Memory impairment in abstinent MDMA ("Ecstasy") users: A longitudinal investigation

Article abstract—To examine the neurotoxic potential of continued MDMA ("Ecstasy") use in humans and its functional consequences over the course of 1 year, 15 MDMA users participated in a longitudinal study in which they completed a brief neuropsychological test battery composed mainly of retrospective and prospective memory tasks. Subjects were abstinent for 2 weeks on initial and 1-year testing. Continued use of MDMA was associated with progressive decline in terms of immediate and delayed recall.

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Konstantine K. Zakzanis, PhD; and Donald A. Young, PhD

Several experimental studies indicate that ±3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy") damages brain serotonin (5-HT) in animals (including nonhuman primates) and possibly humans.[1-3] As such, a significant proportion of users may eventually be at risk for long-term neurotoxicologic effects, particularly in the hippocampus, a brain region believed to play an important role in learning and the consolidation of new memories. Indeed, emerging neuropsychological literature suggests that repeated use of MDMA produces lasting impairments in learning and memory.[4-7]

Despite this evidence, the longitudinal sequela of MDMA use on memory function has received little attention. It is currently unclear whether continued MDMA use produces progressive memory impairment over time. Accordingly, this investigation examined the neurotoxic potential of continued MDMA use in humans and its functional consequences over the period of 1 year. Direct evidence regarding this should address questions regarding the relationship between the neurotransmitter serotonin and higher cognitive processes such as memory.

Methods. *Participants.* Fifteen MDMA users participated in the study. All participants were recruited by word of mouth and, hence, were self-referred, having learned about ongoing research on the consequences of MDMA use. Subjects were all fluent English-speaking individuals. Exclusion from the study was warranted when subjects reported a past or current history of major medical illness (e.g., neurologic, renal, endocrine, or hematologic), current major psychiatric illness as determined by the Structured Clinical Interview of the *Diagnostic and Statistical Manual III–Revised* (DSM-SCI-III-R), a positive drug screen for illicit or prescribed psychoactive drugs, or current alcohol dependence. Subjects were also excluded if they reported a current pregnancy, migraine, dyslexia, or eating disorder. Most participants, however, reported erratic or highly erratic sleep habits, typically coinciding with MDMA use. Hence, given that sleep deprivation is a noted finding in MDMA users and affects cognitive performance, participants were tested both at baseline and follow-up, when they reported at least 7 nights of 7 to 9 hours of continuous sleep. Moreover, all subjects agreed to abstain from all drugs for at least 2 weeks before testing at baseline and follow-up. Their drug-free status was confirmed by urine and blood drug screens. Given that the half-life of MDMA in animals is 1 to 2 hours, the 2-week period of abstinence was deemed long enough to rule out any withdrawal effects, including sleep deprivation.[8] These exclusionary criteria were met at both baseline and follow-up. Participants were not paid for their time but were reimbursed for travel (i.e., parking) expenses. Informed consent was obtained from all participants.

Participants were tested twice over a period of 12 months. No attrition occurred in terms of subject participation over the 12 months. Most participants were male (80%) and had completed approximately 14 years of education. The modal age of participants was 24.1 years at baseline (range 17 to 31 years).

Procedure. Participants completed a brief neuropsychological test battery after describing their characteristic MDMA use and other drug experience. Neuropsychological measures included into the test battery were the Wechsler Adult Intelligence Scale–III (WAIS-III) Vocabulary and Block Design subtests and the Rivermead Behavioral Memory Test (RBMT). The RBMT was developed to detect impairment of everyday memory functioning. Reported interrater reliability with this test is excellent with 100% agreement and test–retest stability for the complete form is good ($r = 0.85$). Standardized profile scores were recorded for all items on the RBMT. The items included are listed below.

First and second name. The subject is shown a photographic portrait and asked to remember the first and second name of the person in the photograph immediately after presentation and after a delay.

Belonging. A possession belonging to the subject is borrowed and secreted (e.g., in a drawer or cupboard). The participant is requested to ask for the belonging at the end of the test session and to remember where it has been hidden.

Appointment. The alarm is set for 20 minutes, and the participant is required to ask a particular question relating to the near future when the alarm sounds.

Pictures. Line drawings of 10 common objects are shown, one at a time, for 5 seconds each. The participant is required to name each picture and after a filled delay, to select the original 10 from a set of 20.

From the Division of Life Sciences (Dr. Zakzanis), University of Toronto; and Centre for Addiction and Mental Health (Dr. Young), Archway Clinic, Toronto, Ontario, Canada.

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Address correspondence and reprint requests to Dr. Konstantine K. Zakzanis, University of Toronto at Scarborough, Division of Life Sciences (Neuroscience), 1265 Military Trail, Toronto, Ontario, M1C 1A4 Canada; e-mail: zakzanis@scar.utoronto.ca

Table 1 *Characteristics of methylenedioxymethamphetamine use at baseline and at 1-year follow-up*

Characteristic	Baseline	One-year follow-up
No. of times used	19 (1–55)	55 (3–225)
Duration of use, mo	18.4 (1–60)	30.4 (13–72)
Usual dose, mg*	117 (50–250)	175 (50–300)
Frequency of use per mo	2.4 (0–8)	2.4 (0–15)
Time since last dose, wk	6 (2–24)	4 (2–36)
Dose, mg/mo†	280 (50–2,000)	420 (50–4,500)

Values are expressed as mean (range).

* Based on number of capsules ingested per day, assuming 100 mg is equal to one capsule.

† Usual dose (mg) multiplied by the frequency per month.

Table 2 *Other drug exposure*

Drug	Baseline	One-year follow-up
Non-MDMA amphetamine	7 (47)	9 (60)
Cocaine	8 (53)	10 (67)
Benzodiazepines	1 (7)	1 (7)
Sedative hypnotics	5 (33)	5 (33)
LSD, other hallucinogens	8 (53)	10 (67)
Cannabis	14 (93)	15 (100)
Organic solvents/inhalants	1 (7)	1 (7)
Opiates	6 (40)	7 (47)
PCP and related drugs	5 (33)	6 (40)
Alcohol	14 (93)	14 (93)
Nicotine	14 (93)	14 (93)

Values are n (%) of individuals within the group who reported any prior use of a drug in the listed drug class at baseline and at 1-year follow-up.

MDMA = methylenedioxymethamphetamine; LSD = lysergic acid diethylamide; PCP = phencyclinide.

Story (immediate and delayed). The participant is asked to listen to a short passage of prose being read aloud. The participant is then required to recall as much of it as possible immediately and again after a delay.

Faces. The participant is shown pictures of five faces, one at a time, for 5 seconds each. After a filled delay, the subject is required to select the original five from a set of 10.

Route (immediate). The examiner traces a short route within the room. The route is composed of five sections. The participant is required to reproduce the route immediately.

Results. *MDMA and other drug use.* To provide an estimate of the intensity, frequency, and duration of MDMA use, detailed information about prior MDMA use was obtained from a structured interview that ascertained the number of milligrams per capsule of MDMA generally taken at one time (each capsule was assumed to equal 100 mg, based on previously published estimates[4]), the number of times that MDMA was taken per month, and the total number of months of MDMA use. A dose variable—a combination of intensity and frequency—was also calculated by multiplying the self-reported milligrams ingested in a single MDMA session (which could last hours and involve several separate doses of MDMA) by the number of MDMA sessions per month.[4] Table 1 summarizes the characteristics of MDMA use at baseline and at follow-up. Table 2 illustrates the other drug exposure in the participant sample at both baseline and follow-up.

Longitudinal analyses. Over the period of 1 year, test scores either declined or remained static, but did not improve (table 3). Paired sample *t*-tests revealed large decline effects in terms of total RBMT score (Cohen's d = 0.92; $p < 0.001$) and in terms of the RBMT story immediate (Cohen's d = 0.57; $p < 0.01$) and delayed (Cohen's d = 0.83; $p < 0.01$) recall.

Interaction effects were computed in terms of change scores (follow-up − baseline) and their correlative relationship to the characteristic MDMA use of the participant sample. Significant relationships were evident in terms of performance on the WAIS-III Vocabulary subtest and frequency of MDMA use ($r = -0.53$, $p < 0.05$); RBMT first and second name task and the total number of times MDMA was used ($r = -0.63$, $p < 0.05$); and RBMT route (immediate recall) and duration of MDMA use ($r = -0.60$, $p < 0.05$).

Discussion. This investigation examined the neurotoxic potential of continued MDMA use in humans and its functional consequences in terms of memory over the period of 1 year. The main finding of the current longitudinal study is that continued use of MDMA is associated with different aspects of memory decline. For example, the ability to recall a short passage of prose being read aloud immediately and after a delay was found to decline significantly. This decline suggests impairment in retrospective memory, given that performance on the three RBMT prospective tests—1) remembering to ask the experimenter to telephone for a taxi; 2) remembering to deliver a message; and 3) remembering to ask for the return of a personal belonging—did not decline with continued MDMA use. Moreover, no changes in test scores were observed in terms of orientation for time and place and knowing the date.

This investigation also indicates that vocabulary and the ability to recall first and second names may be adversely affected by the frequency of MDMA use, and that the ability to immediately recall a route may be related to the duration of MDMA use. With these correlative findings in mind, it may be necessary to examine other cognitive functions in MDMA users (e.g., word retrieval, visuospatial ability, including topographic or navigational ability, supervisory attentional control, and executive functions). Clearly, additional research is necessary to determine the exact neuropsychological mechanism and functional consequences of the neurotoxic effects of this drug.

Additional research will also have to resolve limitations that impede the validity of most human MDMA

Table 3 *Neuropsychological results at baseline and at 1-year follow-up*

Test measure	Baseline, mean (SD)	One-year follow-up, mean (SD)	*d*	*t*	*p* Value
WAIS-III Vocabulary	53.0 (7.6)	52.1 (8.6)	0.11	−1.37	NS
WAIS-III Block Design	49.0 (9.4)	48.4 (9.5)	0.06	0.56	NS
RBMT					
First/second name	1.5 (0.9)	1.3 (1.0)	0.21	1.00	NS
Belonging	1.3 (1.0)	1.3 (1.0)	0.0	—	—
Appointment	1.6 (0.8)	1.6 (0.8)	0.0	—	—
Pictures	1.9 (0.3)	1.8 (0.6)	0.22	1.44	NS
Story immediate	1.5 (0.7)	1.1 (0.7)	0.57	3.50	<0.01
Story delayed	1.8 (0.4)	1.3 (0.8)	0.83	3.28	<0.01
Faces	2.0 (0.0)	1.9 (0.3)	0.67	1.00	NS
Route immediate	1.9 (0.5)	1.6 (0.8)	0.46	1.47	NS
Route delayed	1.9 (0.5)	1.5 (0.9)	0.57	1.87	NS
Message	1.5 (0.8)	1.3 (0.8)	0.25	1.87	NS
Orientation	2.0 (0.0)	2.0 (0.0)	0.0	—	—
Date	2.0 (0.0)	2.0 (0.0)	0.0	—	—
Total	20.9 (2.0)	18.7 (2.8)	0.92	4.58	<0.001

WAIS-III = Wechsler Adult Intelligence Scale–III; RBMT = Rivermead Behavioral Memory Test.

research. For instance, given that little quality control exists for street drugs, most investigations provide only an estimate at best when calculating the MDMA intake for each subject. As such, for legal and ethical reasons, no control existed over MDMA administration nor was there objective confirmation of the dose or purity of MDMA taken. In keeping with published reports of ecstasy content,[9] however, we deduced that all of our participants had indeed used MDMA in various amounts given the "type of Ecstasy" reportedly used. Moreover, Morgan,[5] for example, noted that tablets sold as Ecstasy can contain MDA (3,4-methylene dioxyamphetamine), MDEA (3,4-methylenedioxy-ethylamphetamine), or mixtures of a range of other compounds (e.g., caffeine, ephedrine, selegiline, amphetamine, ketamine, LSD-9). Although some tablets sold as ecstasy contain little or no MDMA, most tablets do contain MDMA, or the related compound MDEA.[5]

Another issue concerns the drug history of the participant sample. That is, self-report of drug-taking behavior in drug users is notoriously unreliable. As such, it remains unclear whether the reported use of MDMA and other drug exposures are gross under or over estimates of actual drug use. Given that this was a self-referred sample of users with an invested interest in its outcome (note the absence of attrition), it is believed that the self-reported drug-taking behaviors of the participants can be loosely described as reliable. It is possible, however, that the memory disturbance may be secondary to polydrug use and not MDMA itself, although indirect evidence suggests otherwise. In a study using a drug-free control group and polydrug-use group comparison, Morgan found that performance of MDMA users was markedly impaired when compared with both control groups, even though the self-reported drug histories of the polydrug group were not significantly different from the MDMA group.[5] Any differences found in the drug histories had little effect on the significant association between recall performance and MDMA use. Thus, memory deficits associated with MDMA do not seem to be an artifact of other drug use. This would seem to shed some light on the possibility that a similar dissociation exists with regard to the current investigation. Of course, this remains quantitatively unresolved and requires further examination.

Accordingly, we should emphasize the difficulty of drawing conclusions about the effects of MDMA in polydrug users. Although we would like to draw neurochemical conclusions based on our longitudinal observations, given the contamination of the group through use of other substances and the relative paucity of information regarding the neurochemical effects of MDMA, our desire to relate MDMA use and memory dysfunction should not be taken well beyond what can be foreseeably derived from our preliminary investigation.

References

1. Aquirre N, Frechilla D, Garcia–Osta A, et al. Differential regulation by methylenedioxy-methamphetamine of 5-hydroxytryptamine 1A receptor density and mRNA expression in rat hippocampus, frontal cortex, and brainstem. J Neurochem 1997;68:1099–1105.

2. Fischer C, Hatzidimitriou G, Wlos J, et al. Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). J Neurosci 1995;15:5476–5485.
3. Schmidt CJ. Neurotoxicity of the psychedelic amphetamine methylenedioxymeth-amphetamine. J Pharmacol Exp Ther 1987;240:1–7.
4. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology 1998;51:1532–1537.
5. Morgan MJ. Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 1999;141:30–36.
6. Parrott AC, Lees A, Garnham NJ, et al. Cognitive performance in recreational users of MDMA of "ecstasy": evidence for memory deficits. J Psychopharmacol 1998;12:79–83.
7. Reneman L, Booij J, Schmand B, et al. Memory disturbances in "ecstasy" users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology 2000;148:322–324.
8. Cho KC, Kumagai Y. Metabolism of amphetamine and other arylisopropylamines. In: Cho AK, Segal DS, eds. Amphetamine and its analogs: psychopharmacology, toxicology, and abuse. New York, NY: Academic Press, 1994:43–77.
9. Wolff K, Hay AWM, Sherlock K, et al. Contents of "ecstasy." Lancet 1995;346:1100–1101.

Head size and cognitive ability in nondemented older adults are related

Article abstract—In a cross-sectional analysis of 818 healthy older individuals (aged 50 to 81 years), head size was found to be related to performance on tests measuring intelligence, global cognitive functioning, and speed of information processing, but not memory. These relations were not confounded by educational level, socioeconomic background, or height. Large head/brain size may protect elderly people against cognitive deterioration, supporting a reserve hypothesis of brain aging.

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Danielle J. Tisserand, MSc; Hans Bosma, PhD; Martin P.J. Van Boxtel, MD, PhD; and Jelle Jolles, PhD

During childhood and adolescence, total brain mass increases and as a consequence so does head size. In the 20s, the volume of the brain starts to decrease, whereas head size remains constant throughout life.[1] Hence, head size is an indicator of maximal mature brain size. Larger brains may contain more neurons and synaptic connections and may therefore provide a greater reserve against cognitive decline when tissue loss or brain damage occurs.[2,3] In elderly subjects, small head/brain size has been found to be a vulnerability factor for cognitive dysfunctioning. Katzman et al.[4] found at autopsy that the main difference between 10 nondemented subjects who had signs of Alzheimer brain pathology and subjects without such signs was that the former had heavier brains and more large neurons. The authors suggested that having a larger brain protected these subjects from developing Alzheimer symptomatology. Several studies have found evidence for such an association between head/brain size and cognitive ability.[5-7] These studies mainly focused on demented subjects. Only one large study[8] focused on a healthy elderly population (n = 825) and reported that smaller head size was associated with low Mini-Mental State Examination (MMSE) scores.

The goal of the current study was to investigate whether we could corroborate the finding that head size and cognitive performance are related in a healthy elderly population. We examined global cognitive functioning with MMSE and administered tests that assess the function of specific cognitive domains. All associations were controlled for the potentially confounding influences of height, socioeconomic background, and educational level. To test these hypotheses, we used data from 818 nondemented elderly subjects who participated in the Maastricht Aging Study (MAAS).[9]

Method. *Subjects.* Participants took part in the MAAS, a longitudinal study into the determinants of cognitive aging.[9] In this study, 1869 subjects, initially nondemented and carefully screened for health problems, will be monitored for 12 years. For the current study, the data of participants 50 years and older (n = 818; 431 men, 387 women) were used.

Measurements. A standard neuropsychological test battery was administered to assess cognitive functioning. A full description of the tests used can be found elsewhere.[9] In short, global cognitive performance was examined with the MMSE. The Stroop Color-Word Task was used to measure speed of information processing. The Word Learning Task was used to assess the ability to learn (WLT Total) and retrieve (WLT Recall) verbal information. To estimate IQ, four subtests of the Groningen Intelligence Test (GIT; comparable to the Wechsler Adult Intelligence Scale) were used: Arithmetic, Vocabulary, Mental rotation, and Analogies.

Head size (in mm) was determined twice with a tape measure placed around the subjects' head, 0.5 cm above the eyebrows and over the occipital protuberance. The mean of the two values was used for further analysis. Height was measured to the nearest millimeter. Educa-

From the Brain & Behavior Institute, Maastricht University, the Netherlands.

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Address correspondence and reprint requests to Dr. D.J. Tisserand, Brain & Behavior Institute, Maastricht University, Dr. Tanslaan 10, 6229 ET Maastricht, the Netherlands; e-mail: d.tisserand@np.unimaas.nl

