et al. 1986; Commins et al. 1987; Schmidt 1987), decreased tryptophan hydroxylase activity (the rate-limiting process in serotonin synthesis) (Stone et al. 1986, 1987; Schmidt and Taylor 1987) and loss of 5-HT transporters (Battaglia et al. 1987, 1988; Commins et al. 1987). In non-human primates, MDMA-induced serotonin neurotoxicity persists for more than a year after a 4-day treatment regimen of MDMA (Ricaurte et al. 1992; Fischer et al. 1995). These observations raise the distinct possibility that recreational MDMA users also incur brain 5-HT injury.

Although it has not been established that human MDMA users develop brain 5-HT neurotoxicity, two validated measures for assessing MDMA-induced brain 5-HT injury strongly suggest that they do. First, a controlled study in human MDMA users found selective decrements in cerebrospinal fluid (CSF) 5-HIAA, the major metabolite of brain serotonin (McCann et al. 1994). Similar reductions in CSF 5-HIAA concentrations have been found in monkeys with documented MDMA-induced 5-HT damage (Ricaurte

et al. 1988c), although reductions in CSF 5-HIAA underestimated the extent of 5HT damage in the cerebral cortex. Second, positron emission tomography (PET) studies using [^{11}C] McN5652, a PET ligand selective for the 5-HT transporter (5-HTT), indicate that MDMA users have significant reductions in 5-HTT binding compared to control subjects, and that loss of transporters is positively correlated with the amount of previous MDMA use (McCann et al. 1998). A similar decrease in [^{11}C] McN5652 binding has been shown in baboons with MDMA-induced neurotoxic lesions subsequently verified post mortem (Scheffel et al. 1998). Thus, both of the currently available validated measures for detecting MDMA-induced 5-HT injury indicate that some human MDMA users also develop brain serotonin neurotoxicity.

Despite biological evidence for brain 5-HT injury in humans, few functional consequences of MDMA-induced 5-HT axonal loss have been identified, either in animals or humans. While the seeming absence of neuropsychiatric sequelae (but see McCann and Ricaurte 1991) from MDMA-induced neurotoxicity could be because near total ablation of serotonin neurons is necessary before obvious behavioral manifestations appear, it could also be due to the difficulty in assessing and detecting alterations in subtle behavioral functions modulated by serotonin neurons. For example, disorders in mood, anxiety, cognitive processing and neuroendocrine function, all thought to involve 5-HT neurons, require sensitive and specific methods for detection (Martin and Reichlin 1987; Lezak 1995). Such difficulties in MDMA users, if detected, could be erroneously attributed to other causes (e.g., acute drug effects or withdrawal).

Several studies suggest that MDMA users may have memory impairments as a consequence of MDMA use (Krystal et al. 1992; Parrott and Lasky 1998; Parrott et al. 1998; Bolla et al. 1999). All of these investigations found that MDMA users had poorer verbal memory performance than control subjects. The study by Bolla and colleagues also found visual memory deficits in MDMA users, and memory disturbances in MDMA users were positively correlated with decrements in CSF 5-HIAA concentrations. While strongly suggestive that prior MDMA use has a negative impact on memory, cognitive performance by subjects in three of the studies (Krystal et al. 1992; Parrott and Lasky 1998; Parrott et al. 1998) may have been influenced by recent psychoactive drug use. The purpose of the present study was to evaluate further a wide variety of cognitive processes in MDMA users who had used no psychoactive drugs (except tobacco) for 3 weeks prior to study, in an effort to determine whether cognitive processes, other than verbal and visual memory, are negatively impacted by MDMA use. Since serotonin neurons innervate virtually every part of the central nervous system, perhaps modulating other neurotransmitter systems, it was reasoned that cognitive functions other than those mediated specifically by serotonin might also be altered. This study was part of a 5-day controlled inpatient protocol designed to assess the long-term effects of MDMA in humans.

Materials and methods

Subjects

Twenty-two individuals with a history of MDMA use and 23 controls participated in a 5-day inpatient protocol designed to determine the neurotoxic potential of MDMA in humans and its functional consequences. The protocol was approved by investigational review boards in both of the institutions involved in the study. All subjects provided informed consent prior to study participation. MDMA subjects had used MDMA on at least 25 separate occasions, and were self-referred. Control subjects were recruited by advertisements and had never used MDMA. Prior use of recreational drugs other than MDMA was allowed for both subject groups. Exclusionary criteria for both groups included past or current history of major medical illness (e.g., neurologic, renal, endocrine, or hematologic), current axis I psychiatric disorder as determined by SCID-I/P version 2.0 (First et al. 1996), a positive drug screen for illicit or prescribed psychoactive drugs, or current alcohol dependence. Subjects agreed to abstain from all recreational drugs for a duration of at least 3 weeks prior to testing, and their drug-free status was confirmed by urine and blood drug screens. Tobacco use was permitted during the study (when subjects were idle, between various assessments), because it was felt that nicotine withdrawal in individuals with nicotine dependence could significantly confound cognitive data, while nicotine use in a regular smoker would not be associated with significant stimulant effects. Participants were paid for their time and travel expenses. Informed consent was obtained from all subjects and the research protocol was approved by the Institutional Review Board.

Procedure

Subjects were admitted for a 5-day inpatient stay in a clinical research setting. All participants underwent physical examinations, structured diagnostic psychiatric interviews using the SCID-I/P version 2.0, EKGs and comprehensive blood and urine laboratory testing to rule out medical illness. Subjects also underwent a battery of biological and behavioral tests to probe for evidence of serotonin injury, including measurement of cerebrospinal fluid (CSF) monoamines, sleep studies, pain testing, personality assessment, and pharmacological challenges with the mixed 5-HT agonist, *m*-chlorophenylpiperazine (*m*-CPP). Only computerized cognitive testing and cerebrospinal fluid measures will be discussed here.

CSF monoamine metabolite concentrations

Concentrations of 5-HIAA and homovanillic acid (HVA) were determined by high performance liquid chromatography coupled with electrochemical detection using the method of Kilpatrick et al. (1986). CSF concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined using the method of Sharpless (1986). Samples of CSF from control and MDMA subjects were processed and assayed in tandem without awareness of the drug condition of each subject.

Cognitive testing

Cognitive performance was measured using a version of the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB; Thorne et al. 1985). The WRAIR PAB is a computerized psychological test battery designed for examining the effects of assorted state-variables on a representative sample of normal psychomotor, perceptual and cognitive tasks. The battery, in various versions, has been used to study the effects of sleep deprivation (Thorne et al. 1983), stimulants (Newhouse et al. 1989) catecholamine depletion (McCann et al. 1992) sustained performance, jet lag, heat stress, physical fatigue, physical conditioning, atropine, hypoxia and sickle cell disease on cognitive performance (Thorne et al. 1985).

The version of the WRAIR PAB utilized in the present study consisted of seven computerized performance tests designed to assess a broad variety of psychomotor and cognitive functions, rather than tasks thought to be modulated by serotonin per se. Since serotonin is known to influence the function of a variety of neurotransmitters, including the catecholamines, it was reasoned that alterations in serotonergic neurotransmission might also lead to alterations in cognitive functions mediated primarily by other neurotransmitters (e.g., arousal and sustained attention, thought to be mediated primarily via brain catecholamine systems). WRAIR PAB measures included, in the order that they were administered: 1) The Time Wall task, a time estimation task. The subject observes an object traveling at constant speed from the top of the computer screen towards the bottom of the screen. Approximately three-quarters of the way down the screen, the object is obscured by a "wall", and the individual is required to press a computer key when he/she estimates that the object will reach the bottom of the screen; 2) the Serial Add and Subtract test, a machine-paced mental arithmetic task requiring sustained attention. Two random digits and a plus or minus sign flash rapidly on the computer screen. The subject performs the addition or subtraction and enters the least significant digit of the result. If the answer is a negative number, the subject must add 10 to obtain the correct response; 3) the Logical Reasoning task, a self-paced task of semantic recognition and transformational grammar. The letter pair "AB" or "BA" is presented along with an active, passive, positive or negative statement that correctly or incorrectly describes the order of the letters within the pair (e.g., "A is not preceded by B.") The subject is required to press a computer key indicating whether the statement is correct or incorrect; 4) the Manikin task, a visuospatial rotation task that tests the ability to mentally manipulate objects and determine the orientation of a specific stimulus. The subject makes a corresponding bilateral response to indicate the hand in which a human figure (presented in various orientations) is holding a target object; 5) Code Substitution, a subject-paced complex attention and incidental learning task similar to the Digit Symbol Task on the Wechsler Intelligence Scale (Wechsler 1981). A code key of nine letter-digit pairs is displayed on the screen and the subject indicates which digit corresponds to individual test letters. After three trial blocks, the code key disappears and the subject either enters each digit from memory for maximum points, or first presses a button to recall the code key; 6) the Matching to Sample task, a machine-paced visual discrimination and working memory task. The subject memorizes a standard visual stimulus (6×6 matrices of 18 random red and yellow cells) and then presses a key to present two comparison stimuli, one of which is identical to the first. The subject is required to identify the identical stimulus; 7) the Delayed Recall test, a test of recent memory. At the conclusion of the test battery, subjects repeat one block of the code substitution task, without the code key and without feedback. Individuals with basic reading and arithmetic skills can perform this version of the WRAIR PAB, and when well-trained, can complete it in approximately 20 min.

Subjects completed three WRAIR PABs per day for 4 days, and a final PAB on the last morning of the study prior to discharge. Subjects were medication-free for the first 3 days of the study, and received intravenous *m*-CPP on the fourth morning of the study. Only performance measures from the first 3 days of the study (prior to *m*-CPP administration) are reported here.

MDMA and other drug use

Detailed information about MDMA and other drug use was obtained from an initial telephone interview, the drug history section of the Addiction Severity Index, a structured interview that ascertained the number of MDMA experiences and the amount and frequency of MDMA use, and the drug use section of the Scheduled Interview for DSM-IV Diagnoses. Blood and urine samples collected on the day of admission were screened for psychoactive drugs by immunoassay.

Statistical analysis

Cognitive tests

Statistical analyses were performed using a 2 (MDMA versus control) $\times$ 5 (time) repeated measures ANOVA with Greenhouse–Geisser adjustments for degrees of freedom. The nine PAB trials completed by each subject during the first 3 days of the study (i.e., three sessions per day) were averaged and reduced to three time points: Baseline performance (mean performance score on day one of the study); Learning curve (mean performance score on day 2 of the study); Peak performance (mean performance score on day 3 of the study). Data from day 4 and day 5 of the study were not included because *m*-CPP administration on day 4 of the study could potentially confound results. When significant main effects of Group or Time, or significant Group $\times$ Time interactions were observed, Bonferroni post-hoc tests were performed at individual time points. Statistical analyses were carried out using SPSS for Windows (SPSS, Chicago, Ill., USA). Significance was set at $P < 0.05$.

Initial comparisons of cognitive performance were made by comparing mean "throughput" scores for the two groups for each of the seven WRAIR PAB tasks. Throughput scores are calculated by multiplying the number of questions completed per minute (i.e., speed) by the percent of correct answers (accuracy). Throughput values are thought to represent the amount of useful work completed per unit time, and are a non-specific estimate of performance sometimes referred to as speed-adjusted accuracy. If a significant main effect of Group or a Group $\times$ Time interaction was found for throughput scores of an individual task, the task was further analyzed to determine whether differences were secondary to decreased accuracy, decreased speed, or both. For the Time Wall Task, which has no "correct" answer, the average response time was utilized for purposes of statistical comparison.

In addition to comparisons of the two subject groups by ANOVA, separate multiple linear regressions were conducted for each of the seven cognitive tasks in an effort to determine whether there were dose-related cognitive deficits associated with MDMA use history. In particular, baseline and peak performance scores (throughput, accuracy and speed) were regressed on the linear combination of status (control or MDMA user) and, respectively, total past MDMA dose, average weekly MDMA dose, and average monthly MDMA dose.

Cerebrospinal fluid monoamine metabolites

CSF 5-HIAA measures were compared using two-tailed Student *t*-tests. Further, in order to determine whether reductions in CSF 5-HIAA values were predictive of declines in baseline or peak accuracy, speed and throughput, bivariate Pearson's correlations analyses were performed for all seven cognitive tasks.

Results

Demographics and drug histories

Demographic and drug use histories for both subject groups are provided in Table 1. MDMA use patterns in MDMA subjects are provided in Table 2.

Toxicological screens

No subject had positive urine or blood screens for any psychoactive drug (including alcohol) at the time of admission.

Cognitive tests

Throughput (Fig. 1; Table 3)

Repeated measures ANOVAs revealed a significant main effect of group for the Logical Reasoning [$F(1,44) = 5.18$, $P = 0.028$] and Code Substitution tasks [$F(1,44) = 4.25$, $P = 0.045$] and significant Group × Time interactions for the Serial Add and Subtract task [$F(2,86) = 7.06$, $P = 0.004$] and the Delayed Recall task [$F(2,86) = 4.15$, $P = 0.019$]. No other main effects of Group or Group × Time interactions were found for throughput scores on any of the seven WRAIR PAB tasks. Group differences on the Logical Reasoning task and Code Substitution task reflected overall lower scores in the MDMA group, with no significant differences in throughput scores between the two groups at any particular time-point. For the Serial Add and Subtract task, Bonferroni post hoc comparisons showed similar baseline scores in the two groups, but lower scores in MDMA users on days 2 and 3 of the study ($P = 0.015$, $P = 0.015$, respectively), indicating a more shallow learning curve and lower peak performance in MDMA users. For the Delayed Recall task, Bonferroni post hoc comparisons revealed significantly lower baseline scores in MDMA users compared to controls ($P = 0.004$).

Table 1 Demographics and recreational drug exposure in MDMA users and control subjects

	Control ($n = 23$)	MDMA ($n = 22$)
Age (year)	30.35 ± 1.98	26.23 ± 1.99
Gender		
Male	16	15
Female	7	7
Education (year)	15.22 ± 0.45	13.36 ± 0.63
Drug exposure[a]		
Non-MDMA amphetamines	10	21
Cocaine	10	21
Sedative hypnotics	7	15
LSD and other hallucinogens	11	22
Cannabis	19	22
Organic solvents/inhalants	7	17
Opiates	10	13
PCP and related drugs	4	6

[a]The number of subjects who reported using the drug more than once

Table 2 Characteristics of MDMA use in MDMA users (mean ± SE)

	MDMA ($n = 22$)
Number of exposures	215 ± 33 (range: 30–725)
Duration of use	4.52 ± 0.71 years (range: 1–14)
Frequency of use	5.72 ± 0.61 per month (range 0.8–15)
Usual dose	272 ± 40 mg (range 100–1000)
Time since last dose	13.91 ± 6.54 weeks (range 3–147)

Accuracy

Two-way repeated measures ANOVAs of accuracy scores on the four tasks that were found to differ significantly in the initial throughput analyses were conducted to determine whether these differences were due to decreased accuracy or decreased speed of performance in the MDMA group. Significant Group × Time interactions were found for the Code Substitution task [$F(2,86) = 3.86$, $P = 0.036$] and the Delayed Recall task [$F(2,86) = 3.86$, $P = 0.036$], with no main effect of Group or Group × Time interactions seen for either the Serial Add and Subtract or Logical Reasoning tasks. Bonferroni post hoc comparisons revealed that the MDMA group was significantly less accurate at baseline on both the Code Substitution ($P < 0.0001$) and the Delayed Recall ($P < 0.003$) tasks.

Speed

Repeated measures ANOVAs of speed scores indicated no significant main effect of Group or Group × Time interactions for the Code Substitution, Delayed Recall or Logical Reasoning tasks. In contrast, a significant Group × Time interaction was found for the Serial Add and Subtract task [$F(2,86) = 7.75$, $P = 0.003$]. Bonferroni post hoc analyses indicated that MDMA users performed more slowly than control subjects on days 2 and 3 of the study ($P = 0.01$, $P = 0.007$ respectively).

Association between cognitive performance and MDMA exposure

Multiple linear regressions revealed a significant association between total MDMA exposure and peak per-

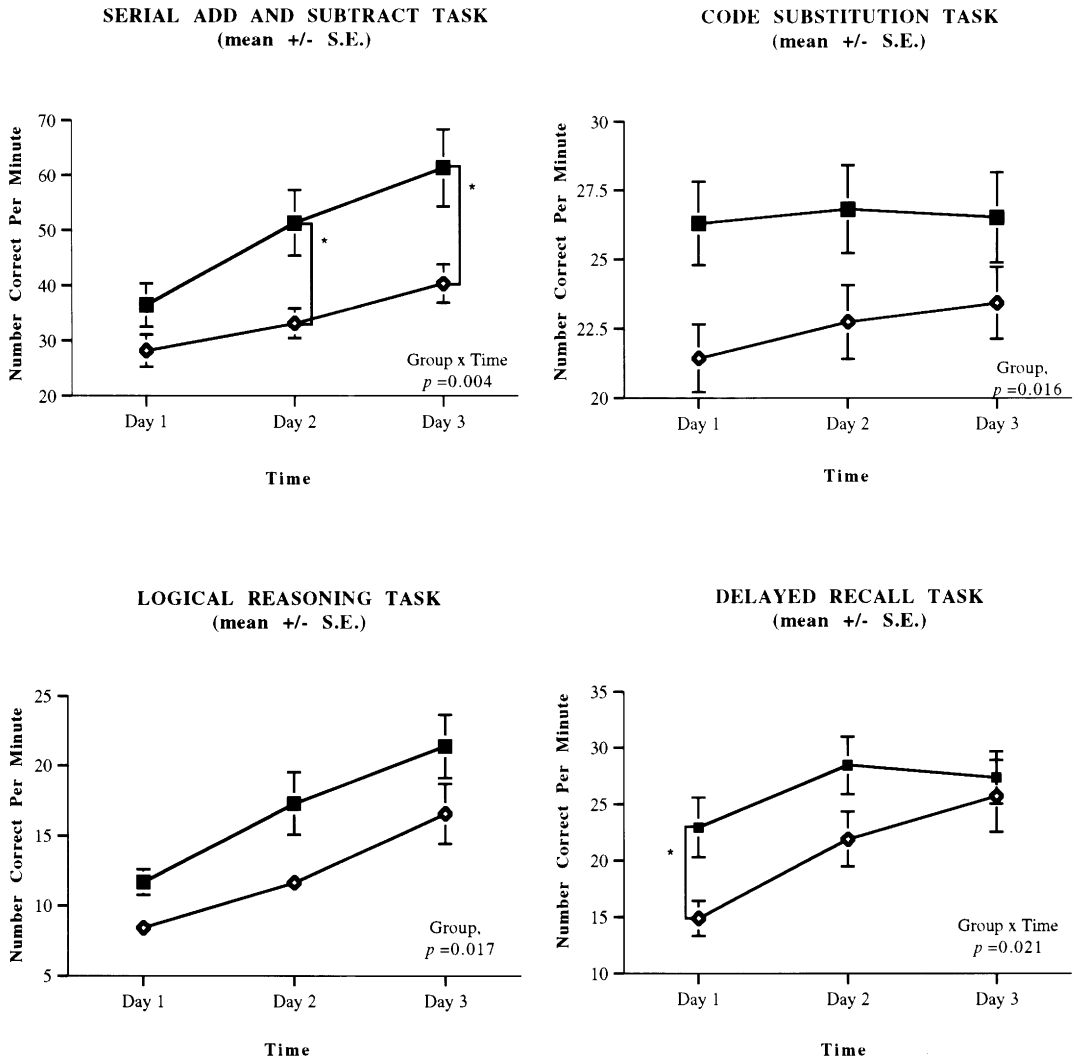

Fig. 1 Mean performance scores on four tasks in the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB) obtained over a 3-day period. Subjects completed three WRAIR PABs per day. Data were analyzed by repeated measures ANOVA. Bonferroni post hoc comparisons of scores from individual days were conducted, when appropriate. Significance was set at $P < 0.05$. ■ Control ($n = 23$), ◇ MDMA ($n = 22$)

formance (mean score from day 3 of the study) on the Code Substitution task. In particular, when peak performance scores were regressed on the linear combination of Group (MDMA versus control) and total MDMA exposure, the equation containing these two variables accounted for 16.81% of the variance in throughput scores ($F(2,42) = 4.24$, $P = 0.018$, adjusted $R^2 = 0.129$] and 19.67% of the variance in speed scores ($F(2,42) = 5.14$, $P = 0.024$, adjusted $R^2 = 0.158$], with increased MDMA exposure associated with decreased throughput and speed. No significant associations between any of the three exposure variables and performance were found for any of the other six cognitive tasks. Additionally, there was no significant relationship between peak cognitive performance and the duration of abstinence from MDMA.

Cerebrospinal fluid monoamine metabolites (Table 4)

Concentrations of CSF 5-HIAA in control subjects were within the range of concentrations previously reported for controls in our (McCann et al. 1994) and others' (Post et al. 1980; Ben Menachem et al. 1989; Hildebrand et al. 1990) studies. As found in our previous study (McCann et al. 1994), subjects exposed to MDMA were found to have significantly lower CSF 5-HIAA concentrations than control subjects with no differences between the two groups on measures of CSF HVA or MHPG (Table 4).

Table 3 Performance scores on WRAIR PAB tasks in control and MDMA subjects (number correct per minute; mean ± SE)

Task	Day 1		Day 2		Day 3	
	Control $n = 23$	MDMA $n = 22$	Control $n = 23$	MDMA $n = 22$	Control $n = 23$	MDMA $n = 22$
Serial Add and Subtract	36.38 ± 3.95	28.15 ± 2.87	51.3 ± 5.98	33.06 ± 2.68	61.36 ± 7.00	40.31 ± 3.53
Code Substitution	26.30 ± 1.51	21.43 ± 1.22	26.52 ± 1.63	22.74 ± 1.32	26.82 ± 1.58	23.42 ± 1.30
Delayed Recall	22.94 ± 2.66	14.89 ± 1.53	27.35 ± 2.32	21.90 ± 2.44	28.46 ± 2.55	25.71 ± 3.17
Time Wall	9.63 ± 0.15	9.56 ± 0.11	9.70 ± 0.18	9.63 ± 0.13	9.72 ± 0.14	9.77 ± 0.18
Logical Reasoning	11.67 ± 0.92	8.43 ± 0.64	17.29 ± 2.23	11.62 ± 0.77	21.38 ± 2.27	16.57 ± 2.14
Mannequin	19.11 ± 1.52	17.34 ± 1.57	26.40 ± 2.37	24.84 ± 2.21	35.86 ± 3.07	33.56 ± 3.03
Matching to Sample	7.76 ± 0.96	9.17 ± 1.07	9.11 ± 1.07	10.99 ± 1.31	16.59 ± 3.52	14.03 ± 1.80

Table 4 Monoamine metabolite levels in CSF of control and MDMA subjects[a]

	n	5-HIAA	HVA	MHPG
Control	23	14.77 ± 1.48[b]	19.53 ± 1.92	9.80 ± 1.02
MDMA	22	10.97 ± 0.81	19.90 ± 1.94	10.61 ± 1.36

[a]Values are means (±SE) expressed in ng/ml
[b]Value significantly higher than that of MDMA subjects, $P = 0.038$

Correlations between cognitive performance and CSF 5-HIAA

Bivariate Pearson's correlations analyses revealed no significant correlations between CSF 5-HIAA and performance on any day for any of the seven cognitive tasks.

Discussion

The principal finding of this study is that, compared to control subjects, drug-free MDMA users have performance deficits on several tasks tested using a computerized performance assessment battery. In particular, MDMA users who had abstained from any psychoactive drug use for at least 3 weeks had impaired performance on four of seven cognitive tests in the Walter Reed Army Institute of Research Performance Assessment Battery. Performance deficits were found on a sustained attention task requiring arithmetic calculations, a task requiring visual discrimination and working memory, a short-term memory task, and a task of semantic recognition and verbal reasoning. Performance deficits on the working memory task were directly associated with extent of previous MDMA use. As before (McCann et al. 1994), MDMA users had selective decrements in CSF 5-HIAA relative to control subjects, suggesting that MDMA-induced 5-HT neurotoxic injury may underlie cognitive deficits observed in MDMA users.

The present findings extend those from previous studies demonstrating deficits in verbal (Krystal et al. 1992; Parrot and Lasky 1998; Parrot et al. 1998; Bolla et al. 1999) and visual (Bolla et al. 1999) memory in MDMA users to include a variety of different psychomotor, perceptive and cognitive tasks. Since this study was not intended explicitly to test verbal or visual memory, it can not be taken as confirmation of previous findings. However, deficits seen in MDMA users on the Delayed Recall task are certainly consistent with previous observations of short term memory problems in MDMA users. The observation that MDMA users have deficits in either accuracy or speed on a variety of different cognitive measures suggests that MDMA-induced 5-HT alterations may lead to long lasting changes in serotonergic modulation of other neurotransmitter systems. For example, performance deficits seen on the Serial Add and Subtract task, a task requiring sustained attention, may be secondary to alterations in serotonergic input on brain catecholamine neurons known to be important in alertness and attention (Robbins and Everitt 1982; Jones 1989).

It is noteworthy that performance impairments seen on the Serial Add and Subtract task were secondary to decreased speed of performance, and not to decreased accuracy. This is the same type of performance deficit that is seen in healthy individuals in the early phases of total sleep deprivation (Newhouse et al. 1989; McCann et al. 1992). In particular, during the course of sleep deprivation, subjects initially decrease their speed of performance on the Serial Add and Subtract task, while maintaining accuracy. It is only after several days of total sleep deprivation that subjects' accuracy on this task deteriorates. It is possible that similar monoaminergic substrates are involved in both of these subject groups. It would be of inter-

est to learn whether MDMA users are more susceptible to the detrimental effects of sleep deprivation on cognitive performance than control subjects.

Notably, MDMA subjects had impaired performance on both the Code Substitution task, a measure of complex attention and incidental learning and the Delayed Recall task, which is the same test given after a time delay. Thus, on the Delayed Recall task, subjects are required to remember the same code that they had learned earlier. As such, poor performance on the Delayed Recall task could either be secondary to altered attentional processes and poor acquisition of the initial code, or to poor short-term memory.

Differences observed between MDMA users and controls are not likely to have been secondary to baseline differences in educational backgrounds or intelligence between MDMA users and controls. There were no differences in the mean educational levels of the two groups. Further, the version of the Walter Reed PAB utilized in the present study is easily completed in individuals with basic reading and mathematical skills. All subjects had these skills, and no subject had difficulty mastering the techniques necessary to complete the PAB. The Code Substitution task, which is a variation of the Digit Symbol task on the Wechsler Intelligence Scale (Wechsler 1981), is a test that is relatively unaffected by intellectual prowess (Erber et al. 1981; Lezak 1995), also arguing against that possibility that baseline differences in intelligence account for differences seen between MDMA users and controls. Rather, the relatively selective nature of performance deficits seen in MDMA users suggests that only certain aspects of cognitive function are altered in MDMA users, potentially as a result of a persistent alteration in brain serotonergic function.

Differences in cognitive function seen in MDMA users and controls were quite subtle, and only detected using a sensitive battery of cognitive tests. Individuals who took part in the study were generally not aware of having cognitive difficulties, and cognitive impairments were not obvious to the investigators. While some could take this observation to indicate that MDMA-related cognitive problems are not clinically significant, there is an alternative interpretation. In particular, because of the subtle nature of symptoms, some individuals may unwittingly continue to use MDMA, unaware of potentially cumulative damage. Further, it is not known whether subtle cognitive difficulties in a youthful individual will become manifest with advanced age and diminished neuronal reserve. Finally, the subtle nature of MDMA-induced neuropsychiatric disturbance could be the basis for the widely held view that only a handful of individuals who have taken MDMA have developed problems. Indeed, the numbers of individuals adversely affected by MDMA use may be considerably larger than generally accepted, and can only be ascertained by direct testing with sensitive tools.

Several potential drawbacks of this study should be noted. First, drug use in both subject groups could only be ascertained by retrospective report. Thus, it is possible that these reports were inaccurate, either because of poor subject recall or because drugs used by subjects may have been impure. Further, although both subject groups were allowed to have used a variety of recreational drugs, the MDMA subject group had used more recreational drugs on average than control subjects. Thus, it is possible that other drugs may also have contributed to cognitive impairments seen in MDMA subjects. However, while other drugs were used by both groups, MDMA was the drug of choice in the MDMA subject group, and was used to a greater extent than other recreational drugs. Similarly, the finding that deficits in performance on the code substitution task were significantly associated with total past MDMA use suggests a direct relationship between MDMA exposure and cognitive deficits. Also, the fact that none of the other drugs used by MDMA users have been shown to damage 5-HT neurons in humans, yet selective 5-HT deficits were observed in MDMA users, suggests that MDMA was responsible for the 5-HT deficits seen in these individuals. Nevertheless, since this study was not prospective, evaluating cognitive function in MDMA users over time, it is not possible to definitively establish a cause-and-effect relationship between cognitive decline and MDMA use.

In contrast to the study by Bolla et al. (1999), cognitive deficits in MDMA users in the present study were not correlated with reductions in CSF 5-HIAA. This contrasting result is possibly due to a lower level of MDMA exposure in the Bolla et al. study and the fact that an entirely different type of cognitive testing was conducted in the two studies. While some may view the lack of a correlation between CSF 5-HIAA and cognitive deficits as evidence that cognitive deficits are unrelated to brain 5-HT changes, there are alternative explanations. While CSF 5-HIAA has been validated as a measure of MDMA-induced 5-HT injury, it is known to underestimate the extent of 5-HT injury produced by MDMA (Ricaurte et al. 1988c). The relative lack of sensitivity of this biological measure could, in part, account for the absence of a correlation between CSF 5-HIAA and cognitive performance.

Future studies in larger numbers of MDMA users utilizing additional cognitive assessment tools will be instrumental in further establishing the prevalence and nature of cognitive dysfunction in MDMA users. Studies in a larger cohort may also make it possible to link cognitive deficits to a biological marker of brain 5-HT neurotoxicity. It will also be important to determine whether similar cognitive deficits are seen in other populations of individuals exposed to other selective 5-HT neurotoxins, such as fenfluramine (McCann et al. 1997). Finally, it will be useful to better define the relationship between MDMA exposure variables (e.g., total past MDMA dose, average monthly dose,

etc.) and cognitive dysfunction and determine whether risk factors for the development of MDMA-related cognitive deficits can be identified (e.g., previous neuropsychiatric history, gender, IQ).

In summary, the present data indicate that drug-free MDMA users have impairments in cognitive function compared to individuals who have never previously used MDMA. In particular, MDMA users were found to have performance deficits on a sustained attention task, a task requiring complex attention and incidental learning, a short-term memory task and a task of semantic recognition and verbal reasoning. MDMA users were also found to have selective deficits in cerebrospinal fluid 5-HIAA. Further, on the complex attention and incidental learning task, performance was inversely related to total past MDMA exposure. Taken together, these findings suggest that cognitive deficits seen in MDMA users may be related to MDMA-induced brain 5-HT neurotoxicity.

Acknowledgements This work was supported by PHS grants DA05707, DA05938, DA00206 (GAR) and the NIMH-IRP (U.D.M.). We would like to thank Dave Luckenbaugh, MA, for his assistance with statistical aspects of the study.

References

Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar MJ, DeSouza EB (1987) 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxy- amphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [^{3}H]paroxetine-labeled serotonin uptake sites. J Pharmacol Exp Ther 242:911–916

Battaglia G, Yeh SY, DeSouza EB (1988) MDMA–induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacol Biochem Behav 29:269–274

Ben Menachem E, Persson L, Schecter PJ (1989) Cerebrospinal fluid parameters in healthy volunteers during serial lumbar punctures. J Neurochem 52:632–635

Bolla KI, McCann UD, Ricaurte GA (1999) Impaired memory function in (±) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. Neurology (in press)

Commins DL, Axt KJ, Vosmer G, Seiden LS (1987) Endogenously produced 5,6-hydroxytryptamine may mediate the neurotoxic effects of parachloroamphetamine. Brain Res 419:253–261

Erber JT, Botwinick J, Storandt M (1981) The impact of age differences in digit symbol performance. J Gerontol 36:586–590

First MB, Spitzer RL, Gibbon M, Williams JBW (1996) Structured clinical interview for DSM-IV axis I disorders – patient edition (SCID-I/P, version 2.0) Biometries Research Dept., New York Psychiatric Institute, New York, New York

Fischer CA, Hatzidimitriou G, Katz JL, Ricaurte GA (1995) Reorganization of ascending serotonin axon projections in animals previously exposed to the recreational drug 3,4-methylenedioxymethamphetamine. J Neurosci 15:5476–5485

Hildebrand J, Bourgeouis F, Buyse M (1990) Reproducibility of monoamine metabolite measurements in human cerebrospinal fluid. Acta Neurol Scand 81:427–430

Jones BE (1989) Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia, London, Toronto, Montreal, Sydney, Tokyo, pp 121–141

Kilpatrick I, Jones M, Phillipson O (1986) A semiautomated analysis method for catecholamines, indoleamines, and some prominent metabolites in microdissected regions of the nervous system: an isocratic HPLC technique employing coulometric detection and minimal sample preparation. J Neurochem 46: 1865–1876

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR (1992) Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function. Am J Drug Alcohol Abuse 18:331–341

Lezak MD (1995) A Compendium of tests and assessment techniques. In: Neuropsychological Assessment, 3rd edn. Oxford University Press, New York, pp 333–802

Martin JB, Reichlin S (1987) Neuropharmacology of anterior pituitary regulation. In: Clinical neuroendocrinology, 2nd edn. F.A. Davis, Philadelphia, pp 45–64

McCann UD, Ricaurte GA (1991) Lasting neuropsychiatric sequelae of (±) methylenedioxymethamphetamine ("ecstasy"). J Clin Psychopharmacol 1:11:302–306

McCann UD, Penetar DM, Shaham Y, Thorne DR, Gillin JC, Sing HC, Thomas MA, Belenky G (1992) Sleep deprivation and impaired cognition: possible role of brain catecholamines. Biol Psychiatry 31:1082–1097

McCann UD, Ridenour A., ShahamY, Ricaurte GA (1994) Serotonin neurotoxicity after (±)3,4-methylenediaxymethamphetamine (MDMA; "ecstasy"): a controlled study in humans. Neuropsychopharmacology 10:129–138

McCann UD, Seiden LS, Rubin LJ, Ricaurte GA (1997) Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. JAMA 278:666–672

McCann UD, Szabo Z, Scheffel U, Matthews WB, Dannals RF, Ravert HT, Musachio JL, Mertl MM, Ricaurte GA (1998) Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in humans beings. Lancet 352:1433–1437

Newhouse PA, Belenky G, Thomas MA, Thorne D, Sing HC, Fertig J (1989) The effects of *d*-amphetamine on arousal, cognition, and mood after prolonged sleep deprivation. Neuropsychopharmacology 2:153–164

O'Hearn E, Battaglia G, DeSouza EB, Kuhar MJ, Molliver ME (1988) Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause ablation of serotonergic terminals in the forebrain: immunocytochemical evidence. J Neurosci 8:2788–2803

Parrott AC (1988) The psychobiology of MDMA or "ecstasy": symposium report. J Psychopharmacol 12:97–102

Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268

Parrott AC, Lees A, Granham NJ, Jones M, Wesnes K (1998) Cognitive performance in recreational users of MDMA or ecstasy": evidence for memory deficits. J Psychopharmacol 12:79–83

Post RM, Ballenger JC, Goodwin FK (1980) Cerebrospinal fluid studies of neurotransmitter function in manic and depressive illness. In: Wood JH (ed) Neurobiology of cerebrospinal fluid. Plenum Press, New York, pp 685–717

Ricaurte GA, Forno LS, Wilson MA, DeLanney LE, Irwin I, Molliver ME, Langston JW (1988a) MDMA selectively damages central serotonergic neurons in the primate. JAMA 260:51–55

Ricaurte GA, Delanney LE, Irwin I, Langston JW (1988b) Toxic effects of 3,4,methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in the primate: importance of route and frequency of drug administration. Brain Res 446:165–168

Ricaurte GA, Delanney LE, Wiener SG, Irwin I, Langston JW (1988c) 5-Hydroxyindoleacetic acid in cerebrospinal fluid reflects serotonergic damage induced by 3,4-methylenedioxymethamphetamine in the CNS of non-human primates. Brain Res 474:359–363

Ricaurte GA, Martello A, Katz JL, Martello MB (1992) Lasting effects of (±) 3,4-methylenedioxymethamphetamine on central serotonergic neurons in non-human primates. J Pharmacol Exp Ther 261:616–622

Robbins TW, Everitt BJ (1982) Functional studies of the central catecholamines. Int Rev Neurobiol 23:303–365

Scheffel U, Szabo Z, Mathews WB, Finley PA, Dannals RF, Ravert HT et al. (1998) In vivo detection of short- and long-term MDMA neurotoxicity. A positron emission tomography study in the living baboon brain. Synapse 29:183–192

Schmidt CJ (1987) Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. J Pharmacol Exp Ther 240: 1–7

Schmidt CJ, Taylor VL (1987) Depression of rat brain tryptophan hydroxylase activity following the acute administration of methylenedioxymethamphetamine. Biochem Pharmacol 36: 4095–4102

Schmidt CJ, Wu L, Lovenberg W (1986) Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analog. Eur J Pharmacol 124:175–178

Sharpless NS, Halbreich U, FeldFogel H (1986) Determination of total 3-methoxy-4-hydroxyphenylglycol in plasma using reversed-phase liquid chromatography with electrochemical detection. J Chromatogr 377:101–109

Stone DM, Stahl DS, Hanson GL, Gibb JW (1986) The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine on monoaminergic systems in the rat brain. Eur J Pharmacol 128:41–48

Stone DM, Hanson GL, Gibb JW (1987) Differences in the central serotonergic effects of 3,4-methylenedioxymethamphetamine (MDMA) in mice and rats. Neuropharmacology 26:1657–1661

Thorne DR, Genser S, Sing H, Hegge F (1983) Plumbing human performance limits during 72 hours of high task load. In: Proceedings of the 24th DRG Seminar on The Human as a Limiting Element in Military Systems. Defense and Civil Institute of Environmental Medicine, Toronto, pp 17–40

Thorne DR, Genser SG, Sing HC, Hegge FW (1985) The Walter Reed performance assessment battery. Neurobehavioral Toxicol Teratol 7:415–416

Wechsler D (1981) WAIS-R manual. The Psychological Corporation, New York