ORIGINAL ARTICLE

Cortical Serotonin Transporter Density and Verbal Memory in Individuals Who Stopped Using 3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy")

Preliminary Findings

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Background: Although the popular drug 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") has been shown to damage brain serotonin (5-HT) neurons in animals, the fate and functional consequences of 5-HT neurons after MDMA injury are not known in humans. We investigated the long-term effects of MDMA use on cortical 5-HT neurons in humans and memory function, because brain 5-HT has been implicated in memory function.

Methods: Twenty-two recent MDMA users, 16 ex-MDMA users who had stopped using MDMA for more than 1 year, and 13 control subjects. The effects of MDMA use on cortical 5-HT neurons was studied by means of single-photon emission computed tomography with iodine 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl) tropane ([^{123}I]β-CIT) by quantification of brain 5-HT transporter densities. Verbal memory performance was assessed with the Rey Auditory Verbal Learning Test.

Results: Mean cortical [^{123}I]β-CIT-labeled 5-HT transporter density was significantly lower in recent MDMA users than in controls (1.17 vs 1.28 [–9%]) but not in ex-MDMA users (1.24 vs 1.28 [–3%]). Recent and ex-MDMA users recalled significantly fewer words than did controls on the immediate recall (47.0 and 48.0 vs 60.0, respectively; $P=.001$) as well as the delayed recall (9.8 and 10.1 vs 13.1, respectively; $P=.003$). Greater use of MDMA was associated with greater impairment in immediate verbal memory. However, memory performance was not associated with [^{123}I]β-CIT binding to cortical 5-HT transporters or duration of abstinence from MDMA.

Conclusion: The present study suggests that, while the neurotoxic effects of MDMA on 5-HT neurons in the human cortex may be reversible, the effects of MDMA on memory function may be long-lasting.

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ALTHOUGH GENERALLY regarded as relatively safe, the popular recreational drug 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") has increasingly been shown to lead to toxic effects on brain serotonin (5-HT) neurons in animals and possibly in humans. In animals, damage to 5-HT neurons has been demonstrated by reductions in various markers unique to 5-HT axons, including the density of 5-HT transporters (SERTs).[1-5] Since the SERT is located on the presynaptic axons and axon terminals of 5-HT neurons, it is considered to be a reliable marker of 5-HT neurotoxic changes. With the development of imaging techniques such as positron emission tomography and single-photon emission computed tomography (SPECT), it is now possible to measure SERT densities in the human brain. Recent imaging studies have shown decreases in central SERTs in MDMA-treated primates and human MDMA users.[6-8]

Few functional consequences of MDMA-induced neurotoxic effects have been identified, however, either in animals or in humans. Since MDMA-induced 5-HT neurotoxic damage may lead to impairment of functions in which 5-HT is involved (eg, memory function), it is important to study the effects of MDMA not only on 5-HT neurons but on memory function as well. Memory function is of particular interest because several studies have found that MDMA users display significant memory impairments, whereas their performance on other cognitive tests is generally normal.[9-11]

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While the short-term neurotoxic effects of MDMA on 5-HT neurons and memory have been studied extensively, little is known about the long-term effects in

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SUBJECTS AND METHODS

PARTICIPANTS

Two groups of ecstasy users were compared with ecstasy-naive controls. Subjects were recruited by means of flyers distributed at venues associated with the "rave scene" in Amsterdam, the Netherlands, with the help of UNITY, an agency that provides harm-reduction information and advice. Experimental and control groups were thus recruited from the same community sources. Subjects selected were group-matched for sex and age (between 18 and 45 years), otherwise healthy, and with no psychiatric history.

Twenty-two recent but abstinent ecstasy users (mean [±SD] time since last dose before study, 2.4±2.4 months; "MDMA group") and 16 ex–ecstasy users (29.0±20.4 months; "ex-MDMA group") were recruited. The eligibility criterion for the MDMA group was lifetime previous use of a minimum of 50 tablets of ecstasy. The ex-MDMA group had to have taken a minimum of 50 tablets but stopped using ecstasy at least 1 year before the study. The 13 controls were healthy subjects with no self-reported previous use of ecstasy.

All participants agreed to abstain from use of psychoactive drugs (including MDMA) for at least 3 weeks before the study and were asked to undergo urine drug screening to assess current exposure to psychoactive drugs (with an enzyme-multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine and metabolite, opiates, and marijuana) before enrollment. After urine samples were tested, exclusion criteria were as follows: a positive drug screen, pregnancy, a severe medical or neuropsychiatric illness that precluded informed consent, and a lifetime psychiatric disorder. Use of prescribed psychotropic medications, such as 5-HT reuptake inhibitors, had to be stopped for at least 3 weeks before the study. Subjects were interviewed with the computer-assisted 2.1. version of the Composite International Diagnostic Interview (Core version 2.1, 1997; World Health Organization, Geneva, Switzerland) to screen for current *DSM-IV* Axis I diagnoses.

Subjects were informed that reimbursement for participation was contingent on no evidence of drug use on the urine sample. The institutional medical ethics committee approved the study. All participants provided written informed consent after the study was completely described to them.

IMAGING

Subjects underwent SPECT imaging (810X tomographic equipment; Strichman Medical Equipment Inc, Medfield, Mass). This 12-detector single-slice scanner has a full-width at half-maximum resolution of approximately 7.5 mm. Each acquisition consisted of approximately 15 slices (acquired in a 64×64 matrix) at 3 minutes per slice (interslice distance, 5 mm). The energy window was set at 135 to 190 keV. Subjects lay supine with the head parallel to the orbitomeatal line. Acquisition was commenced 4 hours after intravenous injection of approximately 3.8 mCi (140 MBq) of [^{123}I]β-CIT (specific activity, >5 mCi/nmol [>185 MBq/nmol]; radiochemical purity, >98%), a time when specific binding to SERTs is stable.[14] Reconstruction and attenuation correction of all images were performed as earlier described.[15]

humans. Studies in nonhuman primates have shown that, up to 7 years after treatment with MDMA, neocortical brain regions remain partially denervated while others show evidence of complete recovery. Therefore, it is of particular interest to establish the long-term fate of cortical 5-HT neurons after MDMA injury in the human brain.

The development of iodine 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl) tropane ([^{123}I]β-CIT), a radioligand that binds with high affinity to SERTs, has made it possible to assess the density of SERTs in the living human brain, by means of SPECT.[12,13]

The purpose of the present study was to investigate the density of cortical [^{123}I]β-CIT–labeled SERTs and memory function in recent MDMA users who were abstaining from use, and in MDMA users who had not been using MDMA for more than 1 year. Also, this study examined whether possible memory deficits in MDMA users correlate with decrements in the density of [^{123}I]β-CIT–labeled SERTs, and whether memory deficits in MDMA users are dose related.

RESULTS

CHARACTERISTICS OF THE SAMPLE

The 3 groups were similar in age and sex distribution. The level of education was significantly lower in MDMA users. However, MDMA users did not differ from controls in verbal intelligence (DART IQ) (**Table**).

Apart from the anticipated differences between groups caused by inclusion criteria, no significant differences between MDMA groups were observed. Whereas the MDMA group had on average not used MDMA for months, the ex-MDMA group had on average not used MDMA for nearly 2.5 years (Table). Recreational drug use of alcohol and tobacco was comparable between the different groups. The MDMA users indicated having used more cannabis in the year before this investigation than had controls, although this difference did not reach statistical significance. The use of amphetamine and cocaine was significantly higher in the MDMA group than in the control and ex-MDMA groups (Table). None of the subjects under study reported using drugs other than the ones listed in the Table, such as phencyclidine hydrochloride or opiates, in the year before this study.

IMAGING

No differences in [^{123}I]β-CIT uptake between cortical brain regions were observed in all groups under study. Analysis of variance showed a significant main effect of group ($F_{2,5}$=4.63, P=.02), with current MDMA users having lower (–9%) mean cortical [^{123}I]β-CIT binding ratios than controls (**Figure 1**). No significant differences in mean cortical binding ratios of ex-MDMA users were observed when compared with control subjects (–3%; Figure 1).

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For binding analysis, a standard template with regions of interest was constructed manually from magnetic resonance images. For positioning we used these images as a guide. A template, including regions of interest for the frontal, temporal, parieto-occipital, and occipital cortex, was placed on 3 consecutive SPECT slices, demonstrating best visualization of the striatum (typically 30 mm above the orbitomeatal line), by an investigator unaware of the participant's history. An additional template was constructed with a region of interest for the cerebellum. The binding in the cerebellum, presumed free from SERTs, was used as a reference for background radioactivity (nonspecific binding + free ligand). Since no differences in [^{123}I]β-CIT uptake ratios between cortical brain regions were observed in all groups under study, we calculated mean cortical SERT densities (mean counts per pixel of frontal, temporal, parieto-occipital, and occipital cortex). Cortical binding ratios were calculated as cortical binding divided by binding in the cerebellum.

MEMORY TESTING

The Dutch Adult Reading Test (DART)[16,17] was administered as an estimate of verbal intelligence. The DART is the Dutch adaptation of the National Adult Reading Test,[18] a short reading test for the estimation of premorbid verbal IQ.

Memory was assessed within 1 day of SPECT imaging by means of the Rey Auditory Verbal Learning Test (RAVLT).[19] The subject memorizes a series of 15 words in 5 learning trials (RAVLT immediate recall). After a 20-minute delay, the subject is asked to recall the words (RAVLT delayed recall), followed by recognition of the 15 items between 15 distractor words (RAVLT recognition). Raw scores are used.

STATISTICAL ANALYSES

Differences in mean cortical [^{123}I]β-CIT binding ratio and RAVLT scores (RAVLT immediate recall, RAVLT delayed recall, and RAVLT recognition) were analyzed by analysis of covariance, with 1 between-group factor (group) and 3 covariants (age, sex, and DART IQ). When a significant main group effect was observed, Bonferroni post hoc tests were performed to analyze differences between groups. Differences between the 3 groups with regard to demographic variables and other drug exposure were analyzed by analysis of variance. Differences in characteristics of MDMA use between both MDMA-using groups were studied with the *t* test.

Pearson correlation analyses were performed between RAVLT scores and mean cortical [^{123}I]β-CIT binding ratio, between RAVLT scores and duration of abstinence from MDMA, between RAVLT scores and extent of previous MDMA, and between RAVLT scores and extent of previous cannabis, amphetamine, and cocaine use. Because age, sex, and vocabulary have been shown to be highly associated with most memory tests, we also performed partial correlations to control for age, sex, and DART IQ on tests for which the correlations were significant. The chance of a type I error (α) was set at .05 by 2-tailed tests of significance. In cases where Bonferroni corrections were made, statistical significance within the text is reported as a corrected *P* (corrected $P = .017$ [$.05 \div 3$] [3 paired comparisons]). All data were analyzed with SPSS version 9.0 (SPSS Inc, Chicago, Ill) and are presented as mean ± SD unless otherwise indicated.

MEMORY PERFORMANCE

As with mean cortical [^{123}I]β-CIT binding ratios, analysis of covariance showed a significant main effect of group on RAVLT immediate recall scores ($F_{2,5} = 8.31$, $P = .001$). Both current and ex-MDMA users recalled significantly fewer words on the immediate RAVLT compared with controls (47.0 ± 8.6 and 48.0 ± 12.5 vs 60.0 ± 6.8, respectively; **Figure 2**). Similar findings were observed for the RAVLT delayed recall ($F_{2,5} = 6.53$, $P = .003$; 9.8 ± 2.9 and 10.1 ± 2.9 vs 13.1 ± 2.1, respectively; Figure 2), but not for RAVLT recognition.

Correlation analysis demonstrated no specific relationships between RAVLT scores and cortical binding ratio, duration of abstinence from MDMA, or extent of previous cannabis, amphetamine, or cocaine use. However, partial correlation analysis with RAVLT immediate recall scores was significant for extent of previous MDMA use ($r_{46} = -0.29$, $P = .049$).

COMMENT

The present study indicates that, in individuals who stopped using MDMA more than 1 year ago, cortical SERT densities did not differ from those of control subjects, whereas recent MDMA users showed global decreases in SERTs. Our findings also indicate that individuals who stopped using MDMA had a deficit in verbal memory, similar to that of current MDMA users, and that higher lifetime doses of MDMA are associated with greater decrements in immediate verbal memory function.

The observed decreases in cortical SERT densities in recent MDMA users most likely reflects MDMA-induced brain 5-HT neurotoxic effects, since reductions in SERT densities have been documented in animals with known MDMA-induced 5-HT injury.[3,6,20-27] For instance, reductions in 5-HT axons in MDMA-treated monkeys vary from approximately –95% in the temporal cortex to –83% in the pyriform cortex.[21] This is a much stronger effect than on human 5-HT axons as observed in the present study (on the order of 9%). Interestingly, Semple and coworkers[8] also reported a 10% reduction in SERT densities in the occipital cortex of recent MDMA users by means of [^{123}I]β-CIT SPECT. Even though cortical β-CIT uptake is low, displacement studies in rats and monkeys have shown that cortical uptake of β-CIT is associated with SERTs.[13-28] Furthermore, [^{123}I]β-CIT has been shown to adequately detect changes in cortical as well as subcortical SERT densities secondary to 5-HT neurotoxic effects.[13,29] However, it is an assumption that a decrease in SERT density directly reflects axonal loss. Several factors, such as allosteric changes in the actual binding unit of the protein, also could result in decreased binding. Nevertheless, it has been shown that central 5-HT levels also are reduced after MDMA treat-

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Characteristics of Subjects*

	Control Subjects (n = 13)	MDMA Users (n = 22)	Ex-MDMA Users (n = 16)
Demographics			
Age, y	25.0 (3.6)	26.2 (5.3)	25.3 (5.4)
Sex, No. M/F	7:6	11:11	8:8
Years of education	14.5 (1.3)	12.6 (2.2)†	11.8 (2.4)†
DART-IQ	105.8 (7.2)	105.2 (8.5)	103.9 (9.8)
MDMA use			
Duration of use, y	NA	5.5 (2.7)	4.6 (2.6)
Usual dose, No. of tablets/occasion	NA	2.2 (0.7)	2.1 (1.0)
Lifetime dose, tablets	NA	485 (598)	268 (614)
Time since last tablet, mo	NA	2.4 (2.4)	29.0 (20.4)‡
Use of other drugs in past year			
Alcohol, No. of consumptions	478.8 (452.0)	490.5 (372.9)	323.7 (256.4)
Tobacco, No. of cigarettes	3590.4 (1952.7)	3302.4 (3857.6)	4572.5 (2996.5)
Cannabis, No. of joints	15.3 (16.0)	326.9 (514.9)	456.7 (881.9)
Amphetamine, No. of times used	0	12.8 (18.7)§	0
Cocaine, No. of times used	0.07 (0.28)	7.2 (6.4)‖	1.5 (3.3)
LSD, No. of times used	0	1.9 (3.5)	3.3 (12.9)
Psilocybin, No. of times used	0.08 (0.28)	1.5 (2.3)	2.9 (9.2)

*Data are expressed as mean (SD). MDMA indicates 3,4-methlyenedioxymethamphetamine (or "ecstasy"); DART, Dutch Adult Reading Test; NA, not applicable; and LSD, lysergic acid diethylamide.

†Significantly lower level of education in MDMA users compared with control subjects (analysis of variance [ANOVA]: $F_{50} = 6.5$, $P = .003$; post hoc analysis: MDMA group vs control group, Bonferroni corrected $P = .03$; ex-MDMA group vs control group, $P = .003$).

‡Significantly longer time since last dose in ex-MDMA group compared with MDMA group (t test: $t_{36} = -6.1$, $P < .001$).

§Significantly more amphetamine consumption in the past year in MDMA users compared with control subjects and ex-MDMA users (ANOVA: $F_{50} = 5.9$, $P = .005$; post hoc analysis: MDMA group vs control group, Bonferroni corrected $P = .02$; MDMA group vs ex-MDMA group, $P = .001$).

‖Significantly more cocaine consumption in the past year in MDMA users compared with control subjects and ex-MDMA users (ANOVA: $F_{50} = 11.8$, $P < .001$; post hoc analysis: MDMA group vs control group, Bonferroni corrected $P < .001$; MDMA group vs ex-MDMA group, $P = .002$).

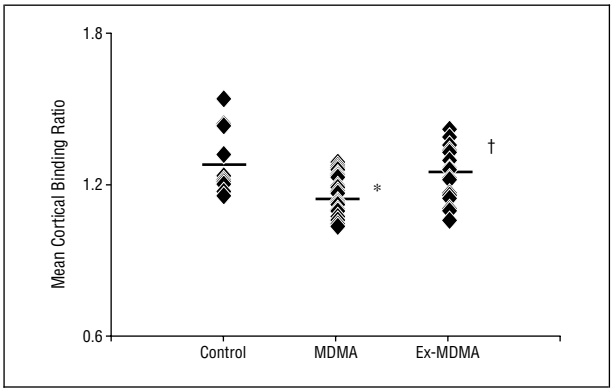

Figure 1. Mean and individual iodine 123–2β-carbomethoxy-3β-(4-iodophenyl) tropane binding ratio in the cortex in control subjects (n=13) vs 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") users (n=22) and ex-MDMA users (n=16). Cortical binding ratios were calculated as cortical binding divided by binding in the cerebellum. Asterisk indicates statistically significant difference in cortical binding ratio between recent MDMA users and control subjects (mean±SD, 1.17±0.08 vs 1.28±0.12, respectively) (analysis of variance: $F_{2,5}=4.63$, $P=.02$; Bonferroni corrected $P=.03$). Dagger indicates no statistically significant difference in cortical binding ratio between ex-MDMA users and control subjects (mean±SD, 1.24±0.11 vs 1.28±0.12) (analysis of variance: $F_{2,5}=4.63$, $P=.02$; Bonferroni corrected $P>.99$).

ment.[30] Furthermore, correlative anatomic studies indicate that loss of presynaptic SERTs in MDMA-treated animals is related to damage of 5-HT axons and axon terminals.[3,22,23]

The absence of decreases in SERT densities in ex-MDMA users suggests reversibility of MDMA-induced changes in brain SERTs in MDMA users. In line with this, autoradiographic studies have shown a partial recovery of [^{125}I]β-CIT binding 16 weeks after lesion induction in the frontal cortex of rats, and complete recovery by 32 weeks.[29] In nonhuman primates, cortical 5-HT terminal markers remain decreased up to 7 years after MDMA treatment, although significant recovery occurs compared with 2 weeks after the lesion induction.[21]

Our findings of memory impairment in recent MDMA users are consistent with those of previous reports.[9-11,31-34] In agreement with these studies, we observed that greater use of MDMA is associated with greater impairment in immediate verbal memory. Interestingly, Shum and coworkers[35] reported on RAVLT scores of patients with age and educational level similar to those of our subjects who had suffered from severe traumatic brain injury 2 years previously. Criteria for severe traumatic brain injury were a Glasgow Coma Scale score less than 9 or a duration of posttraumatic amnesia of more than 7 days. Scores on the immediate RAVLT were 59.4 in controls vs 47.4 in the patients with traumatic brain injury, and approximately 13.8 vs 10.8, respectively, on the delayed recall. These scores are comparable with the scores observed in this study in recent and ex-MDMA users (Figure 2), which may indicate the severity and clinical significance of the memory disturbances induced by MDMA use.

Studies in rats and monkeys have shown that MDMA produces serotonergic neurodegeneration in various brain areas important for memory function, including the hippocampus.[21] Unfortunately, because of the relatively low resolution of the SPECT imaging technique, it was not possible to study all brain regions implicated in learning and memory.

Several studies suggest that SERTs may play an important role in cognitive processes such as memory func-

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tion.[36] It has been shown that selective 5-HT reuptake inhibitors in nondemented elderly depressed patients improved both mood and cognitive function.[37] However, we did not observe a correlation between memory function and cortical SERT densities. It could be argued that memory testing is more sensitive to MDMA's neurotoxic effects than are SERT densities. Furthermore, the observed memory deficits in ex-MDMA users may not be attributable to MDMA-induced 5-HT deficits at all. However, we did observe a negative correlation between extent of previous MDMA use and immediate verbal memory recall, suggesting that immediate verbal memory deficits may be at least partially attributable to MDMA use. Another explanation may be that SERT densities in brain areas implicated in learning and memory of former MDMA users are still decreased but could, unfortunately, not be visualized with SPECT (eg, hippocampus or hypothalamus). Finally, although loss of SERTs is indicative of neuronal degeneration, their restoration does not necessarily imply normal axonal or neuronal regeneration and therefore normal behavioral recovery. For instance, after 5-HT axonal degeneration induced by 5,6-dihydroxytryptamine, abnormal reinnervation patterns of 5-HT axons coincide with the return of tritiated 5-HT uptake.[38] Since it was previously observed by our group that mean (postsynaptic) cortical 5-HT_{2A} receptor binding positively correlated with RAVLT recall in MDMA users,[39] it could be hypothesized that functional consequences of MDMA-induced brain 5-HT neurotoxic lesions may be related to postsynaptic rather than presynaptic 5-HT neurons.

The implications of our findings are relevant to people who use MDMA. In the present study we identified that MDMA use is associated not only with short-term consequences (5-HT neurotoxic effects and memory impairment) but with long-term consequences as well (memory impairment). These findings will provide a cogent argument for consumers to make informed decisions about recreational drug use. In addition, since the consequences of loss of the "serotonergic" reserve in later life is difficult to predict but could be clinically significant, the present study indicates the necessity of, and would probably justify, prospective studies of psychiatric morbidity in MDMA users to foresee future demands on health care. Furthermore, the present study of MDMA-exposed individuals with highly selective brain SERT deficits adds to our knowledge about a neurotransmission system thought to be involved in the cause and treatment of very common psychiatric illnesses, such as depression.

Several potential limitations of the current study should be mentioned. First, as with all retrospective studies, there is a possibility that preexisting differences between MDMA users and control subjects underlie differences in SERT densities. People with low SERT densities may be predisposed to use MDMA and to have low SERT densities and/or lower performance on memory tests. Future studies taking the recently described functional polymorphism in the promoter for the SERT gene into account could be of interest.[40] Second, observed decreases in brain [^{123}I]β-CIT–labeled SERT densities and memory performance are unlikely to be caused by immediate pharmacologic effects of MDMA or other drugs, since MDMA-using participants reported that they had abstained from use of MDMA or other

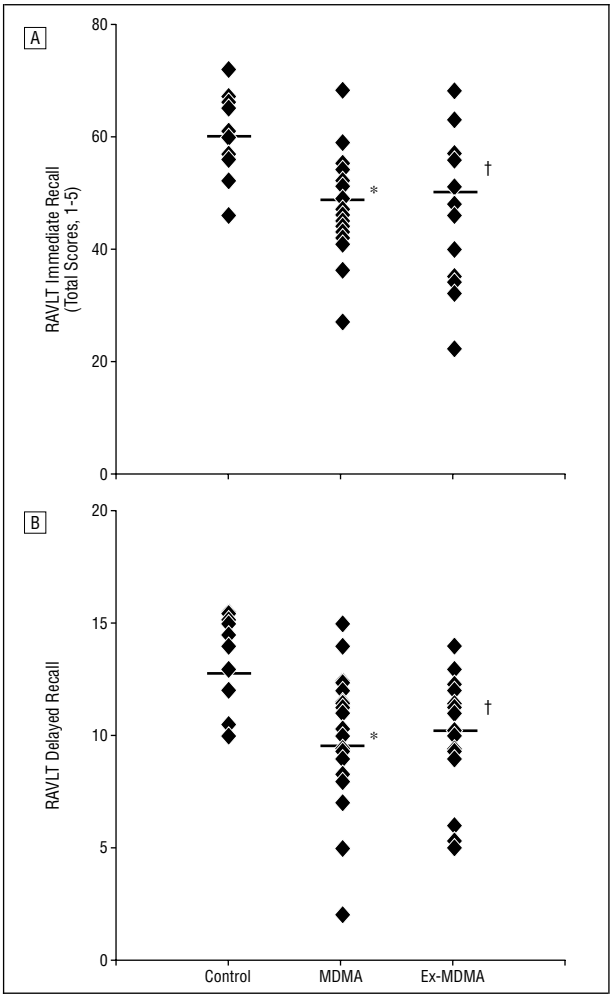

Figure 2. Mean and individual Rey Auditory Verbal Learning Test (RAVLT) immediate (A) and delayed (B) recall scores in control subjects (n=13) vs 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") users (n=22) and ex-MDMA users (n=16). Asterisk indicates significantly fewer words recalled by recent and ex-MDMA users compared with control subjects on RAVLT immediate recall (analysis of variance: $F_{2,5}=8.31$, $P=.001$; Bonferroni corrected $P=.001$ and .005, respectively). Dagger indicates significantly fewer words recalled by recent and ex-MDMA users compared with control subjects on RAVLT delayed recall (analysis of variance: $F_{2,5}=6.53$, $P=.003$; Bonferroni corrected $P=.004$ and .02, respectively).

psychoactive drugs for at least 3 weeks before the study. Unfortunately, we were not able to ensure abstinence from MDMA for more than 1 year in the ex-MDMA users. In future studies, hair-sample analysis may be useful to ascertain long periods of abstinence from MDMA. Third, follow-up studies in human subjects with known MDMA-induced neurotoxic effects need to be conducted to allow definite conclusions on reversibility or permanence of MDMA-induced changes in the human brain. Finally, although the MDMA users in our study had more experience with other recreational drugs than did control subjects, none of the drugs is a known 5-HT neurotoxin in human beings, and they were therefore not likely to account for changes in SERTs or memory performance. In addition, since recent MDMA users had used significantly more amphetamine and cocaine than controls and ex-MDMA users, but memory impairments were observed in both recent and ex-MDMA users, amphetamine and cocaine are not likely to account for changes is SERTs and/or

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memory performance. In support of this, we did not observe an association between RAVLT scores and extent of previous amphetamine or cocaine use. Furthermore, since no statistical differences in the use of LSD (lysergic acid diethylamide) and psilocybin were observed between the 3 groups under study, it seems unlikely that the findings of the present study should be attributed to substances other than MDMA. We cannot, however, completely rule out the possibility that the observed memory impairment in the MDMA-using subjects is unrelated to cannabis use. However, no association between RAVLT scores and extent of previous cannabis use was observed. In addition, the adverse effects of long-term cannabis use on cognitive skills have not been clearly demonstrated in the literature and seem to contradict each other.[41] For instance, Gouzoulis-Mayfrank and coworkers[33] did not observe differences in cognitive performance between cannabis users and ecstasy users or control subjects.

In summary, our data suggest that MDMA use can lead to neurotoxic changes in human cortical 5-HT brain neurons and that these changes may be reversible. However, our data also suggest that the functional consequences of MDMA on cortical brain 5-HT neurons may not be reversible because individuals who had stopped using MDMA more than 1 year earlier had impaired memory function, similar to that of recent MDMA users.

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