Thinking of ecstasy: neuropsychological aspects of ecstasy use

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Chapter 6

Long term neuropsychological effects of ecstasy in first generation ecstasy users

Thelma Schilt, Maarten W.J. Koeter, Johan P. Smal, Mathilde N. Gouwetor, Wim van den Brink, Ben Schmand

Submitted
Abstract

Background
Studies reporting ecstasy-induced serotonin-toxicity and (neuro)psychological dysfunctions have been conducted in young adults. Little is known about ecstasy-effects later in life, when serotonin levels and cognition decrease. This study aimed to assess whether negative effects of ecstasy add to age-related neuropsychological decline.

Methods
Attention, verbal and visual memory, visuospatial ability, self-reported depression, sensation-seeking and impulsivity, were assessed in middle-aged ecstasy users (n=17) and compared with ecstasy-naive polydrug users (matched for age, gender, intelligence and other drugs; n=16) and drug-naive controls (n=20).

Results
Ecstasy users performed significantly worse on a verbal memory task than polydrug users and drug-naives. Ecstasy users also differed significantly from drug-naives on measures of depression, sensation-seeking and impulsivity, but not from polydrug users.

Conclusion
A negative effect of ecstasy was found on verbal memory adding to age-related memory decline; no evidence was found for an interaction between effects of ecstasy use and age-related memory decline or mid-life depression.
Introduction

Between the mid 1980s and today, numerous studies have been conducted looking at the effects of the party drug ecstasy or +/- 3,4-methylenedioxymethamphetamine (MDMA) on the brain and brain functions in both animals and humans, providing converging evidence for damage to the brain serotonin system (see for reviews 191). Since serotonin is vital to mnemonic processes, cognition, mood, impulsivity and sensation-seeking, 37,147,167 many studies on the effects of ecstasy have focussed on these mental functions and behavioural characteristics. Deficits in neuropsychological functions have been reported repeatedly, with the most consistent finding being a decline in verbal memory in frequent ecstasy users 84,117,123. Findings about the effect of ecstasy use on mood, impulsivity or sensation-seeking are less conclusive and it has been argued that elevated levels of psychopathology are associated with polydrug use in general rather than specifically with the use of ecstasy (for reviews: 84,85,96).

All previous studies on the sustained (neuro)psychological effects of ecstasy have been performed in adolescents and young adults and little is known about the effect of ecstasy on memory and mood later in life. With increasing age, serotonin levels and the number of serotonin receptors gradually reduce 78,142,146,147. In addition, the interaction between serotonin and neurotransmitters like acetylcholine, seems to worsen with age 201. These and other biochemical changes are associated with age-related memory decline and depression 146. Alzheimer’s disease, with memory impairment as a main symptom, is also associated with reductions in 5-HT 122 and with a cholinergic-serotonergic imbalance. 72,146 While depressive symptoms seems to increase with age, impulsivity and sensation-seeking are thought to dwindle with age 275. Taken together, it is conceivable that frequent ecstasy use and its sustained effects on the serotonin system leads to memory impairments and depressive symptoms that are more outspoken than those observed in the normal ageing brain.

However, no research about the effects of frequent ecstasy use on the ageing brain has been done yet, for the simple reason that older ecstasy users barely exist. Ecstasy was introduced as a recreational drug only in the mid 1980s and was then used mainly by youngsters. In the current study we targeted this first generation of ecstasy users who were young adults in the 1980s and are now between 40 to 55 years old. A complication, however, in investigating the effects of ecstasy is that most ecstasy users also use other drugs. 85 Therefore, observed deficits could also be due to the use of psychotropic substances other than ecstasy or to a combination of other substances and ecstasy, rather than to the use of ecstasy per se. For example, various negative effects of cocaine, amphetamine, cannabis and alcohol on neuropsychological functions have been reported in the scientific literature (e.g. 131). In order to control for the use of other substances, we compared older, first generation ecstasy users with a group of older polydrug users and with an older group of drug-naive controls. We hypothesized that the negative effect of ecstasy on the serotonin system adds to the age-related decrease in serotonin, and that this should become visible in stronger verbal memory decrements and higher rates of depressive symptoms in older ecstasy users compared to older ecstasy-naive polydrug controls. Since our previous study on the specific effects of ecstasy in a polydrug sample,215 only revealed negative effects of ecstasy on verbal memory and not on other cognitive domains, we expect to find only verbal memory
deficits in the current study with older, first generation ecstasy users compared to older ecstasy-naive polydrug users.

**Methods and materials**

This study is a supplement to the larger Netherlands XTC Toxicity (NeXT) study, investigating long term ecstasy neurotoxicity 47.

**Participants and design**

In a cross-sectional design, a group of 20 moderate to heavy ecstasy users (minimum 240 tablets of ecstasy lifetime), 18 ecstasy-naive polydrug users (minimum 50 gram cocaine and/or amphetamine and/or more than 1000 joints cannabis lifetime, and not more than 15 tablets of ecstasy lifetime), and 20 drug-naive controls (social alcohol drinking and tobacco use allowed) were recruited for comparison of neuropsychological functions. Recruitment took place by means of website and newspaper advertisements; flyers; targeted site sampling at pubs, supermarkets, licensed liquor stores; and snowball sampling. Inclusion criteria for all subjects were: age between 39 and 55 years, and Dutch as native language. Exclusion criteria for all subjects were: a major systemic, neurological or neuropsychiatric disorder, and the use of psychotropic medications such as 5-HT reuptake inhibitors (SSRIs). Required abstinence from substances prior to examinations was at least 10 days for (illegal) drugs and at least four days for alcohol. On the day of testing, urinalysis was performed in the drug using groups: enzyme-multiplied immunoassay for amphetamines, ecstasy, opiates, cocaine, benzodiazepine, cannabis, and alcohol.

A detailed drug use history questionnaire was obtained from all subjects. Lifetime use of ecstasy (tablets), alcohol (units), cannabis (number of joints), amphetamines (grams), cocaine (grams), and tobacco (cigarettes), were measured. The Dutch Adult Reading Test (DART) was administered to estimate verbal intelligence for description of the sample and comparison of the groups. The DART was chosen because it is relatively insensitive to cognitive impairment caused by neurological disorders 217.

The study was approved by the local ethics committee. After a complete description of the study, all subjects gave written informed consent. Except for the drug-naive control group, subjects were paid € 40 for participation.

**Neuropsychological assessments**

The neuropsychological test battery in the current project includes tests that have shown to be sensitive to ecstasy-related neurotoxicity and tests related to functions or brain areas that are thought to be affected by ecstasy use (e.g. prefrontal cortex, occipital cortex, hippocampus).

*Attention / working memory*

- **PASAT (Paced Auditory Serial Addition Test)** 94: Subjects have to add numbers to a preceding number presented by a recorded male voice. Numbers are presented at a speed of 1.6 sec per digit. The outcome parameter is the total number of correct calculations per trial (max. 60).
• Digit Span\textsuperscript{267}: Subjects have to repeat a series of digits read aloud by the examiner; first in forward order, than in backward order. The outcome parameter is the number of correctly reproduced series of digits (max. 28).

\textit{Verbal Memory}

• A Dutch version of the Rey Auditory Verbal Learning Test (RAVLT)\textsuperscript{195,250}: Subjects have to memorize a series of 15 nouns in five learning trials. Immediate recall is tested after each trial. The outcome parameter is the sum of correctly reproduced words over five trials (max. 75). Delayed recall is measured after 20 minutes. Outcome parameter is total number of correctly reproduced words (max. 15).

\textit{Visual Memory}

• The Memory for Designs test\textsuperscript{89}: The original test with 14 geometrical figures was split into two separate tests to obtain two parallel versions. The mode of administration was adapted to mimic the RAVLT. After presentation of seven figures during five seconds each, subjects have to draw the figures from memory. This is repeated five times. Outcome parameter is the number of correctly reproduced elements (max. 3 points per figure) in five learning trials (max. 105). Delayed reproduction is measured after 15 minutes; outcome parameter is the number of correctly reproduced elements (max. 21).

\textit{Visuospatial functioning}

• A computerized and adapted version of the Judgment of Line Orientation (JoLO)\textsuperscript{12}: The JoLO requires subjects to identify which 2 of 11 lines presented in a semicircular array have the same orientation in a two-dimensional space as two target lines. The original JoLO was made more difficult to reduce its ceiling-effect and to increase its sensitivity to brain dysfunction. The target lines in our assessments were only shown for one second, directly followed by the 11 lines. The outcome parameter is the number of correctly judged pairs of lines (max 30).

• The Mental Rotation Task (MRT)\textsuperscript{228}: Participants are presented with 20 pairs of block designs drawn from different points of view. They have to judge whether pairs of designs are identical or different. Outcome parameter is the total number of correct answers in 6 minutes (max. 40).

\textbf{Self-report questionnaires}

\textit{Depressive symptoms}

• The Beck Depression Inventory (BDI) was used to assess current depressive symptoms\textsuperscript{11}. The BDI consists of 21 items that measures characteristic attitudes of depression in the week prior to assessment; higher scores indicate more depressive symptoms. The BDI showed high reliability and validity\textsuperscript{10,22}.

\textit{Impulsivity}

• Impulsivity was assessed with The Dutch version of the Barratt Impulsiveness Scale (BIS-11)\textsuperscript{178}. The Dutch BIS-11 contains 31 self-report items that have to be scored from 1 to 4. The total BIS-score was used for the purpose of this study. The BIS-11 has adequate reliability.

\textit{Sensation Seeking}

• Sensation seeking was measured with the Spannings Behoeftes Lijst (SBL)\textsuperscript{62,63}, a Dutch adaptation of the American Sensation Seeking Scale\textsuperscript{276}. The SBL contains 51 sensation seeking items and 16 filler items, on a five-point Likert scale. The total general
sensation seeking score was calculated as the sum of the four subscale scores each divided by its number of items. The SBL has proven to be a reliable measure for various aspects of sensation seeking in research populations 62,63.

**Statistical analyses**

*Characteristics of the sample*

Differences in age and DART-IQ between the groups were analysed with one-way analyses of variance (ANOVA), with Gabriel’s post hoc procedures where appropriate. Group differences in gender were investigated using a Chi-Square test. Differences in not normally distributed drug use variables between the groups were investigated with non-parametric Kruskall-Wallis tests and Mann-Whitney post hoc analyses.

*Neuropsychological assessment*

Differences between the three groups in neuropsychological test scores were analysed using univariate ANCOVA, with Group (ecstasy/polydrug/drug-naive) as between group factor. Because gender, age and DART-IQ were correlated with the cognitive outcome parameters, these variables were added as covariates.

In order to test whether the amount of ecstasy use was related to neuropsychological performance, we calculated Spearman correlations between total amount of ecstasy tablets and cognition scores in the group of ecstasy users.

*Self-report questionnaires*

Differences between the three groups in self-reported depression and impulsivity were analysed with non-parametric Kruskall-Wallis tests and Mann-Whitney post hoc analyses, because these variables were not normally distributed. Sensation seeking was analysed using univariate ANCOVA, with Group (ecstasy/polydrug/drug-naive) as between group factor.

All analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Given the explicit hypotheses about the effects of heavy ecstasy use on cognitive functions and depressive symptoms, significance tests were one-sided (α=0.10). Because we did not have a specific hypothesis about the effects of ecstasy on self-reported impulsivity and sensation-seeking (see introduction), the scores on SBL and BIS questionnaires were tested two-sided (α=0.05). Bonferroni corrections for multiple comparisons were applied for the number of group comparisons: ecstasy versus polydrug, and ecstasy versus drug-naive with alpha set at 0.10/2=0.05 for cognitive tests and BDI, and at 0.05/2=0.025 for the SBL ad BIS.

<table>
<thead>
<tr>
<th></th>
<th>Ecstasy (n=17)</th>
<th>Polydrug (n=16)</th>
<th>Drug-naive (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
<td>10/7</td>
<td>7/9</td>
<td>10/10</td>
</tr>
<tr>
<td>Age</td>
<td>45.6±5.3</td>
<td>45.0±4.5</td>
<td>46.3±3.6</td>
</tr>
<tr>
<td>IQ (DART score)</td>
<td>103±11</td>
<td>107±12</td>
<td>103±12</td>
</tr>
</tbody>
</table>
Long term effects of ecstasy in first generation ecstasy users

Results

Characteristics of the sample
Urine drug screening revealed one subject positive on benzodiazepines and four subjects positive on cannabis. These five subjects were excluded from the analyses, leaving 17 ecstasy users, 16 polydrug users, and 20 drug-naive controls for statistical analyses. The three groups did not differ significantly in DART-IQ ($F_{2,50}=0.53; P=0.59$), age ($F_{2,50}=0.39; P=0.68$) and gender distribution ($\chi^2_{4}=0.76; P=0.68$) (descriptives shown in Table 1). Drug use patterns and group comparisons in drug use are presented in Table 2. As a consequence of the inclusion criteria, ecstasy use was infrequent and significantly lower in the polydrug group than in the ecstasy group. No significant differences existed between the ecstasy group and the polydrug group in the lifetime exposure to amphetamines, cocaine, cannabis, alcohol, and tobacco. The drug-naive group by definition did not use illegal drugs and used significantly less alcohol and tobacco than the ecstasy group.

Table 2 Comparison of drug use characteristics of the three groups [mean ± SD]

<table>
<thead>
<tr>
<th></th>
<th>Ecstasy users n=17</th>
<th>Polydrug users n=17</th>
<th>Drug-naive users n=20</th>
<th>XTC vs. polydrug</th>
<th>XTC vs. drugnaive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecstasy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablets lifetime</td>
<td>888±678</td>
<td>9±6</td>
<td>-</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>Weeks since last use</td>
<td>76±119</td>
<td>406±212</td>
<td>-</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>n=13</td>
<td>n=10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grams lifetime</td>
<td>318±517</td>
<td>287±799</td>
<td>-</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Cocaine</td>
<td>n=16</td>
<td>n=16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grams lifetime</td>
<td>530±753</td>
<td>290±525</td>
<td>-</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Cannabis</td>
<td>n=16</td>
<td>n=15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joints lifetime</td>
<td>7436±10747</td>
<td>9579±9395</td>
<td>-</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>n=17</td>
<td>n=16</td>
<td>n=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Units lifetime</td>
<td>31018±32418</td>
<td>39703±29362</td>
<td>11190±11128</td>
<td>ns</td>
<td>0.024</td>
</tr>
<tr>
<td>Tobacco</td>
<td>n=14</td>
<td>n=15</td>
<td>n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes lifetime</td>
<td>96270±62774</td>
<td>144203±177397</td>
<td>61056±60853</td>
<td>ns</td>
<td>0.012</td>
</tr>
</tbody>
</table>

ns = not significant

Neuropsychological testing
Descriptive data and group comparisons of neuropsychological tests are depicted in Table 3. Univariate ANCOVA with neuropsychological test scores as dependent variables, and gender, age and DART-IQ as covariates demonstrated a significant group effect on RAVLT immediate recall and RAVLT delayed recall. Post hoc analyses showed that the RAVLT immediate and delayed recall scores of the ecstasy group were significantly lower than those of the polydrug group and the drug-naive group. Adding scores on the BDI, BIS and SBL as covariates did not change the results.

Self-report questionnaires
Groups differed significantly on the BDI, BIS and the SBL. Post hoc analyses showed that all self-report questionnaire scores were significantly higher in the ecstasy group.
compared to the drug-naives, but not compared to the polydrug group, indicating the absence of a specific effect of ecstasy use on depression, impulsivity and sensation-seeking.

**Relationship between outcome parameters, amount of ecstasy use, and abstinence duration**

Within the group of ecstasy users, no significant dose-response relationship was found between the cumulative number of ecstasy tablets and RAVLT immediate recall (Spearman’s rho=0.17; \( P=0.25 \)) or RAVLT delayed recall (Spearman’s rho=0.28; \( P=0.14 \)). Also no significant associations were found between verbal memory performance and abstinence period (RAVLT immediate recall: Spearman’s rho=0.14; \( P=0.30 \); RAVLT delayed recall: Spearman’s rho=0.24; \( P=0.17 \)).

To further explore whether ex-ecstasy users improve after quitting the use of ecstasy, we divided the group of ecstasy users in current ecstasy users (last use < 6 months; \( n=11 \)) and ex-ecstasy users (last use > 18 months; \( n=6 \)). Ex-ecstasy users recalled 45.5 (s.d.=11.3) words on the RAVLT immediate recall and 9.8 (s.d.=3.2) words on the RAVLT delayed recall, whereas current ecstasy users recalled 43.3 (s.d.=6.4) and 7.7 (s.d.=2.4) words on immediate and delayed recall respectively. Univariate ANCOVA with test score as dependent variable, group (current use/ex-use) as independent variable, and age, gender, DART-IQ and number of ecstasy tablets lifetime (log transformed) as covariates, showed that the differences in test scores were not significant (\( F_{1,11}=0.08; \ P=0.78 \) and \( F_{1,11}=1.79; \ P=0.21 \), respectively).

### Table 3 Comparison of cognitive task performance and psychopathology questionnaires between the three groups

<table>
<thead>
<tr>
<th></th>
<th>Raw scores mean ± SD</th>
<th>ANCOVA</th>
<th>Post-hoc test (significance ( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ecstasy (( n=17 ))</td>
<td>Polydrug (( n=16 ))</td>
<td>Drug-naive (( n=20 ))</td>
</tr>
<tr>
<td>Attention/Working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span (max 28 series)*</td>
<td>14.4±2.3</td>
<td>17.3±3.3</td>
<td>16.8±4.3</td>
</tr>
<tr>
<td>PASAT1.6 (max 60 hits)*</td>
<td>35.8±8.7</td>
<td>38.2±7.7</td>
<td>41.4±10.5</td>
</tr>
<tr>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT immediate (max 75 words)*</td>
<td>44.1±8.2</td>
<td>50.9±9.8</td>
<td>52.2±5.4</td>
</tr>
<tr>
<td>RAVLT delayed (max 15 words)*</td>
<td>8.5±2.8</td>
<td>10.9±2.8</td>
<td>11.4±2.2</td>
</tr>
<tr>
<td>Visual memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MfD immediate (max 105 elements)*</td>
<td>71.6±17.4</td>
<td>78.5±18.9</td>
<td>74.6±16.2</td>
</tr>
<tr>
<td>MfD delayed (max 21 elements)*</td>
<td>18.3±2.9</td>
<td>19.0±3.2</td>
<td>18.8±2.9</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JOLO (max 30 pairs)*</td>
<td>20.7±3.8</td>
<td>20.7±4.5</td>
<td>22.7±2.9</td>
</tr>
<tr>
<td>MRT (max 40 hits)*</td>
<td>18.5±6.5</td>
<td>16.7±6.1</td>
<td>20.3±4.8</td>
</tr>
<tr>
<td>Mood/Impulsivity/Sensation seeking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>6.9±5.8</td>
<td>7.8±7.7</td>
<td>2.7±2.1</td>
</tr>
<tr>
<td>Barratt Impulsiveness Scale</td>
<td>69.5±10.0</td>
<td>69.4±8.1</td>
<td>59.4±6.7</td>
</tr>
<tr>
<td>Sensation Seeking Scale</td>
<td>12.9±2.1</td>
<td>11.9±1.9</td>
<td>9.7±1.5</td>
</tr>
</tbody>
</table>

*corrected for age, IQ and gender

#after correction for BDI, BIS and SBL
Discussion

Most human studies on the neuropsychological effects of ecstasy use were conducted in adolescents and young adults. The current study investigated the effects of ecstasy use on neuropsychological functions in a middle-aged sample: the first generation of recreational ecstasy users (mean age 45.5, s.d.=5.3). The results showed that they performed significantly worse on a verbal memory task compared to ecstasy-naive polydrug users (matched for age, verbal intelligence and substance use other than ecstasy) and drug-naive controls. After correction for differences in depression, impulsivity and sensation seeking these differences remained unchanged. Middle-aged ecstasy polydrug users showed more depressive symptoms, and higher impulsivity and sensation-seeking than drug-naive controls, but they did not differ from ecstasy-naive polydrug users.

Effects of ecstasy on verbal memory

Our findings of a decreased verbal memory performance in older ecstasy users are in line with many other studies reporting decreased memory functioning in young ecstasy users (for review and meta-analyses: 84,117,123,255). Assuming that the negative effects of ecstasy increase with ageing, one would expect to find greater deficits in older ecstasy users compared to younger ecstasy users, leading to larger effect sizes in the current study in middle-aged subjects compared to the effect sizes in studies including younger subjects. In the current study in middle-aged subjects, differences in verbal memory performance between ecstasy users and polydrug users were substantial (Cohen’s d=0.75 for verbal immediate learning and d=0.84 for delayed recall). These effect sizes are difficult to compare with effect sizes in other studies, because studies including a polydrug group with a comparable amount of other drug use as in the ecstasy group hardly exist. Several ecstasy studies tried to minimize the confounding effects of other drugs either by excluding users with concomitant drug use other than ecstasy or by including a polydrug group with drug use patterns comparable to the ecstasy group. However, a close match appeared to be difficult. Laws and Kokkalis (2007) evaluated six studies in which verbal memory performance in ecstasy users was compared with drug-naive controls and calculated an effect size of d = 1.06 123. In our study with middle-aged participants, the effect size based on performance of ecstasy users versus drug-naive controls was only slightly larger (d = 1.14 with Hedges’d correction for small sample sizes) 102. In some studies that were evaluated by Verbaten (2003) ecstasy users were compared with ecstasy-naive subjects who also used other drugs, but the amount of drug use always appeared to be lower in the control group than in the ecstasy users 255. Effect sizes of four studies in younger populations using the same verbal memory test as in our study, ranged between 0.92 and 1.48 for immediate recall and between 0.29 and 1.25 for delayed recall. The effect sizes in our study are well within in range of effect sizes summarized by Verbaten (2003). A meta-analysis of the effects of ecstasy on cognition, which was based on 12 studies, showed an effect size of d=0.85 for verbal memory 117. However, across those samples, the amount of ecstasy use, abstention periods, and the use of other drugs varied substantially. Some of these studies included controls who used other drugs like cannabis or amphetamines, but the amount of drug use was always lower in controls compared to ecstasy users. Since we have compared middle-aged abstinent ecstasy users with controls who used similar amounts of drugs other than ecstasy, the effect size of 0.84 in our study
is probably more striking. Despite this relatively large effect size of ecstasy use on verbal memory in middle-aged subjects, it seems too early to conclude that the harmful effect of ecstasy on verbal memory is stronger in middle-aged subjects than in younger subjects, and therefore it is too early too conclude that the negative effect of ecstasy on memory increases with age, i.e. the current study and the comparison with other studies in youngsters suggest that the effects of ecstasy use and normal ageing on memory are additive rather than multiplicative. It is conceivable that the subjects in the current study (39-55 years) were not old enough to allow the detection of an age by ecstasy (multiplicative) interaction. Something similar has been asserted for chronic alcoholism. To illustrate, also in chronic alcoholism, an age by alcohol interaction in neuropsychological studies is not consistently found. Because most studies about the effects of alcohol on cognition included subjects between 30 and 60 years old, and because brain imaging studies clearly show increasing negative effects of alcohol on brain structures with ageing (e.g. 182), it is postulated that ageing only plays a role beyond the age of sixty. Therefore, follow-up of the current study sample may provide better information about potential age by ecstasy interactions.

Dose- response relationship
We failed to find a relationship between verbal memory performance and lifetime amount of ecstasy tablets. This is at odds with some other studies, including our own study in younger ecstasy users, but it is in agreement with a meta-analysis of ecstasy studies by Verbaten (2003). Perhaps it does not matter how much ecstasy is used above a certain threshold. Another explanation for the absence of a dose-response relationship might be that individuals differ in genetic vulnerability, or that the study samples (including our own) have been too small to detect a dose-response relationship.

In the current study, no association was found between verbal memory performance and the duration since last ecstasy use (abstention period). Moreover, negative effects of ecstasy on verbal memory did not differ between current ecstasy users (ecstasy use within the last 6 months) and long term abstainers (no ecstasy use in the past 1.5 years, range 1.5-8 years). This may indicate that verbal memory decrements related to ecstasy use are not reversible; a finding that is in accordance with a study of Reneman c.s. that found sustained verbal memory deficits after an abstention period of one year.

Effects of ecstasy on psychopathological symptoms
In the current study, we found elevated psychopathology scores in middle-aged ecstasy users compared to drug-naive subjects, but not compared to polydrug users. It seems that depressive symptoms, impulsivity and sensation-seeking are related to polydrug use in general and not specifically to the use of ecstasy. This conclusion has also been proposed by others. However, it remains unclear whether psychopathology predisposes to the use of drugs, or whether psychopathology is a consequence of using drugs.

Strengths and limitations
The study has both strengths and limitations. The most important strengths of the study are the good match between the groups of heavy ecstasy users and the group of polydrug users, and the broad range of neuropsychological and self-report measures that was
available for all subjects. We are also well aware of the limitations of the current study. First of all, inherent to the cross-sectional design, pre-morbid differences cannot be excluded. The subjects were recruited by various methods, which may have led to selection bias. A second limitation is that we had to rely on self-reported drug use histories. In addition, there was no certainty about the purity of ecstasy tablets that were used by the subjects in this study. In the 1980s, when most of our subjects started with ecstasy, there was no control on the content of ecstasy tablets yet. By 2004, drug monitoring services in The Netherlands showed that the percentage of ecstasy tablets containing MDMA, MDEA and/or MDA as their main component was 97.5%. In 1997 however, this percentage was noticeably lower: 65.9%^{240}. Furthermore, although acute effects of the psychoactive substances were minimised by the requirement of a minimal abstention period of 10 days (which turned out to be at least two weeks for 98% of the participants), influence of recent drug use on the memory results cannot be completely excluded. Finally, we did not investigate environmental circumstances in which the drugs were used or simultaneous use of different drugs, while influence of these factors may play an important role in the neuropsychological damage of ecstasy^{173}.

**Conclusion**

In conclusion, this study confirms a negative effect of ecstasy use on verbal memory that adds to age-related memory decline, but does not provide sufficient support for the hypothesis that ecstasy use and age-related memory decline and late-life depression are multiplicative. Further research, including studies with larger sample sizes and with subjects older than 60 years, are needed to better test whether and how ecstasy use adds to the age-related decrease in serotonin levels. Both neuropsychological assessments and brain imaging techniques should be used in these studies.

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