

# Cognition in Novice Ecstasy Users With Minimal Exposure to Other Drugs

## *A Prospective Cohort Study*

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**Context:** Ecstasy (street name for [ $\pm$ ]-3,4-methylenedioxyamphetamine [MDMA]) use has been associated with cognitive deficits, especially in verbal memory. However, owing to the cross-sectional and retrospective nature of currently available studies, questions remain regarding the causal direction and clinical relevance of these findings.

**Objective:** To examine the relationship between Ecstasy use and subsequent cognitive performance.

**Design:** A prospective cohort study in Ecstasy-naive subjects with a high risk for future first Ecstasy use, as part of the Netherlands XTC Toxicity study. The initial examination took place between April 10, 2002, and April 28, 2004; follow-up was within 3 years after the initial examination.

**Setting and Participants:** One hundred eighty-eight healthy Ecstasy-naive volunteers (mean age, 22 years) were recruited. Of these, 58 subjects started using Ecstasy (mean cumulative dose, 3.2 tablets; median cumulative dose, 1.5 tablets). They were compared with 60 persistent Ecstasy-naive subjects matched on age, sex, intelligence, and use of substances other than Ecstasy. Differences in cognition between Ecstasy users and Ecstasy-naive subjects were adjusted for differences in cannabis and other recreational drug use.

**Main Outcome Measures:** Change scores between the initial examination and follow-up on neurocognitive tests measuring attention, working memory, verbal and visual memory, and visuospatial ability.

**Results:** At the initial examination, there were no statistically significant differences in any of the neuropsychological test scores between persistent Ecstasy-naive subjects and future Ecstasy users. However, at follow-up, change scores on immediate and delayed verbal recall and verbal recognition were significantly lower in the group of incident Ecstasy users compared with persistent Ecstasy-naive subjects. There were no significant differences on other test scores.

**Conclusions:** Our findings suggest that even a first low cumulative dose of Ecstasy is associated with decline in verbal memory. Although the performance of the group of incident Ecstasy users is still within the normal range and the immediate clinical relevance of the observed deficits is limited, long-term negative consequences cannot be excluded.

*Arch Gen Psychiatry.* 2007;64:728-736

**E**CSTASY (STREET NAME FOR [ $\pm$ ]-3,4-METHYLENEDIOXY-methamphetamine [MDMA]) is an illicit recreational drug that is popular and widely used among young people. As there is growing evidence that the drug is potentially neurotoxic in humans, this is of great public health concern. Animal studies have shown long-lasting damage to distal axons of serotonergic neurons after single and multiple doses of MDMA.<sup>1-7</sup> In several studies,<sup>1,2,8</sup> the hippocampus and parahippocampus displayed relatively high rates of serotonergic denervation after MDMA exposure and relatively low recovery after abstinence. Some brain imaging studies have shown that similar effects may occur in humans.<sup>9-14</sup> Because

serotonin is involved in mood and cognition,<sup>15,16</sup> it is not surprising that many studies have revealed effects on these functions. Selective neuropsychological effects of Ecstasy use have been summarized in various reviews.<sup>17-20</sup> Deficits in verbal memory are among the most consistent findings.<sup>12,18-29</sup> In addition, decreased performance in visual memory and executive functioning in Ecstasy users has been demonstrated in some studies<sup>22,30-34</sup> but not in others.<sup>11,35,36</sup> Most research has been performed in frequent Ecstasy users, and no human data are currently available regarding the sustained effects of a single or low dosage of Ecstasy. It is therefore still not clear whether a low cumulative dose of Ecstasy could be neurotoxic in human beings.<sup>37,38</sup>

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Even though the scientific literature on the effects of Ecstasy use on cognition is increasing, some important issues regarding the causality and clinical relevance of the potential neurotoxicity of Ecstasy remain unclear, generally because of methodological limitations. Interpretation of findings is complicated because of inadequate sampling of participants, the lack of analysis of drug use, and the use of cross-sectional and retrospective study designs with a lack of baseline data and inadequate control of potential confounders.<sup>39-41</sup> Particularly, the use of other substances such as amphetamines, cocaine, cannabis, alcohol, and tobacco could be major confounders in almost all of the existing Ecstasy studies because most Ecstasy users are polydrug users.<sup>29</sup> Although most investigators did match their groups for age, education, and sex and adjusted for other drug use, none of these methods could exclude the possibility of preexisting differences in cognitive functioning.<sup>42-45</sup> Therefore, it has been advocated by several investigators that prospective studies should be conducted with measurements before and after a period of Ecstasy use.<sup>46</sup> The best results would be provided by a long-term prospective study in which Ecstasy-naive individuals are randomly assigned to Ecstasy or placebo conditions with different dosages in a laboratory setting. However, given the existing data on brain abnormalities in Ecstasy-treated animals and in human Ecstasy users, such a study is ethically unacceptable if it is solely for the purpose of detecting negative cognitive effects.

In an attempt to avoid the earlier-mentioned limitations, we carried out a prospective study in which we observed the behavior of a group of Ecstasy-naive subjects who were considered to be at risk for Ecstasy use in the near future. We wanted to know whether decreased cognitive performance can be regarded as a consequence of Ecstasy use. Because we monitored incident Ecstasy users during a limited period of follow-up, the amount of Ecstasy use was relatively low. Neurocognitive deficits were often described after heavy Ecstasy use, but there is a need for more empirical data on novice users.<sup>47</sup> We hypothesized that incident Ecstasy users would show slightly decreased scores on verbal memory tests and possibly also on tests for working memory and visuospatial functions (after controlling for potential confounders) in comparison with persistent Ecstasy-naive controls.

## METHODS

This study is part of the Netherlands XTC Toxicity study, a larger study investigating causality, course, and clinical relevance of Ecstasy neurotoxicity. A detailed description of the Netherlands XTC Toxicity study can be found in a special design article.<sup>48</sup>

### PARTICIPANTS

The original sample consisted of 188 Ecstasy-naive volunteers (aged 18-35 years) who considered starting Ecstasy use in the near future. They were recruited between April 10, 2002, and April 28, 2004, using a combination of targeted site sampling at locations such as dance events, youth fairs, universities, colleges, and parks; advertisement through a Web site about the project and an internet campaign; and snowball sampling. Main

criteria for inclusion were intention to probably or certainly use Ecstasy for the first time in the near future and preferably having 1 or more friends who had already used Ecstasy.

Exclusion criteria included the following: Ecstasy use in the past (by the initial examination), a major medical, neurological, or neuropsychiatric disorder (in the last year), use of medications (in the last year) that may influence cognition, pregnancy, and use of intravenous drugs. Subjects had to abstain from using psychoactive substances for at least 2 weeks and from consuming alcohol for at least 1 week prior to examinations. Drug use during the days before the assessment was checked through urinalysis (enzyme-multiplied immunoassay for amphetamines, MDMA, opiates, benzoylcegonine, benzodiazepines, 11-nor- $\Delta^9$ -tetrahydrocannabinol-carboxylic acid, and ethanol). Subjects were paid for their participation (€100 or €150 per session depending on the number of assessments).

### STUDY DESIGN

At the initial examination, all of the 188 subjects underwent neuropsychological assessment. All of the subjects had to complete questionnaires about their drug use sent to them by mail every 3 months during a follow-up period of approximately 18 months.

Within 3 years after the initial examination, all of the incident Ecstasy users and an individually matched (sex, age, verbal IQ) control group of persistent Ecstasy-naive subjects were invited for a follow-up session during which the neuropsychological assessment was repeated. The examiner (T.S.) was blind to whether a subject had used Ecstasy. In the same project, subjects underwent brain imaging that will be analyzed and described by other investigators in separate articles.

The study was approved by the medical ethics committee of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. To rule out any suggestion that we would stimulate the use of Ecstasy in Ecstasy-naive subjects, subjects were informed by an informational brochure about the potential negative consequences of Ecstasy use. Each subject signed an informed consent form stating that the subject had read and understood the information and that participation was voluntary.

### DEPENDENT VARIABLES

#### Attention and Working Memory

The Paced Auditory Serial Addition Test<sup>49</sup> was administered to measure working memory and information processing accuracy. Subjects must add numbers presented by a recorded male voice to a preceding number. Numbers are presented at a speed of 2.4 and 1.6 seconds per number, respectively. The outcome parameter is the total number of correct calculations (maximum of 60 points each). In addition, a Dutch adaptation of the Digit Span scale, a subtest of the Wechsler Adult Intelligence Scale-Revised,<sup>50</sup> was used to measure attention and working memory.<sup>51</sup> The adapted Dutch version was used in this study, as it is more reliable than the standard version because subjects are offered 3 instead of 2 series of digits per length. The outcome parameter is the number of correctly reproduced series of digits in forward and backward order (maximum, 21 series each).

#### Verbal Memory

A Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) was administered.<sup>52,53</sup> Subjects must memorize a se-

ries of 15 words in 5 learning trials. Immediate recall is tested after each trial. The outcome parameter is the sum of correctly reproduced words over 5 trials. Delayed recall and recognition are measured after 20 minutes. Outcome parameters are the total number of correctly reproduced and recognized words (maximum, 15 and 30 words, respectively).

### Visual Memory

To obtain comparable test parameters as in verbal memory assessment, a computerized adaptation of the Memory for Designs test was used.<sup>54</sup> The original test with 14 geometrical figures was split into 2 separate tests to obtain parallel versions. After presentation of 7 figures during 5 seconds each, subjects must draw the figures from memory. The outcome parameters are the number of correctly reproduced elements in 5 learning trials (maximum, 105 elements) and the number of trials needed to memorize all of the figures (maximum, 5 trials). Delayed reproduction is measured after 15 minutes; the outcome parameter is the number of correctly reproduced elements (maximum, 21 elements).

### Visuospatial Functioning

In the Mental Rotation Task,<sup>55</sup> participants are presented with 20 pairs of block designs drawn from different points of view. The subjects must judge whether pairs of designs are identical or different. The outcome parameter is the total number of correct answers in 6 minutes (maximum, 40 hits). In addition, a computerized and adapted version of the Judgment of Line Orientation<sup>56</sup> was used to test visuospatial working memory. The Judgment of Line Orientation requires subjects to identify which 2 of 11 lines presented in a semicircular array have the same orientation in a 2-dimensional space as 2 target lines. The target lines in our assessments were only shown for 1 second, directly followed by the 11 lines. The outcome parameter is the number of correctly judged pairs of lines (maximum, 30 pairs).

## INDEPENDENT VARIABLES

Future Ecstasy use (Ecstasy use between the initial examination and follow-up) was categorized in a binary variable (yes=1, no=0). The cumulative dosage of Ecstasy was measured as the number of tablets and duration of Ecstasy use in the weeks between the first and last Ecstasy use. This was assessed at a follow-up session using validated substance-use questionnaires.<sup>57</sup>

## POTENTIAL CONFOUNDERS

Substance use was measured using validated questionnaires at the initial examination and at follow-up sessions.<sup>57</sup> Use of alcohol (number of standard drinks per week in the last year), tobacco (number of cigarettes per week in the last year), cannabis (number of joints used in the last year), and amphetamines and cocaine (number of times used in the last year) was measured. At the initial examination, verbal intelligence was estimated to describe the sample and to use as a covariate in the statistical analyses. For this purpose, the Dutch version of the National Adult Reading Test,<sup>58</sup> the Dutch Adult Reading Test, was administered because it is relatively insensitive to cognitive impairment caused by neurological disorders.<sup>59</sup>

## STATISTICAL ANALYSES

Unpaired *t* tests were used to analyze whether the groups of incident Ecstasy users and persistent Ecstasy-naïve controls were

statistically different in terms of age and verbal IQ. Level of education and substance use (cannabis, alcohol, tobacco, cocaine, and amphetamines) at the initial examination and at follow-up were analyzed with nonparametric Mann-Whitney tests because they were not normally distributed. Group differences in sex were investigated using the  $\chi^2$  test. Paired *t* tests, or Wilcoxon signed rank tests if not normally distributed, were used to assess in both groups whether the earlier-mentioned variables changed between the initial examination and follow-up.

Because substance use variables were not normally distributed, all of the following analyses used log-transformed measures of substance use.

Differences in cognitive test results between the 2 groups at the initial examination were analyzed using multivariate analysis of covariance, with future Ecstasy use and sex as fixed factors and other potential confounders (age, Dutch Adult Reading Test IQ, and use of substances other than Ecstasy) as covariates.

To test whether Ecstasy had an effect on test results at follow-up, change scores between performance at the initial examination and follow-up examination were calculated for each subject and used in an analysis of covariance, with the same fixed factors and covariates as described earlier. In addition, the baseline performance score was added to the model as a covariate. Because RAVLT recognition was not normally distributed and showed very little variation, scores were transformed into a dichotomous variable in which a decline was labeled 1 and no decline was labeled 0. Logistic regression analysis was performed with decline as the dependent variable and use of Ecstasy and other substances, sex, and IQ as covariates.

To test whether the amount of Ecstasy use was related to changes in cognition, Pearson correlation analyses were performed in the group of incident Ecstasy users with the total number of Ecstasy tablets and cognition change scores as variables. If an association was found, partial correlations were carried out with change scores of cognitive tests as the dependent variable and controlled for age, IQ, sex, and use of substances other than Ecstasy. Because the RAVLT recognition change score was transformed into a dichotomous variable (decline), logistic regression analysis was performed with decline as the dependent variable and the total amount of Ecstasy and other substances, sex, IQ, and age as covariates.

All of the analyses were performed using SPSS statistical software version 12.0.1 (SPSS, Inc, Chicago, Ill). Only  $P < .05$  was considered statistically significant.

## RESULTS

### CHARACTERISTICS OF THE SAMPLE AND SUBSTANCE USE

Of the 188 Ecstasy-naïve subjects (77 men, 111 women; mean  $\pm$  SD age, 21.8  $\pm$  3.0 years) at the initial examination, 158 completed the last follow-up questionnaires about drug use sent to them by mail. The other 30 volunteers were regarded as dropouts either because they refused to participate in follow-up or because we could not reach them anymore. Of the 158 subjects, 64 declared that they had started to use Ecstasy since inclusion in the study, whereas the other 94 subjects declared to be continuously Ecstasy naïve. Of the 64 incident Ecstasy users, 59 were willing to participate in the follow-up session, together with 61 matched (sex, age, Dutch Adult Reading Test IQ) persistent Ecstasy-naïve sub-

**Table 1. Characteristics of Use of Ecstasy and Other Substances**

Characteristic	Ecstasy Users (n = 58)		Ecstasy-Naive Subjects (n = 60)	
	Initial Examination	Follow-up	Initial Examination	Follow-up
Sex, male/female, No.	25/33	NA	25/35	NA
Age, mean ± SD (median; range), y	21.8 ± 3.1 (21.1; 18-29)*	22.7 ± 3.2 (21.9; 19-30)*	21.5 ± 2.1 (21.3; 18-29)†	23.0 ± 2.1 (22.9; 19-30)†
DART-IQ, mean ± SD (median; range)	103.4 ± 9.0 (101.5; 85-126)	NA	105.5 ± 10.2 (104.5; 85-126)	NA
Subjects at education level, No.‡				
Prevocation	1	1	0	0
Junior general secondary or vocation	9	7	3	1
Senior general secondary education, vocation colleges	45	46	55	55
Universities	3	4	2	4
Ecstasy, mean ± SD (median; range)				
Cumulative dose, tablets	NA	3.2 ± 5.2 (1.5; 0.5-30)	NA	NA
Time since using first tablet, wk	NA	18.6 ± 17.6 (11.1; 2-70)	NA	NA
Time since using last tablet, wk§	NA	11.8 ± 12.0 (7.9; 2-59)	NA	NA
Duration of Ecstasy use, wk	NA	6.8 ± 12.5 (0.0; 0-12)	NA	NA
Other substances used in last year, mean ± SD (median; range)				
Alcohol, units/wk	8.6 ± 7.8 (6.1; 0-31)	8.9 ± 7.8 (7.3; 1-36)	9.8 ± 9.0 (7.9; 0-55)	8.2 ± 7.9 (6.6; 0-54)
Tobacco, cigarettes/wk	33.9 ± 47.8 (1.0; 0-160)	33.6 ± 61.8 (5.0; 0-350)	26.4 ± 54.9 (0.0; 0-280)	24.4 ± 46.2 (0.0; 0-200)
Cannabis, joints in last year	48.8 ± 100.4 (15.8; 0-635)¶	53.6 ± 120.8 (18.5; 0-830)#	17.2 ± 25.1 (15.5; 0-133)¶	20.5 ± 50.3 (2.3; 0-315)#
Amphetamine, No. of times used last year	0.1 ± 0.8 (0.0; 0-6)	2.9 ± 20.5 (0.0; 0-156)	0.0 ± 0.0 (0.0; 0-0)	0.0 ± 0.0 (0.0; 0-0)
Cocaine, No. of times used last year	0.8 ± 2.1 (0.0; 0-6)	1.4 ± 2.8 (0.0; 0-12)#	0.3 ± 1.3 (0.0; 0-6)	0.3 ± 1.3 (0.0; 0-6)#

Abbreviations: DART, Dutch Adult Reading Test; NA, not applicable.

\* $P < .05$  (paired  $t$  test) for future Ecstasy users at initial examination vs Ecstasy users at follow-up.

† $P < .05$  (paired  $t$  test) for controls at initial examination vs follow-up.

‡Translation from the Central Bureau of Statistics, the Netherlands.

§Minimal time since using the last tablet had to be at least 2 weeks.

||Related by Wilcoxon signed rank test for controls at initial examination vs follow-up.

¶ $P < .05$  (Mann-Whitney test) for future Ecstasy users vs controls at initial examination.

# $P < .05$  (Mann-Whitney test) for Ecstasy users vs controls at follow-up.

jects. One incident Ecstasy user was excluded because results of a urine test were positive for cocaine, and 1 Ecstasy-naive control was excluded because of dyslexia and attention-deficit disorder diagnosed in youth. Analyses included 58 incident Ecstasy users and 60 matched controls.

Sociodemographic data and patterns of drug use are shown in **Table 1**. The 2 groups were similar in terms of sex ( $\chi^2 = 0.03$ ;  $P = .88$ ), age ( $t_{116} = -0.67$ ;  $P = .50$ ), verbal IQ ( $t_{116} = 1.18$ ;  $P = .24$ ), and level of education ( $U = 1563$ ;  $P = .13$ ). At the initial examination, the 2 groups were not significantly different in terms of smoking or use of alcohol, d-amphetamines, and cocaine. However, cannabis use was significantly higher in the group of future Ecstasy users than in the group of Ecstasy-naive controls (mean ± SD, 48.8 ± 100.4 joints vs 17.2 ± 25.1 joints, respectively, in the year before the initial examination;  $U = 1363$ ;  $P = .04$ ). Time between the initial and follow-up measurements was a mean ± SD of 11.1 ± 6.2 months in the Ecstasy group and 19.1 ± 7.5 months in the control group ( $t_{116} = 6.30$ ;  $P < .001$ ).

At follow-up, incident Ecstasy users reported to have used a mean of 3.2 Ecstasy tablets (range, 0.5-30 tablets; median, 1.5 tablets) in a mean period of 1.6 months during the average follow-up period of 11.1 months. Last Ecstasy use took place a mean ± SD of 11.8 ± 12.0 weeks before the follow-up assessment. At follow-up, incident Ecstasy users reported to have used more cannabis and

cocaine in the last year than persistent Ecstasy-naive subjects (cannabis: mean ± SD, 53.6 ± 120.8 joints vs 20.5 ± 50.3 joints, respectively,  $U = 1089$ ,  $P < .001$ ; cocaine: 1.4 ± 2.8 times vs 0.3 ± 1.3 times, respectively,  $U = 1436$ ,  $P = .006$ ). In comparison with the initial examination, persistent Ecstasy-naive subjects used less alcohol at follow-up (mean ± SD, 9.8 ± 9.0 standard drinks/wk vs 8.2 ± 7.9 standard drinks/wk, respectively;  $z = -2.89$ ;  $P = .004$ ).

## NEUROPSYCHOLOGICAL TESTING

**Table 2** shows the neuropsychological test scores for both groups. Multivariate analyses of covariance (Pillai trace statistics) with Ecstasy use and sex as fixed factors and age, Dutch Adult Reading Test IQ, and use of substances other than Ecstasy as covariates did not reveal any significant differences in neuropsychological test results at the initial examination ( $F_{12,96} = 0.73$ ;  $P = .72$ ; partial  $\eta^2 = 0.08$ ).

Univariate analysis of covariance with change scores of test performance as the dependent variable demonstrated a significant group effect on RAVLT immediate recall ( $F_{1,108} = 4.62$ ;  $P = .03$ ; partial  $\eta^2 = 0.04$ ) and delayed recall ( $F_{1,108} = 4.67$ ;  $P = .03$ ; partial  $\eta^2 = 0.04$ ) scores. Logistic regression analyses with decline in RAVLT recognition (decline = 1; no decline = 0) as the dependent variable and Ecstasy use, sex, IQ, and other substance use

**Table 2. Cognitive Performance**

Test	Ecstasy Users, Mean (SD) (n = 58)		Ecstasy-Naive Subjects, Mean (SD) (n = 60)		Change Score for Ecstasy Users, Mean (SD) (n = 58)	Change Score for Ecstasy-Naive Subjects, Mean (SD) (n = 60)	B (95% CI)*	P Value†
	Initial Examination	Follow-up	Initial Examination	Follow-up				
RAVLT immediate, words	58.7 (6.3)	59.6 (6.5)	57.8 (5.8)	61.7 (5.9)	0.86 (5.5)	3.90 (5.8)	2.23 (0.17 to 4.29)	.03
RAVLT delayed recall, words	13.8 (1.6)	13.2 (2.0)	13.5 (1.6)	14.1 (1.2)	-0.52 (1.8)	0.65 (1.8)	0.63 (0.05 to 1.22)	.03
RAVLT recognition, words	29.95 (0.2)	29.66 (0.8)	29.88 (0.4)	29.93 (0.3)	22.4% decline‡	6.7% decline‡	1.77 (1.36 to 25.37)	.02§
MFD immediate, elements	96.1 (7.2)	94.4 (7.8)	95.2 (7.6)	96.8 (6.6)	-1.74 (9.4)	1.67 (9.1)	1.04 (-1.35 to 3.43)	.39
MFD, No. of trials	3.1 (1.4)	3.3 (1.3)	3.4 (1.3)	3.1 (1.4)	0.12 (0.9)	0.10 (0.6)	-0.32 (-0.86 to 0.23)	.25
MFD delayed, elements	20.7 (0.9)	20.8 (0.5)	20.8 (0.5)	20.9 (0.3)	0.21 (1.8)	-0.33 (1.8)	0.04 (-0.10 to 0.19)	.56
Digit span forward, series	15.1 (2.5)	15.5 (2.8)	14.9 (2.3)	15.1 (2.2)	0.40 (2.4)	0.23 (1.8)	0.19 (-0.81 to 1.18)	.43
Digit span backward, series	11.6 (2.0)	11.8 (2.4)	11.4 (2.5)	11.4 (2.9)	0.22 (2.6)	0.00 (2.6)	-0.18 (-1.38 to 1.02)	.25
PASAT 2.4 s, hits	52.2 (6.0)	55.0 (5.0)	51.8 (7.6)	54.9 (5.0)	2.78 (4.5)	3.07 (5.1)	0.14 (-1.30 to 1.58)	.85
Pasat 1.6 s, hits	43.1 (7.2)	45.5 (8.0)	42.8 (7.3)	46.3 (8.4)	2.38 (5.0)	3.45 (6.4)	0.52 (-1.70 to 2.74)	.64
JOLO total, pairs	22.5 (3.9)	24.1 (3.5)	22.4 (3.6)	23.3 (3.8)	1.62 (3.1)	0.87 (2.7)	-0.69 (-1.77 to 0.39)	.21
Mental rotation test, hits	23.8 (7.3)	26.2 (8.1)	22.3 (6.7)	24.4 (6.4)	2.40 (4.7)	2.10 (4.4)	-0.73 (-2.38 to 0.92)	.38

Abbreviations: B, regression coefficient of general linear model; CI, confidence interval; JOLO, Judgment of Line Orientation; MFD, Memory for Designs test; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test.

\*For the models with significant Ecstasy effects, homogeneity of regression was obtained for all of the covariates.<sup>60</sup>

†P values are from univariate analysis of variance with correction for sex, age, IQ, and use of substances other than Ecstasy.

‡Percentage of subjects who showed decline.

§In the logistic regression, the odds ratio was 5.9 and P = .02.

as covariates showed a significant effect of Ecstasy use on recognition decline (odds ratio = 5.87; Wald  $\chi^2 = 5.62$ ;  $P = .02$ ). No significant sex  $\times$  Ecstasy interaction effect on RAVLT scores was found.

A covariance effect of cocaine and d-amphetamine use on RAVLT delayed recall scores was observed, but this was not observed with the use of alcohol, tobacco, or cannabis. After excluding users of cocaine and amphetamines, the analysis was repeated with 43 incident Ecstasy users and 57 Ecstasy-naive controls; the effect of Ecstasy use on RAVLT delayed recall scores remained statistically significant ( $F_{1,92} = 6.62$ ;  $P = .01$ ; partial  $\eta^2 = 0.07$ ).

#### RELATIONSHIP BETWEEN NEUROPSYCHOLOGICAL TEST PERFORMANCE AND AMOUNT OF ECSTASY USE

Because we had specific hypotheses with respect to the direction of the effects, all of the tests were 1-tailed. The total cumulative dose of Ecstasy was significantly associated with RAVLT delayed recall and recognition change scores (Pearson  $r = -0.24$ ,  $P = .04$  and Pearson  $r = -0.29$ ,  $P = .02$ , respectively) but not with immediate recall scores (Pearson  $r = -0.16$ ;  $P = .12$ ). When controlling for age, IQ, sex, and use of substances other than Ecstasy in partial correlations, there remained a significant association between the extent of Ecstasy use and RAVLT recognition scores (Pearson  $r = -0.30$ ;  $P = .02$ ) but not for delayed recall scores (Pearson  $r = -0.21$ ;  $P = .08$ ). No associations were found with the duration of Ecstasy use and the abstinence period.

To further explore the association between the amount of Ecstasy used and RAVLT recognition scores, logistic regression analysis was performed. It showed a significant independent contribution of the log-transformed number of Ecstasy tablets on decline in RAVLT recog-

nition (odds ratio = 15.18; 95% confidence interval, 1.10-210.14; Wald  $\chi^2 = 4.12$ ;  $P = .04$ ). With the non-log-transformed raw number of Ecstasy tablets, a smaller and only marginally significant dose-response relationship was observed (odds ratio = 1.30; 95% confidence interval, 0.96-1.75; Wald  $\chi^2 = 2.88$ ;  $P = .09$ ).

#### COMMENT

This prospective study examined the relationship between Ecstasy use and subsequent cognitive performance. At the initial examination, future Ecstasy users and a matched group of persistent Ecstasy-naive subjects were similar in terms of sociodemographics, neurocognitive performance, and substance use, with the exception that future Ecstasy users used significantly more cannabis prior to the initial assessment. The difference in cannabis use between future Ecstasy users and Ecstasy-naive subjects as well as the total amount of cannabis that was used by the subjects did not significantly change in the follow-up period. At follow-up, Ecstasy-naive subjects demonstrated a normal retest effect on a verbal memory task,<sup>53</sup> whereas in the group of incident Ecstasy users, such an effect failed to appear (even after controlling for the use of cannabis, cocaine, amphetamines, tobacco, and alcohol). No differences between the 2 groups were observed on other neurocognitive tests. No differential effect was found for sex, in contrast to some other studies<sup>13,61-63</sup> that have reported stronger Ecstasy-induced effects in females than in males. Overall test performance of all of the participants remained within the normal range of a sex- and age-comparable general population.<sup>53</sup>

There are several conceivable explanations besides an effect of Ecstasy for the observed differences in verbal

memory performance between the 2 groups. First, some investigators<sup>64-67</sup> have suggested a possible combined effect of cannabis and Ecstasy on cognitive functioning. Ecstasy users in our study used more cannabis than persistent Ecstasy-naïve subjects; therefore, a possible confound of cannabis use cannot totally be excluded. However, no significant effects of cannabis or Ecstasy × cannabis interaction effects on cognitive functioning were observed in our study. There was a confounding effect of cocaine and d-amphetamine use, but this effect did not fully account for the cognitive differences between the 2 groups. Also, effects remained significant after excluding all of the users of cocaine and d-amphetamines. Second, some other confounding factors may be responsible for the observed relationships between Ecstasy use and verbal memory parameters. In a previous article<sup>68</sup> on self-reported levels of depression, impulsivity, and sensation seeking in the same study population, novice Ecstasy use was associated with increased sensation seeking. Hypothetically, it is possible that higher sensation seeking leads to impatience, tediousness, and less effort in highly demanding tests, which could result in lower test performance. Still, this does not explain why only verbal memory test scores are affected, whereas scores on other highly demanding tests, for example, attention and working memory tests, are not affected. It has also been suggested that Ecstasy might cause depression,<sup>69</sup> which in turn could result in lower performance on, for example, verbal memory tests. Although we found no indications in the larger Netherlands XTC Toxicity study sample that incident Ecstasy users become more depressed after their first Ecstasy use,<sup>68</sup> we cannot fully exclude an effect of depression on test scores because the current subsample was slightly different from the total sample. Third, it is conceivable that the information we gave prior to the study about the potential risks of Ecstasy use created a self-fulfilling prophecy. Again, however, we found no indications for this possibility in the total sample.<sup>68</sup>

The current findings are well in line with numerous previous studies<sup>12,18,21-27</sup> that reported a specific negative effect of Ecstasy use on verbal memory. In our study, the association between Ecstasy dose and verbal memory performance was rather weak. This is not surprising given the relatively low doses that were used and the short duration of Ecstasy use resulting in very limited variation in Ecstasy use parameters. Most studies<sup>28,70,71</sup> have focused on effects of heavy Ecstasy use in which the dose-response relationship was more obvious. Only a few other studies<sup>25,72,73</sup> have also demonstrated decreased memory in novice Ecstasy users. However, in these studies, assessment took place within 7 days after the last drug exposure, whereas in our study, the assessment took place on average 11.8 weeks after the last Ecstasy use. Moreover, Bhattachary and Powell<sup>25</sup> found that increasing the duration of abstinence up to 15 days was associated with higher recall scores, implying that the deficits in these studies were short-term pharmacological effects. Other studies<sup>22,45,70,74</sup> did not detect significant deficits in subjects who used a low to moderate dose of Ecstasy. One possible reason might be that sample sizes in those studies were too small to detect effects. It is also conceivable

that these cross-sectional and retrospective studies had selection bias and residual confounding. These limitations are less likely to occur in a prospective study with carefully matched subjects and extensive adjustment for potential confounders. However, residual confounding can never be fully excluded.

The fact that we did not find any effect of Ecstasy use on neurocognitive functions other than verbal memory could be owing to low cumulative doses of Ecstasy that were used. Moreover, subjects in our study used few other drugs in comparison with subjects in other studies. It might be possible that other neurocognitive deficits described in some studies<sup>22,30,33</sup> were caused by exposure to or an interaction with drugs other than Ecstasy. It is also conceivable that we missed effects on other neurocognitive functions because the tests we used were not sensitive enough. It could therefore be valuable to add additional tests that might capture deficits better.

Because in our study only verbal memory was significantly affected after low-dose Ecstasy use, it can be hypothesized that medial temporal areas, in particular the hippocampal area, are specifically vulnerable to Ecstasy use. This theory has also been advocated by others<sup>70,75</sup> who only observed decreased functioning on temporal lobe tests. Imaging studies in animals have shown changes in the hippocampal and (pre) frontal lobes after exposure to Ecstasy.<sup>1,2,4,8,76</sup> A functional magnetic resonance imaging study revealed that adolescent Ecstasy users fell short in deactivating the left hippocampus during verbal working memory load.<sup>73</sup> The main underlying factor seems to be a depletion of serotonin in Ecstasy users,<sup>10-12,77,78</sup> a depletion that might be reversible.<sup>63</sup> Serotonin is involved in several cognitive functions<sup>16,79</sup> but might be especially relevant to learning and memory.<sup>80,81</sup> Serotonergic depletion seems to result in impaired consolidation, leaving attention unaffected.<sup>82</sup>

Although this prospective study adds to the knowledge base in this field, we are well aware of its methodological limitations. First, although prospective, the study design was not experimental and therefore still offers no indisputable evidence of causality. An undefined confounding factor not (adequately) measured might still underlie the observed relationships and be responsible for the findings. In this respect, a limitation could be that information about the medical and neuropsychiatric history was based on self-report of the subjects (ie, non-standardized interviews and questionnaires); therefore, unnoticed medical history could have biased the results. It should be noted, however, that this was a non-treatment-seeking population of young healthy people with a very small a priori probability of serious medical and/or neuropsychiatric disorders. Also, owing to the non-experimental design of the study, potential confounding of lifestyle differences cannot be totally excluded. The pattern of use and the environment in which the drug was used were not investigated. Some studies<sup>83</sup> claim interaction effects between the neurocognitive damage and ambient heat, dehydration, alcohol use, and other drug use. However, it would be impossible to control for all of these factors, particularly because Ecstasy users do not tend to use only Ecstasy. In addition, we did not suc-

ceed in following a strict time frame because subjects started to use Ecstasy at different periods after entering the study and because Ecstasy-naive subjects could only be matched after the novice Ecstasy users were known. As a consequence, follow-up duration in the Ecstasy-naive group was longer than in the novice Ecstasy users. However, given the fact that retest effects become smaller with time, these differences in follow-up duration between the 2 groups cannot explain the lower performance in the group using Ecstasy. Next, there was no control of the purity and amount of MDMA within the Ecstasy tablets used by the subjects. However, results from pill testing in the Netherlands confirm that in 2003 and 2004, 95% of the tablets sold as Ecstasy did contain MDMA as the major component.<sup>84-86</sup> Moreover, the sample was not representative for the general population of young adults, which might limit the generalizability of the results. Subjects with higher education or intelligence were more likely to participate in our study than subjects with lower levels of education or intelligence. They participated in a fairly demanding research project including brain imaging and blood sampling. This probably induced selection of subjects with high motivation, which may have influenced the results. Results cannot be generalized to a group of young adults with lower levels of education or intelligence. According to the brain reserve hypothesis,<sup>87-90</sup> it is more difficult to determine decreases in cognitive functioning in higher-educated persons than in lower-educated persons. This implies that our finding may have underestimated the effect of Ecstasy. A final limitation is that this study does not answer the question of whether the observed short-term effects will remain after quitting the use of Ecstasy. Monitoring this cohort is worthwhile.

In conclusion, our data indicate that low doses of Ecstasy are associated with decreased verbal memory function, which is suggestive for Ecstasy-induced neurotoxicity. Further research on the long-term effects of Ecstasy as well as on the possibility of additive effects of Ecstasy use on aging of the brain is needed.

**Submitted for Publication:** February 28, 2006; final revision received October 5, 2006; accepted October 7, 2006.

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**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by grant ZonMw 310-00-036 from the Netherlands Organization for Health Research and Development as part of their Addiction Program.

**Acknowledgment:** Questionnaires on drug use were obtained courtesy of the Addiction Research Institute of the University of Utrecht. We thank Hylke Vervaeke, MSc, for subject recruitment and Ivo Bisschops and Sarah Dijkink for their assistance with the logistics and data collection.

## REFERENCES

- Hatzidimitriou G, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci*. 1999;19:5096-5107.
- Ricaurte GA, Martello AL, Katz JL, Martello MB. Lasting effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. *J Pharmacol Exp Ther*. 1992; 261:616-622.
- Ricaurte GA, DeLanney LE, Irwin I, Langston JW. Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. *Brain Res*. 1988;446:165-168.
- Colado MI, Murray TK, Green AR. 5-HT loss in rat brain following 3,4-methylenedioxymethamphetamine (MDMA), p-chloroamphetamine and fenfluramine administration and effects of chlormethiazole and dizocilpine. *Br J Pharmacol*. 1993;108:583-589.
- Ricaurte GA, Yuan J, McCann UD. (+/-)3,4-Methylenedioxymethamphetamine ("Ecstasy")-induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology*. 2000;42:5-10.
- Schmidt CJ, Wu L, Lovenberg W. Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analogue. *Eur J Pharmacol*. 1986;124:175-178.
- O'Shea E, Granados R, Esteban B, Colado MI, Green AR. The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ("ecstasy"). *Neuropharmacology*. 1998;37:919-926.
- Fischer C, Hatzidimitriou G, Wlos J, Katz J, Ricaurte G. 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.
- Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R. Serotonergic function after (+/-)3,4-methylene-dioxymethamphetamine ("Ecstasy") in humans. *Int Clin Psychopharmacol*. 1998;13:1-9.
- McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet*. 1998;352:1433-1437.
- Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. *Br J Psychiatry*. 1999;175:63-69.
- Reneman L, Booij J, Schmand B, van den Brink W, Gunning B. Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. *Psychopharmacology (Berl)*. 2000;148:322-324.
- Reneman L, Booij J, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, den Heeten GJ, van den Brink W. Effects of dose, sex, and long-term abstinence from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet*. 2001; 358:1864-1869.
- Green AR, Mehan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev*. 2003;55:463-508.
- Cohen Z, Bonvento G, Lacombe P, Hamel E. Serotonin in the regulation of brain microcirculation. *Prog Neurobiol*. 1996;50:335-362.
- Meneses A. 5-HT system and cognition. *Neurosci Biobehav Rev*. 1999;23:1111-1125.
- Parrott AC. Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Hum Psychopharmacol*. 2001;16:557-577.
- Back-Madruga C, Boone KB, Chang L, Grob CS, Lee A, Nations H, Poland RE. Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. *Clin Neuropsychol*. 2003;17:446-459.

19. Verbaten MN. Specific memory deficits in ecstasy users? the results of a meta-analysis. *Hum Psychopharmacol.* 2003;18:281-290.
20. Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? *Addiction.* 2006;101:348-361.
21. Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR. Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? *Am J Drug Alcohol Abuse.* 1992;18:331-341.
22. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology.* 1998;51:1532-1537.
23. Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. Cognitive performance in recreational users of MDMA of "ecstasy": evidence for memory deficits. *J Psychopharmacol.* 1998;12:79-83.
24. Morgan MJ. Memory deficits associated with recreational use of "ecstasy" (MDMA). *Psychopharmacology (Berl).* 1999;141:30-36.
25. Bhattachary S, Powell JH. Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or "ecstasy": evidence for cognitive impairment. *Psychol Med.* 2001;31:647-658.
26. Zakzanis KK, Young DA. Memory impairment in abstinent MDMA ("Ecstasy") users: a longitudinal investigation. *Neurology.* 2001;56:966-969.
27. McCardle K, Luebbers S, Carter JD, Croft RJ, Stough C. Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology (Berl).* 2004;173:434-439.
28. Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry.* 2001;58:901-906.
29. Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoltdt A. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology (Berl).* 2003;167:85-96.
30. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry.* 2000;68:719-725.
31. Verkes RJ, Gijsman HJ, Pieters MS, Schoemaker RC, de Visser S, Kuijpers M, Pennings EJ, de Bruin D, Van de Wijngaart G, Van Gerven JM, Cohen AF. Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology (Berl).* 2001;153:196-202.
32. Wareing M, Fisk JE, Murphy J, Montgomery C. Verbal working memory deficits in current and previous users of MDMA. *Hum Psychopharmacol.* 2004;19:225-234.
33. McCann UD, Merti M, Eligulashvili V, Ricaurte GA. Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology (Berl).* 1999;143:417-425.
34. Wareing M, Fisk JE, Murphy PN. Working memory deficits in current and previous users of MDMA ("ecstasy"). *Br J Psychol.* 2000;91:181-188.
35. Rodgers J. Cognitive performance amongst recreational users of "ecstasy." *Psychopharmacology (Berl).* 2000;151:19-24.
36. Simon NG, Mattick RP. The impact of regular ecstasy use on memory function. *Addiction.* 2002;97:1523-1529.
37. Vollenweider FX, Gamma A, Liechti M, Huber T. Is a single dose of MDMA harmless? *Neuropsychopharmacology.* 1999;21:598-600.
38. McCann UD, Ricaurte GA, Molliver ME. "Ecstasy" and serotonin neurotoxicity: new findings raise more questions. *Arch Gen Psychiatry.* 2001;58:907-908.
39. Morgan MJ. Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology (Berl).* 2000;152:230-248.
40. Turner JJ, Parrott AC. "Is MDMA a human neurotoxin?": diverse views from the discussants. *Neuropsychobiology.* 2000;42:42-48.
41. Boot BP, McGregor IS, Hall W. MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks. *Lancet.* 2000;355:1818-1821.
42. Morgan JF. Toxic effect of MDMA on brain serotonin neurons. *Lancet.* 1999;353:1268-1269.
43. Curran HV. Is MDMA ("Ecstasy") neurotoxic in humans? an overview of evidence and of methodological problems in research. *Neuropsychobiology.* 2000;42:34-41.
44. Parrott AC. Human research on MDMA (3,4-methylene-dioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology.* 2000;42:17-24.
45. Halpern JH, Pope HG Jr, Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D. Residual neuropsychological effects of illicit 3,4-methylenedioxyamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug Alcohol Depend.* 2004;75:135-147.
46. Gouzoulis-Mayfrank E, Daumann J. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *J Psychopharmacol.* 2006;20:188-193.
47. Rycroft N, Golding JF. Cognitive performance in current occasional and ex-users of Ecstasy (MDMA) and controls. *J Psychopharmacol.* 2002;16(suppl):a59.
48. De Win MM, Jager G, Vervaeke HK, Schilt T, Reneman L, Booij J, Verhulst FC, Den Heeten GJ, Ramsey NF, Korf DJ, Van den Brink W. The Netherlands XTC Toxicity (NeXT) study: objectives and methods of a study investigating causality, course, and clinical relevance. *Int J Methods Psychiatr Res.* 2005;14:167-185.
49. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. *Percept Mot Skills.* 1977;44:367-373.
50. Wechsler D. *WAIS-R Manual.* San Antonio, Tex: Psychological Corp; 1981.
51. Lindeboom J, Matto D. Digit series and Knox cubes as concentration tests for elderly subjects [in Dutch]. *Tijdschr Gerontol Geriatr.* 1994;25:63-68.
52. Rey A. *L'examen clinique en psychologie.* Paris, France: Presses Universitaires de France; 1964.
53. Van den Burg W, Saan RJ, Deelman BG. *15-woordentest: Provisional Manual.* Groningen, the Netherlands: University Hospital; 1985.
54. Graham FK, Kendall BS. Memory-for-design: revised general manual. *Percept Mot Skills.* 1960;11:147-188.
55. Shepard RN, Metzler J. Mental rotation of three-dimensional objects. *Science.* 1971;171:701-703.
56. Benton AL, Varney NR, Hamsher KD. Visuospatial judgment: a clinical test. *Arch Neurol.* 1978;35:364-367.
57. Van de Wijngaart G, Braam R, de Bruin D, Fris M, Maalsté N, Verbraeck H. *Ecstasy in het uitgaanscircuit [Ecstasy and the Dutch Rave Scene: A Socio-epidemiologic Study on the Nature and Extent of, and the Risks Involved in Using Ecstasy and Other Party Drugs at Dance Events].* Utrecht, the Netherlands: Addiction Research Institute; 1997.
58. Nelson HE, O'Connell A. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex.* 1978;14:234-244.
59. Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: a measure of premorbid intelligence level [in Dutch]. *Tijdschr Gerontol Geriatr.* 1991;22:15-19.
60. Tabachnick BG, Fidell L. *Using Multivariate Statistics.* Boston, Mass: Allyn & Bacon; 2001.
61. Bond AJ, Verheyden SL, Wingrove J, Curran HV. Angry cognitive bias, trait aggression and impulsivity in substance users. *Psychopharmacology (Berl).* 2004;171:331-339.
62. Liechti ME, Gamma A, Vollenweider FX. Gender differences in the subjective effects of MDMA. *Psychopharmacology (Berl).* 2001;154:161-168.
63. Buchert R, Thomasius R, Wilke F, Petersen K, Nebeling B, Obrocki J, Schulze O, Schmidt U, Clausen M. A voxel-based PET investigation of the long-term effects of "Ecstasy" consumption on brain serotonin transporters. *Am J Psychiatry.* 2004;161:1181-1189.
64. Sala M, Braidia D. Endocannabinoids and 3,4-methylenedioxyamphetamine (MDMA) interaction. *Pharmacol Biochem Behav.* 2005;81:407-416.
65. Verdejo-Garcia AJ, Lopez-Torreillas F, Aguilar de Arcos F, Perez-Garcia M. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. *Addict Behav.* 2005;30:89-101.
66. Dafters RI, Hoshi R, Talbot AC. Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. *Psychopharmacology (Berl).* 2004;173:405-410.
67. Croft RJ, Mackay AJ, Mills AT, Gruzeliér JG. The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology (Berl).* 2001;153:373-379.
68. de Win MM, Schilt T, Reneman L, Vervaeke H, Jager G, Dijkink S, Booij J, van den Brink W. Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study. *J Psychopharmacol.* 2006;20:226-235.
69. Sumnall HR, Cole JC. Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. *J Psychopharmacol.* 2005;19:84-92.
70. Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry.* 2003;27:819-827.
71. Fox HC, Toplis AS, Turner JJ, Parrott AC. Auditory verbal learning in drug-free Ecstasy polydrug users. *Hum Psychopharmacol.* 2001;16:613-618.
72. Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology (Berl).* 1998;139:261-268.
73. Jacobsen LK, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. *Psychopharmacology (Berl).* 2004;173:383-390.

74. Reneman L, Schilt T, de Win MM, Booij J, Schmand B, van den Brink W, Bakker O. Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users. *J Psychopharmacol.* 2006;20:389-399.
75. Fox HC, McLean A, Turner JJ, Parrott AC, Rogers R, Sahakian BJ. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology (Berl).* 2002;162:203-214.
76. Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther.* 1987;241:338-345.
77. Molero-Chamizo A. 3,4-methylenedioxymethylamphetamine ("ecstasy"): its long-term emotional and cognitive effects, and serotonin depletion [in Spanish]. *Rev Neurol.* 2005;41:108-114.
78. Ricarte GA, McCann UD, Szabo Z, Scheffel U. Toxicodynamics and long-term toxicity of the recreational drug, 3, 4-methylenedioxymethylamphetamine (MDMA, "Ecstasy"). *Toxicol Lett.* 2000;112-113:143-146.
79. Buhot MC, Malleret G, Segu L. Serotonin receptors and cognitive behaviour: an update. *IDrugs.* 1999;2:426-437.
80. Hunter AJ. Serotonergic involvement in learning and memory. *Biochem Soc Trans.* 1989;17:79-81.
81. Meneses A, Hong E. Modification of 8-OH-DPAT effects on learning by manipulation of the assay conditions. *Behav Neural Biol.* 1994;61:29-35.
82. Harrison BJ, Olver JS, Norman TR, Burrows GD, Wesnes KA, Nathan PJ. Selective effects of acute serotonin and catecholamine depletion on memory in healthy women. *J Psychopharmacol.* 2004;18:32-40.
83. Topp L, Barker B, Degenhardt L. The external validity of results derived from ecstasy users recruited using purposive sampling strategies. *Drug Alcohol Depend.* 2004;73:33-40.
84. Drugs Informatie en Monitoring Systeem. *Jaarbericht 2003.* Utrecht, the Netherlands: DIMS/Trimbos-instituut; 2003.
85. Drugs Informatie en Monitoring Systeem. *Jaarbericht 2004.* Utrecht, the Netherlands: DIMS/Trimbos-instituut; 2004.
86. Nabben T, Benschop A, Korf DJ. *Antenne 2004 Trends in alcohol, tabak en drugs bij jonge Amsterdammers.* Amsterdam, the Netherlands: Rozenberg Publishers; 2005.
87. Stern Y, Zarahn E, Hilton HJ, Flynn J, DeLaPaz R, Rakitin B. Exploring the neural basis of cognitive reserve. *J Clin Exp Neuropsychol.* 2003;25:691-701.
88. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia: a test of the brain reserve hypothesis. *Psychol Med.* 1997;27:1337-1344.
89. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med.* 2006;36:441-454.
90. Satz P, Morgenstern H, Miller EN, Selnes OA, McArthur JC, Cohen BA, Wesch J, Becker JT, Jacobson L, D'Elia LF, van Gorp W, Visscher B. Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). *J Acquir Immune Defic Syndr.* 1993;6:503-511.

### Correction

**Error in Table.** In the Original Article by Osborn et al titled "Relative Risk of Cardiovascular and Cancer Mortality in People With Severe Mental Illness From the United Kingdom's General Practice Research Database," published in the February issue of the *Archives* (2007;64:242-249), an error appeared in Table 3. The final category under "Cause of Death by Age Group, y" should have been "Respiratory tumor," and the age groups of 18-49, 50-75, and  $\geq 75$ , along with their corresponding data, should have appeared directly underneath. We regret the error. This article was corrected online for typographical errors on April 11, 2007.