Does Ecstasy cause memory deficits?
A review of studies of memory function in Ecstasy users

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An increasing number of scientific studies have recently been published that all report memory deficits of some sort in Ecstasy users. The media have made a lot of fuss about these findings, but often in superficial and sensational ways, leaving many concerned Ecstasy users and other people alone with their need for competent and balanced information. I’d like to address these concerns by attempting a critical review of these studies that is, so I hope, accessible to interested readers outside the scientific community. The 15 studies listed below will be reviewed. These practically exhaust all published research that has been done on the subject to date.¹ For the sake of brevity and legibility, I’ll refer to these papers by the name of the first author (e.g. „Morgan found that…“), on the understanding that all co-workers are meant to be included.

I will proceed as follows: I’ll start by giving some background on why these studies are methodologically problematic in general, then provide a brief review of each of them, summarize the data and discuss several possible explanations for the findings, thus offering a tentative answer to the question in the title. I will conclude by outlining some consequences for the recreational and clinical use of MDMA.


¹ Case reports are not included here, as well as three clinical studies concerned with the topic: Thomasius has recently conducted a large study in 107 Ecstasy users in Hamburg, Germany. It will be published in a forthcoming book that is not available yet. A media report by the German magazin „Stern“ claims that the study shows memory and other impairments. Curran and Travill (Addiction 92:821-831, 1997) have compared verbal recall in Ecstasy users and alcohol drinkers during a Saturday night dance while on-drug, as well as one and four days later. They found overall lower scores in Ecstasy users, but the statistical analysis used does not allow us to distinguish whether this difference is due only to the Ecstasy intoxication on Saturday or whether it was also present on day one and four. Thus, the study cannot address the issue of memory performance in drug-free Ecstasy users. Finally, Dafters (Psychopharmacology 145:82-90, 1999) tested cognitive performance in Ecstasy users, but did not include a control group, so that no conclusions can be drawn regarding potentially abnormal scores.
Why a causal effect of Ecstasy use on memory is difficult to prove

The reason why reports of memory impairment in Ecstasy users are still a matter of debate and disagreement is that studies comparing Ecstasy users with Ecstasy-naïve control subjects face a number of substantial methodological problems. To see this, let us first imagine an idealized experiment to test whether Ecstasy use has indeed detrimental effects on memory. We take a large number of subjects, all drug-naïve, and split them into two groups that do not differ with regard to age, sex, physical and psychological constitution, intelligence, education, socio-economic status, lifestyle, etc. Both groups are extensively tested for their memory performance. Then one group receives regular monthly or weekly doses of Ecstasy for say, a year, and the other group is given placebo instead. During this time, all subjects are instructed to avoid anything that may interfere with their memory skills. After the year has passed, both groups are again tested for their memory performance. If Ecstasy impairs memory, then the Ecstasy group will show reduced memory scores over time while the placebo group won’t. Since both groups were matched in all possible respects except their use of Ecstasy, the drug remains as the most likely cause of the observed memory deficits.

An experiment like this would come as close as possible to a „proof“ of the memory-impairing effect of Ecstasy. But such a study design has not been used due to widespread concerns about the ethicality of administering repeated doses of a potentially neurotoxic substance such as Ecstasy/MDMA to healthy humans. Thus, existing research has resorted to much less scientifically satisfactory study designs: test performance of a group of Ecstasy users is compared with that of a group of Ecstasy-naïve controls at a certain point in time. There is no data available on how Ecstasy users performed before they started taking Ecstasy, therefore it is not possible to compare memory scores before and after Ecstasy like it was in our idealized study. Instead, memory is compared between two groups, one that uses Ecstasy and one that doesn’t. But since there are likely to be many other differences between these groups apart from their Ecstasy use, worse memory performance in the Ecstasy group may in fact be due to some of these other differences and not to

2 A semantic clarification is in place: There will be plenty of talk about „impaired“ memory or memory „impairments“ in this paper. In the present context, these terms are only meant to indicate that Ecstasy users performed worse than control subjects in some cognitive tests and should not be taken to imply an impairment of Ecstasy users’ normal functioning in their everyday work and social lives.

3 In what follows, when I talk about „Ecstasy users“ without further specification, I have in mind someone who goes or has been going to clubs and raves several times a month for more than a year, each time consuming one or more Ecstasy pills. This, at least for the European countries, appears to be the typical, most widespread pattern of Ecstasy use. Towards the end, I will say something about differential implications of heavy versus moderate use as well as low-frequency clinical-therapeutic uses of MDMA.

4 One interesting exception is the case of fenfluramine, which is similar in many ways to MDMA: it is chemically related to MDMA, produces the release of the neurotransmitter serotonin (5-HT), and is neurotoxic to 5-HT neurons, even twice as much as MDMA by some estimates. Despite its neurotoxic potential, fenfluramine has been available by prescription as an appetite suppressant for the last 30 years. Only recently it has been withdrawn from the market, but, ironically, not because of its neurotoxic potential.
Ecstasy itself. To reduce the confounding effect of these differences, researchers therefore attempt to match the two groups in as many respects as possible that may have an influence on memory performance. The most common matching variables are age and sex. For the present case, several further matching variables are of great importance: level of education, the use of drugs other than Ecstasy/MDMA, lifestyle, and psychiatric history. I’ll say a few words about each of these.

Doubtlessly, high education is often associated with high cognitive (including memory) skills. A person with high education may therefore score higher on a memory task than someone with lower education. Thus, if memory is assessed in Ecstasy users with lower education than the control group, users may score worse simply by virtue of their lower educational level, without Ecstasy entering into it. As we will see, this is in fact a problem in some of the reviewed studies.

Most Ecstasy users are polydrug users, which raises the possibility that one or several of these other drugs are responsible for worse memory performance. To control for this possibility, researchers try to find control subjects who have consumed similar amounts of non-MDMA drugs as the user group. This is not easy, since many people who use these other drugs also use Ecstasy, but some studies managed to find suitable controls.

Lifestyle is another factor related to cognitive performance. Ecstasy users’ way of life, which typically includes periods of excessive physical exercise (dancing) and audiovisual stimulation at raves, insufficient rest and recuperation and diminished food intake, may have detrimental effects on memory. Since this way of life is practically exclusive to Ecstasy users, it is very difficult for researchers to find a control group entertaining the same lifestyle without concomitant use of Ecstasy. None of the existing studies except one has made an effort to separate possible effects of Ecstasy from lifestyle-related effects on memory, which provides a further obstacle to the interpretation of current findings.

There may also be relevant differences between the groups that go further back in time. For example, Ecstasy users, as opposed to controls, may have suffered from psychiatric disturbances before they started to take Ecstasy. These disturbances may have a negative effect on memory which could explain the lower memory scores. In this case, not the use of Ecstasy but a pre-existing psychiatric difference would account for the observed differences in test performance. In fact, it is perfectly plausible that these very psychiatric disturbances could be the motivation (not necessarily conscious) for the use of Ecstasy – as a self-medication in the attempt to treat the adverse psychiatric condition. This self-medication hypothesis cannot be addressed in principle by study designs using between-group comparisons. However, careful subject screening procedures that serve to exclude applicants with a known history of psychiatric disorders are common practice in the present studies. These procedures usually do a good job in minimizing possible confounding effects of pre-existing psychiatric disturbances on test scores. Note, though, that subclinical psychiatric conditions cannot be detected and excluded in this way.

A final issue concerns sample size. The larger the number of subjects included in a study, the more reliable is the statistical data analysis that produces the results.

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5 When I talk about „worse“ performance, or „lower“ scores without specifying a reference, I always refer to studies of Ecstasy users scoring lower or performing worse than the corresponding control subjects.

6 Two points may be worth mentioning: First, Ecstasy tablets are often chemically impure, i.e., do not always contain MDMA alone (sometimes no MDMA at all). Thus, even someone who restricts drug use to Ecstasy will inevitably entertain some level of polydrug use. Second, not even a perfect matching for the use of non-MDMA drugs could control for the effects of pharmacological interactions between Ecstasy and other drugs, since these exclusively occur in Ecstasy users.
Thus, large sample sizes are desirable in scientific studies, particularly those based on between-group statistical comparisons. In practice, however, sample size is not only a matter of statistical consideration, but also of the time available for a study and pressures for publication, so that some studies rely on small samples only. The presently discussed studies show a considerable variation in the number of subjects tested.

**Review of studies on Ecstasy use and memory**


Nine polydrug Ecstasy users with an estimated average lifetime consumption of 99 times 135 mg Ecstasy and an average of 66 days of abstinence from the drug were tested with the paragraph and figure recall sections of the Wechsler Memory Scale. Subjects were a subgroup of the 24 individuals who took part in a prior study by Ricaurte et al (Ann. NY. Acad. Sci. 600:699-710, 1990) that reported lower than normal 5-HIAA levels in the cerebrospinal fluid (CSF) in these users. (MAPS helped in subject selection and funded the neuropsychological testing on which the Krystal study is based.) It is important to note that the nine participants in Krystal’s study were preselected out of the larger sample of Ricaurte’s study for low CSF 5-HIAA levels. The rationale for this decision was the idea that if there were neuropsychological problems in Ecstasy users at all, they would be most prominent in users with presumably the lowest serotonin levels. If, on the other hand, even those users showed no impairments, then there might simply be no problem to worry about.

No control group was included. Instead, test scores were compared to published norm values. Some users showed mild-to-moderate impairments in tests of verbal and visual memory, but not in other neuropsychological tests that were also applied. Memory scores did not correlate with lifetime use of Ecstasy.

Methodologically, this study does not match up to the standards of current research in this area. It faces limitations that strongly restrict the scope of its findings. The use of published control data precluded matching for sex, education, and general drug use (age matching was possible). Most Ecstasy users had significant personal and/or family histories of substance abuse and affective disorders that may have affected their performance. Further, many Ecstasy users were administered tryptophan about three hours prior to memory testing (tryptophan is the amino acid precursor of serotonin in the human brain). Although researchers waited until behavioral and neuroendocrine responses to tryptophan had returned to baseline, it cannot be completely ruled out that the tryptophan challenge influenced memory scores. Another potential influence on memory scores may have come from travel fatigue. Many of the subjects in this study flew in from other states (e.g., California, which is three time zones away) the day before or the day of the study. Finally, even

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7 5-HIAA is the name of the primary metabolite of serotonin. 5-HIAA levels in the cerebrospinal fluid are taken to be an indicator for brain levels of serotonin, and thus possibly for the integrity of the serotonergic system.

8 In a personal letter, the neuropsychologist who conducted the memory tests mentioned to Rick Doblin, that "...the memory findings [...] are not uncommon in patients especially when anxiety, fatigue, or difficulties in attention or concentration exist in the individual. It is quite possible that the large number of impaired scores on the paragraph measures in this population are related to travel fatigue, being in a new environment, or being stressed in some way following the challenge testing that each subject performed" (Rick Doblin, personal communication). Unfortunately, these possible explanations are not discussed in the actual paper.
if memory findings are explained by Ecstasy use, the subject sample is not representative of the average Ecstasy user due to the above-mentioned preselection bias. The results may at best hold for a subgroup of Ecstasy users with particularly low levels of cerebrospinal 5-HIAA. For all these reasons, the Krystal study cannot make a strong case for a connection between Ecstasy use and memory impairments. However, it has to be credited for being the earliest published work to draw attention to this connection and prompting the plethora of subsequent research.


and


Six years after Krystal, Parrott published two similarly designed studies on the putative link between Ecstasy and memory. Both examined groups of novice (1-9 times Ecstasy) and regular (>9 times Ecstasy) users and a Ecstasy-naïve control group. Both used tests of immediate verbal recall, where subjects have to repeat from memory a list of words that are presented to them. Parrott (a) also measured delayed verbal recall, where subjects have to recall the same list of words after a delay.

Parrott (a) included ten subjects in each study group and found that both novice and regular users performed worse than controls in both immediate and delayed verbal recall. The difference was in the range of 35% (1-2 standard deviations (SDs)). No differences were found in other neuropsychological tests.

The problem with this study is that the subject description is incomplete. No information is given on education, time of abstinence from Ecstasy at testing and the use of non-MDMA drugs. Thus, it can be assumed there was no matching for education and use of other drugs. Also, sex is only well-matched between novice users and controls but not between the other groups (this problem is removed in Parrott (b)).

Parrott (b) included an increased number of 15 subjects in each study group. The experimental protocol is different from Parrott (a). Memory was assessed on four different days. First, at the subjects' home or in the laboratory; second, at a dance club, while users were on Ecstasy (controls were not); third, two days after; and fourth, seven days after. The main finding is that immediate verbal recall was significantly worse in regular users compared to controls at all time points, and also worse in novice users except two days after clubbing. The magnitude of these differences was up to 20% (no SDs given).

Parrott (b) confirms and gives more weight to the findings of Parrott (a). It has, however, the same weakness in that no information is given on education, the use of non-MDMA drugs and time of abstinence from Ecstasy prior to testing. These are confounding factors for both studies. It is not unlikely that the Ecstasy users consumed more other drugs than the controls, which could partly account for the observed differences (in Parrott (b), the discussion states that controls and users took similar amounts of other drugs, but no data are given).
Twenty-four Ecstasy users and 24 controls were studied. On average, users had taken 60 times 158 mg Ecstasy and were 30 days (= median value) abstinent at the time of the experiments. They had used more non-MDMA drugs than controls, in particular cannabis, cocaine, hallucinogens, amphetamines and benzodiazepines. Controls had two years more education than users (17 v 15 years).

Several memory tests were applied: The Wechsler Memory Scale (as in Krystal’s study), an auditory verbal learning test measuring immediate and delayed verbal recall (as in Parrott’s studies) and a test for visual memory.

The authors report no difference in memory function between the groups when not taking into account the average monthly dose of Ecstasy. However, when doing so, increasing monthly doses were associated with decreasing immediate and delayed verbal recall and decreasing delayed visual memory. In the discussion section of the paper, it is added that „only subjects with high exposure to Ecstasy had memory deficits“, but the statistics supporting this are not shown. The authors also found significant correlations between immediate/delayed verbal recall and monthly Ecstasy dose, however not with lifetime dose or duration of Ecstasy use. The study further found lower levels of CSF 5-HIAA in the Ecstasy users and a positive correlation of CSF 5-HIAA levels with visual memory scores and with monthly dose of Ecstasy. Ecstasy users had lower verbal intelligence than controls.

This study strikes me as problematic. Not primarily because of the imperfect matching for education and for the use of non-MDMA drugs (although these are not unimportant limitations), but because of the way the data is presented. In the title and throughout the paper the authors talk of memory impairments, suggesting that a statistical comparison between the two study groups had revealed lower memory scores in the Ecstasy group. However, this does not seem to be the case. The only statement in the results section regarding possible group differences says that „...when memory function in the two groups was compared without taking the average monthly MDMA dose into account, differences were not found.“ I take this to mean that a simple, straightforward statistical comparison between the memory scores of the two groups revealed no impairment in Ecstasy users. When the authors did include monthly dose into their statistical analysis, associations were found between dose and memory function. But the finding that increasing monthly doses of Ecstasy are associated with decreasing memory performance in the user group is unrelated to the question whether Ecstasy users on average have lower memory scores than the control group. It would also be compatible with the possibility that Ecstasy users have higher or equal memory performance. In the discussion section, the authors partly clarify this issue by stating that „...only subjects with high total monthly MDMA dosages were found to have memory deficits in the current study.“ However, the relevant data are not shown in the paper.

Upon personal inquiry, Bolla kindly provided a table of these data listing means and standard deviations of memory scores of the Ecstasy and the control group, as well as of two subgroups, one of heavy Ecstasy users (> 440 mg per month, n=11) and the other of all other subjects (i.e., controls, n=24, and „non-heavy“

Note that this does not represent a new finding. The subject group in Bolla’s study was the same as in the previous study by Ricaurte et al (Ann. NY. Acad. Sci. 600:699-710, 1990), from which, you may recall, a subgroup of nine subjects was selected for the Krystal et al study reviewed here. Thus, Bolla et al have not assessed CSF 5-HIAA levels in an independent group of Ecstasy users but merely re-reported an earlier finding from the Ricaurte et al study.
users, n=13). Since no statistics are given, I performed simple t-tests based on means, standard deviations and number of subjects. This analysis essentially confirms the statements made in the paper. It shows no significant differences in memory performance between the Ecstasy and the control group, although the former consistently scored about 10% (0.5 SDs) lower in all memory tasks. The only exception is logical memory, where the Ecstasy group scored significantly lower than controls in both immediate and delayed memory. When comparing heavy Ecstasy users with all other subjects, the heavy users showed significantly worse verbal memory function, while the non-heavy users (who had consumed < 440 mg per month) had similar scores as the controls.

Where does that leave us? In my understanding, the major finding of this study is that increasing monthly doses of Ecstasy are associated with decreasing memory performance. It is certainly a serious possibility that these decrements may be a dose-related consequence of Ecstasy use, particularly since increasing monthly doses of Ecstasy were also correlated with decreasing 5-HIAA levels, which in turn were correlated with decreasing performance in visual memory. Furthermore, the generally lower scores and the significantly (on my analysis) lower scores for logical memory are certainly in line with the other studies. Contrary to its title, however, the paper does not demonstrate generally impaired memory in the Ecstasy group, and the data presentation is insufficient.


This study compared 150 Ecstasy users who had, for various reasons, visited the Drug Addiction Centre in Padua, Italy, with 20 control subjects. The users had taken Ecstasy 11 times on average (range 1 – 125 times) and had used other drugs such as cannabis, cocaine, opiates, LSD, nitrites, alcohol and benzodiazepines, while controls were completely drug-naïve. It is reported that groups were matched for age and education, although age and educational level are not given for the control group. Nothing is said about matching for sex, and the sex ratio for the control group is not given (it must be assumed that there is no matching). Also, it is not reported for how long users were drug-abstinent prior to being tested.

The Rivermead Behavioral Memory Test (RBMT) was used to assess memory. A Tower of London test was applied to test planning and strategic abilities associated with frontal executive function. A comprehensive psychiatric assessment was obtained from all subjects.

Ecstasy users scored significantly lower than controls in the RBMT. They also performed worse in the Tower of London test. Unfortunately, neither the magnitude of these differences nor a specification of the sub-tests of the RBMT that showed differences is reported.

This study has more the character of a comprehensive clinical-epidemiological description of a large sample of Ecstasy users than that of a well-designed experimental assessment of cognitive function. A lot of important information is missing, in particular, the control group is not characterized at all. Although matching for age and education is asserted, the data is lacking to independently confirm this information. Furthermore, nothing is said about matching for sex, the length of the drug-free period prior to testing, the experimental protocol and the magnitude and specific nature of cognitive differences. When it comes to possible conclusions regarding cognitive performance, what we know about the study reveals serious
limitations. For one thing, there is a complete lack of matching for the use of non-
MDMA drugs. But the major limitation of this study is probably that the Ecstasy users
were self-referred, and many were seeking help because of psychiatric disorders.
This sample is therefore clearly not representative of the general Ecstasy-using
population, and the observed cognitive impairment, although in line with other
studies, may partially be a concomitant of psychiatric disorders not related to Ecstasy
use.

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA (1999). Cognitive performance in
(±) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled

This study comes from the same group of researchers as Bolla’s. As the authors say,
it is not primarily designed to assess memory function, but a variety of cognitive
skills. Twenty-two users with an estimated lifetime use of 215 times 272 mg Ecstasy
and an average of 14 weeks of abstinence from the drug were compared to 23
controls. On average, Ecstasy users were four years younger than controls (26 v 30
years) and had two years less education (13.4 v 15.2 years). There was also no
matching for the use of non-MDMA drugs: considerably more users were
experienced with amphetamines, cocaine, LSD, sedative hypnotics and
solvents/inhalants.

A computerized neuropsychological test battery was administered. The
memory-relevant test was the Code Substitution Task, which requires subjects to
memorize a code of letter-digit pairs and then recall the corresponding digits when
shown the letters only. At the end of the test battery, subjects again had to recall the
letter-digit code (delayed recall condition). Subjects were tested three times per day
on three consecutive study days.

Ecstasy users performed worse than controls in the Code Substitution Task on
all study days and also on the delayed recall of the code on study day one. The
difference was up to 35% (no SDs given). They also scored lower on tests requiring
attention, arithmetic calculations and logical reasoning. Increasing lifetime Ecstasy
use correlated with decreasing performance in the Code Substitution Task, but only
on day three. No other correlation between cognitive performance and drug exposure
variables was found.

The relevance of this study for the present question is limited, since no typical
memory tests were applied. Although the Code Substitution Task requires working
memory, it also requires other skills such as forming associations. The delayed recall
condition can be expected to more specifically tap memory function. Two things,
however, are noteworthy: users scored worse in delayed code recall on day one only;
and this difference may be at least partially explained by the fact that they already
scored worse in the Code Substitution Task itself. If users are worse at immediately
recalling the letter-digit codes, it is very likely that they also score worse in delayed
code recall. In this sense, these two findings may not present independent, but
related, pieces of evidence. Finally, the higher educational level of the controls may
have given them an advantage in this test. All in all, the importance of this study for
the present question is basically to show that cognitive functions other than memory
can also be altered in Ecstasy users.
Twenty-five Ecstasy users were compared to 22 polydrug, non-Ecstasy controls and 19 non-drug controls. Polydrug controls were generally well matched to the Ecstasy users for the use of non-MDMA drugs, except for LSD and cannabis, the latter of which Ecstasy users had used 48% more in terms of weekly frequency and 65% more in terms of lifetime dose (these differences were not significant, however). Groups were also matched for age, sex and education. The average lifetime exposure to Ecstasy was 50 times and the average time of abstinence was 65 days. Five subjects had consumed MDMA within seven days prior to testing.

Memory was tested by means of the Rivermead Behavioral Memory Test, which includes the immediate and delayed written recall of an acoustically presented news story.

Ecstasy users performed up to 30% (< 1 SD) worse than both control groups in immediate and delayed verbal recall. Further analysis showed that users who were abstinent from Ecstasy for more than 6 months showed equal memory performance to non-drug controls and better performance than those who were abstinent for less than six months. This result is preliminary, however, since there were only three users with more than a half year drug abstinence. Worse immediate story recall correlated with increasing duration of Ecstasy use. Neither immediate nor delayed recall, however, correlated with the lifetime dose of Ecstasy. Increasing cannabis use correlated with decreasing immediate recall in the Ecstasy and polydrug groups and also with delayed recall in the Ecstasy group. Morgan’s study stands out as the first to include a control group generally well matched for the use of non-MDMA drugs (with the notable exception of cannabis) His results are relevant in several respects: His data provide first evidence that memory performance may normalize over time in abstinent users. Thus, possible negative effects of Ecstasy use on memory function may be reversible and may not reflect permanent damage to the brain serotonin system. Furthermore, Morgan’s data indicate that besides Ecstasy, cannabis may also contribute to the observed memory impairments. In fact, since Ecstasy users had consumed substantially more cannabis then the polydrug controls, it is even possible that the Ecstasy users performed worse not primarily because of their exposure to Ecstasy but because of their frequent cannabis use. A further limitation of the study is that five subjects had taken Ecstasy less then seven days prior to testing, so that sub-acute, short-term effects of Ecstasy may have influenced memory performance.


Ten users with an average lifetime consumption of 672 Ecstasy tablets and an average time of abstinence of 18 days were compared to 10 control subjects. The 10 controls were selected out of a larger group of 18 subjects to provide for optimal matching for age, sex, education and the use of non-MDMA drugs.

An auditory verbal learning test similar to Parrott’s and Bolla’s studies was applied: subjects had to recall words from a list presented to them, both immediately and after a delay. The main aim of the study, however, was to use brain imaging to measure serotonin transporter binding.

Semple found no significant difference in memory performance between the groups, although users had slightly lower scores (personal communication).
However, increasing lifetime exposure to Ecstasy clearly correlated with decreasing memory performance. Serotonin transporter binding was significantly lower in Ecstasy users in several brain areas. The time of abstinence from Ecstasy correlated with serotonin transporter levels, indicating that possible Ecstasy-induced reductions in serotonin transporter levels may recover with increasing time of abstinence.

This study appears to be methodologically sound. As the authors state, however, the sample size was rather small, so that the statistical analysis lacked the power to detect more than major neuropsychological deficits. Possibly, the slightly lower memory scores in Ecstasy users may have become significant in a larger subject sample.


This is a small study comparing five Ecstasy users with nine controls. Users had a lifetime exposure to 218 tablets and had been abstinent from Ecstasy for an average of 4.6 months. They had two years less education than controls (13 v 15 years). Groups were not matched for sex nor for the use of non-MDMA drugs (controls were completely drug-naïve).

Memory was tested with the same auditory verbal learning test as administered in Parrot (a), Semple and Bolla. No information on other neuropsychological tests is given in the paper. The study mainly explored 5-HT\textsubscript{2A} receptor binding using brain imaging.

Ecstasy users scored significantly worse (33%, corresponding to 2-2.5 SDs) in the delayed recall condition. Further, delayed recall was correlated with mean cortical 5-HT\textsubscript{2A} binding, indicating decreasing verbal recall with decreasing levels of 5-HT\textsubscript{2A} receptors. Decreasing delayed recall performance was also correlated with increasing lifetime dose of Ecstasy (personal communication). Cortical 5-HT\textsubscript{2A} receptor levels were lower in Ecstasy users.

The study supports previous findings of worse verbal recall in Ecstasy users. The reported correlation indicates that memory function in Ecstasy users could be dependent on neurobiological alterations in the 5-HT system, which may be caused by the repeated use of MDMA. There are many caveats, however. The small sample size renders these findings provisional and the confounding effect of imperfect matching for sex, education and non-MDMA drug use could be particularly devastating in this small sample. In particular, both higher education and a much greater number of women in the control group (5 v 1) could substantially contribute to this group's better memory performance. It is known that women tend to have better memory skills than men (Bolla's study, using the same test, reports significantly better delayed verbal memory scores in women). Further, a higher education is likely to be associated with better verbal intelligence, including better verbal memory. A final point is that the number of words recalled in the delayed recall condition in Reneman's Ecstasy group are strikingly lower than those in Bolla's users (8.1 v 11 words), although controls recalled equally many words in both studies (12.3 v 12). It is unclear whether this is due to lower education of Reneman’s vs Bolla’s Ecstasy users (13 v 15 years), to the possibility that Reneman’s users had more lifetime exposure to Ecstasy, to differences in the test procedure, or to subject selection effects (e.g., only users with cognitive problems apply for participation). Overall, Reneman’s memory findings are tentative, but clearly in accord with other studies.

This study was first described in a letter to Lancet in reply to the McCann et al study on brain serotonin transporter levels in Ecstasy users (Lancet 1998, 352:1433-1437). Due to space limitations, the information given is incomplete. What is reported is that 36 Ecstasy users who had consumed Ecstasy 235 times on average (range 12-2600 times) were compared with 19 age-matched controls. Ecstasy users had been abstinent for an average of 79 days (2-400), while controls were completely drug-naïve. Information on (matching for) sex and education as well as use of non-MDMA drugs is not provided.

Tests for verbal recall, learning and recognition were administered (which of these are not specified). In addition, verbal fluency was tested, and present psychiatric state, including depressive symptomatology, was assessed.

Ecstasy users scored significantly worse than controls in tests for immediate verbal recall, face recognition and spatial learning. The magnitude of these differences is not specified. Compared to normative data for the learning and memory tests, three users scored below 2 SDs in two tests and eight users in one test, whereas only one control scored lower than 1 SD in one test. Verbal fluency and psychiatric state were not significantly different between the groups, although four users were diagnosed with neurotic depression.

The use of other drugs did not correlate with test scores in Ecstasy users, although there was a trend-level correlation for frontal impairment (as measured with the working memory and verbal fluency tests) and cannabis use.

Due to the frugal nature of data presentation, conclusions from this study remain tentative. The reported impairments in verbal recall parallel those of other studies. The finding of impaired face recognition is novel and, although consistent with reports on visual memory impairments in other studies, certainly calls for independent confirmation. The fact that working memory was not altered in Ecstasy users seems to be at odds with the results of Gouzoulis-Mayfrank, McCann, and Wareing who found working memory impairments, although differences in the nature of tests are likely to at least partly explain this discrepancy.

There are some known and possible confounding factors in this study. There was no matching for non-MDMA drug use (Ecstasy users were obviously polydrug users and controls were drug-naïve), and possibly also educational level and sex ratio were different between groups. Any of these differences could have substantially contributed to the observed cognitive differences. We also don’t know for how long users had been drug-free prior to being examined, hence the possibility of short-term drug effects interfering with test performance.


Twenty-eight Ecstasy users were compared with 28 cannabis controls and 28 non-drug controls. The cannabis group had the same exposure to cannabis as the Ecstasy group, but no other regular drug use. The groups were well-matched for age, sex and education (with slightly lower education in Ecstasy users). Ecstasy users had taken an estimated average lifetime dose of 93 tablets and had been abstinent for an average of 41 days at testing (median: 23 days). Four subjects had taken MDMA 7-10 days before testing. None had any regular use of other illicit drugs.
A variety of cognitive tests were administered. Memory was assessed using an auditory verbal learning test (as in Parrot (a), Bolla, Semple and Reneman; delayed recall, however, was not assessed), a digit span test to tap working memory (subjects had to repeat a list of orally presented digits, forward and backward) and a visual memory task.

Test scores in all three groups were within the normal range. Ecstasy users scored significantly lower (up to 20%, corresponding to 1 SD) than non-drug controls in immediate verbal and visual recall and in working memory (digit span backward), and required more repetitions to learn the word list. The Ecstasy group also performed worse than the cannabis users in immediate visual recall and required more repetitions to learn the word list. Ecstasy users further showed worse performance than the other two groups in tests of selective attention, logical thinking, problem solving and general knowledge. Decreasing immediate verbal recall and working memory performance correlated with increasing lifetime doses of Ecstasy. An increasing frequency of cannabis use correlated with an increasing number of repetitions required to learn the word list.

This study appears to be very well designed and has a large number of subjects, which allows us to put more confidence in the findings. The study is remarkable insofar that the authors have managed to recruit a sample of Ecstasy users with no regular use of other illicit drugs except for cannabis. Another merit of the study is that the use of cannabis, which is probably the most frequently co-administered drug in Ecstasy users, is well controlled for by including exclusive cannabis users as a control group. The results show that worse memory performance in Ecstasy users cannot be solely accounted for by concomitant cannabis use (although a cannabis-MDMA interaction may play a role). Nevertheless, it is interesting that Ecstasy users scored worse in immediate verbal recall than non-drug controls, but not than cannabis controls. This is in line with Morgan’s finding that immediate verbal recall decreases with increasing cannabis use, raising the possibility that cannabis use may contribute to the observed differences in immediate verbal recall. The study further shows that Ecstasy users do not have worse performance only in the memory domain, but also in other cognitive domains.

Overall, this study provides the most convincing evidence so far for a relationship between frequent Ecstasy use and lower memory scores.


This study included three groups of ten subjects each: Previous users of Ecstasy who had been abstinent for at least six months, 10-11 months on average; current Ecstasy users who had taken their last dose an average of eight days prior to testing (range 2–21 days); and a control group of non-drug users without experience with MDMA, amphetamine, cocaine, LSD and marijuana. Previous users had taken an estimated average of 1280 tablets, and current users an average of 1349 tablets. About equal numbers of previous and current users were experienced with non-MDMA drugs, the only noticeable difference being that six previous users had taken LSD compared to only three in the group of current users. Groups were well-matched for age, sex and education.

Memory was tested with a word span task requiring immediate word recall, a visual memory task and a random-letter generation tasks that requires working memory, but also other cognitive functions. In this test, subjects had to speak
consonants (not vowels!) aloud in a random sequence at various speeds (1, 2 or 4 consonants per second). The main outcome measures of this task included the number of consonants produced and the number of vowel intrusions. Further tests applied included assessments of information processing speed, verbal fluency, state anxiety and arousal, and self-reported health.

There were no group differences in the word span and visual memory tasks. However, both user groups had significantly more (240-360%, corresponding to 1.4-2.8 SDs) vowel intrusions than controls at all speed levels, with current users generally scoring worst. Also, both groups of users produced less consonants than the controls, and this difference was significant for the one word-per-second speed level (37%, 4.5 SDs). Here, previous users scored the worst of all groups.

The other results showed that Ecstasy users scored significantly worse in the most demanding condition of the test of information processing speed, and non-significantly worse in the less demanding conditions. Anxiety during the experiments was significantly higher in current users than in controls, and non-significantly higher in previous users. Arousal was highest in previous users, lowest in current users (this difference was significant) and on an intermediate level in controls. Both user groups rated their health worse than controls. The worst ratings were given by current users. There were no group differences in verbal fluency.

I see two main themes emerging from this study. The first is that cognitive deficits in Ecstasy users seem to be particularly evident (and mostly significant only) in conditions of high cognitive demand, in other words, conditions that are mentally stressful. The other is that there is no evidence for recovery of cognitive function, since previous Ecstasy users with almost a year of abstinence did not generally score better than current users. This is in disagreement with Morgan’s tentative evidence for recovery of memory.

But all this comes with a number of substantial caveats: There is a complete lack of matching for non-MDMA drugs between users and controls which makes an attribution of the findings to the effects of one particular drug impossible. A limitation that could be particularly severe in the present study is the fact that the last use of Ecstasy in current users was about eight days prior to the experiments, with a range of 2–21 days. This means that those users who had taken Ecstasy only a couple of days before participating in these tests may have suffered the well-described sub-acute effects such as low mood, difficulty concentrating, lack of motivation and a feeling of being burnt-out that could have substantially decreased their test scores. In this light, the results of the current users appear particularly suspect.

Another issue concerns the extent of Ecstasy use, which seems to be extremely heavy in the present subjects compared to other studies. Both groups of users had taken an estimated lifetime average of around 1300 tablets, corresponding to 3-4 tablets twice weekly for 4 years. This is considerably more than the use of a typical Ecstasy user as assumed in this review (see footnote 3). Thus, the present findings are not representative of the Ecstasy-using population in general, at best for a segment of very heavy users. As such, they are certainly not in disagreement with the body of studies in more moderate users that show scores mostly in the normal range.

Finally, if we’re interested in memory function in particular, it should be noted that the one memory test that revealed group differences (the other two did not), namely the random-letter generation test, does not tap classical memory functions such as recall and recognition, but assesses a more complex spectrum of cognitive functions including domains other than memory (e.g., speech production and the
maintenance of a quite complex experimental context, i.e., a complex set of instructions).


One primary goal of this study was to assess the contribution of cannabis use to the potential cognitive, particularly memory, impairments in Ecstasy users. Three groups of 15 subjects each were enrolled: Ecstasy users who had taken Ecstasy on an average of 20 occasions; cannabis users without any other drug use; and a control group with no reported use of illicit drugs. All groups were matched for age, sex and education. Cannabis and Ecstasy users were matched for their cannabis use. The former group had taken cannabis four days a week for about 11 years, the latter group for about 10 years. Both groups had stopped taking cannabis one month prior to the study. With regard to drugs other than MDMA and cannabis, the Ecstasy group was not matched to the other groups. However, Ecstasy users reported only rare and occasional use of other drugs.

Memory was assessed with the Wechsler Memory Scale which includes measures for verbal and visual memory (both immediate and delayed) as well as attention and concentration. A further series of tests assessed basic visual and auditory, as well as complex reaction time. Participants were also asked for a subjective rating of the frequency of various cognitive slips during the past four weeks using the Cognitive Failures Questionnaire.

Ecstasy users scored considerably lower (40%, 2.6 SDs) than controls in one test of immediate verbal recall, which required them to retell brief stories from memory, but not in another one that required memorizing associated word pairs. Cannabis users showed the same pattern of significantly lower scores in the former, but not latter test for immediate verbal recall. Ecstasy users were also substantially worse than controls (50%, 2 SDs) and cannabis users in tests of verbal and visual delayed recall. In the delayed story recall condition, both cannabis and Ecstasy users scored significantly worse than controls. No group differences were found in tests of immediate visual memory, attention, concentration, and basic and complex reaction time. There was also no difference in subjective ratings of cognitive functioning, i.e., both users and control subjects perceived themselves as cognitively unimpaired.

In contrast to Wareing, this study tested very light users of Ecstasy (20 times on average). Considering, on the other hand, the heavy use of cannabis in the Ecstasy group, it appears more appropriate to say that this study tested regular cannabis users with an occasional use of Ecstasy than to speak of Ecstasy users with concomitant cannabis use. From this viewpoint, the fact that the additional light Ecstasy use in one of the cannabis groups was associated with lower scores in delayed memory performance over and above those seen in exclusive cannabis users seems quite remarkable. Thus, the main suggestion offered by this study is that cannabis use could be responsible for some proportion of the lowered memory scores (particularly in immediate verbal recall), but that additional, even moderate, Ecstasy use can extend the impact on memory to include delayed memory performance. This view is in partial agreement with Gouzoulis-Mayfrank who reports that "...cannabis use is likely to have affected cognition and to have contributed to some extent to the poorer performance of Ecstasy users...". However, in her study, cannabis users did not perform significantly worse than non-drug controls. The reason for this may be that their use of cannabis, although comparable in frequency
to the present cannabis users, had spanned only three years compared to 11 years in the present cannabis users.

The lack of matching for the use of drugs other than MDMA and cannabis in this particular study is less worrisome than in others, since Ecstasy users reported only very rare and occasional use of these drugs. A possibly more serious limitation is the fact that both cannabis-using groups had stopped using the drug one month prior to the experiments. It cannot be excluded that they may have been handicapped by cannabis withdrawal symptoms during the time of testing. In this case, the difference in scores between the cannabis-using groups and the controls that may be attributed to the effects of regular drug use would be overestimated.

Results of the the Cognitive Failures Questionnaire are consistent with other studies and show that neither Ecstasy nor cannabis users perceive any cognitive impairment in their everyday lives. Here we must, however, at least consider the possibility that the very cognitive, in particular memory, impairments users are supposed to rate may interfere with their ability to remember occurrences of such cognitive impairments in their lives.


In this study from the Netherlands, three groups of male subjects were included: 21 „heavy“ Ecstasy users (> 48 times, average lifetime dose 741 tablets), 21 moderate users (12-48 times, average lifetime dose 169 tablets) and 20 Ecstasy-naïve controls. All subjects were recruited from the population of regular rave visitors. Subjects were matched for age and sex. School levels were highest in controls, and lowest in the heavy users, but the difference was not significant. Both user groups had consumed considerably more cannabis and also more amphetamines and cocaine than controls. Cannabis lifetime and recent consumption did not differ between the two user groups (1850 lifetime joints in heavy users, 1890 in moderate users). Heavy users had a higher recent amphetamine use than moderate users. The average time since last Ecstasy use was 9 days in heavy, 16 days in moderate users, with a minimum of 2 days for both groups. All subjects were instructed to abstain from illicit drug use for 1 week before the first tests, which was controlled by urine analysis.

Memory was assessed using tests for visuospatial memory span as well as word and figure recognition. Further cognitive tests for simple reaction time and information-processing were applied. Psychological assessments included questionnaires for depression, trait anxiety, hostility, impulsiveness, novelty seeking, harm avoidance and reward dependence. On a different day, prolactin and cortisol responses to a serotonergic challenge using 30 mg of D-fenfluramine were measured. This challenge is frequently used as an indicator for the integrity of brain serotonergic systems.

Visuospatial memory span and figure recognition were worse in both Ecstasy using groups compared to controls (by 10-18% [0.6-0.7 SDs] and 15-17% [0.9-1 SDs], respectively, in the moderate users; and by 14-18% [0.8-0.85 SDs] and 18-23% [1.2-1.3 SDs], respectively, in the heavy users), but did not differ between the two groups. In addition, heavy users showed a worse recognition for words than moderate users and controls (by 12-14% [0.9-2.2 SDs] vs. controls), without any difference between the latter two groups. Heavy users were significantly slower in
the reaction time experiments than moderate users and controls, but this difference was no longer significant after statistically removing the effects of school level and depression score. Heavy users had higher scores for depression and trait anxiety than moderate users and controls, which again, was no longer significant after statistically removing the effects of school level and the presence of attention deficit with hyperactivity disorder (ADHD) in childhood. The two user groups showed slightly higher scores for novelty seeking than controls. Heavy Ecstasy users had visited 47 raves during the previous year compared to about 33 in the two other groups. This difference was not statistically significant.

Both user groups had lower plasma cortisol levels in response to D-fenfluramine than controls. There were no significant group differences in prolactin levels, although heavy users had the lowest, and controls the highest plasma concentrations. Plasma cortisol levels were significantly correlated with scores in the spatial memory span test.

Comparing it with the other studies in this field, this study stands out by its effort to achieve some degree of matching for lifestyle by recruiting all subjects (including controls) from the same population of rave visitors and party-goers. Matching, however, was incomplete because, although moderate users and controls had been to the same number (33) of parties during the previous year, heavy users had visited nearly 50% more raves (47) than the other two groups. That means that the heavy users were substantially more often exposed to the detrimental effects of the „rave setting“ including lack of sleep, excessive physical exercise and malnutrition. Thus, it is still possible that the psychological differences found between heavy and moderate users (i.e. word recognition, reaction time, depression, trait anxiety) were related to that remaining difference in lifestyle between these two Ecstasy-using groups. To achieve some control over this, Verkes could have included the number of raves visited as a confounding variable into their statistical analysis, which, however (to my surprise I should say), they neglected to do.

The findings of heightened depression and anxiety as well as blunted neuroendocrine responses to a serotonergic challenge are in line with previous studies and with the possibility of neurotoxic effects of MDMA on the serotonin system and subsequent mood impairment.

In the light of growing recent evidence for the involvement of cannabis in the cognitive impairment in Ecstasy users (see e.g. the Croft study below), the major limitation of this study with regard to the present question is the complete lack of matching for cannabis use between the Ecstasy-using groups and the controls. Ecstasy users had smoked 5 times as many joints in their lives as controls (about 1900 compared to 379, respectively). The differences found between the Ecstasy users and controls could therefore be explained by cannabis, not Ecstasy, use. It is of note, however, that cannabis use had no statistical influence on the results of the study when it was controlled for by an analysis of covariance. Furthermore, some of the impairments found in this study were significantly more pronounced in the heavy as compared to the moderate users (word recognition, depression, trait anxiety) despite their comparable use of cannabis. These results are compatible with a dose-dependent effect of Ecstasy, which may exist in addition to a possible cannabis effect.

Further limitations of the study are the incomplete matching for education and the possibility of short-term adverse effects of Ecstasy influencing test scores in some users, given that they had used Ecstasy up to three days before being tested.
Eleven Ecstasy users (lifetime dose: 41.9 tablets) with concomitant cannabis use were compared to 18 cannabis users (without Ecstasy use) and 31 non-drug controls. The controls were slightly (2-3 years) younger than the users. Subjects were matched for education but not for sex. There were much less women in the cannabis group than in the other two groups. Ecstasy and cannabis users had both used a substantial amount of cannabis (10965 vs. 7762 lifetime joints, respectively). Ecstasy users had been abstinent from Ecstasy for more than a week, and from cannabis for an average of 47.3 hours, before testing. Cannabis users had been abstinent from cannabis for an average of 66.5 hours before testing.

The measures of memory performance used were auditory verbal learning and a similar test using designs instead of words (design learning), word and face recognition and forward/backward digit span. Further cognitive measures/tasks included verbal fluency, spatial/non-spatial associative learning, the Stroop test, a pegboard test, where grooved pegs had to be put in matching holes, and verbal intelligence as assessed by the National Adult Reading Test.

The only difference between Ecstasy and cannabis users were higher scores in design learning and the pegboard test in the Ecstasy group. The pooled Ecstasy and cannabis groups performed worse than non-drug controls in tests for auditory verbal learning (~9%, 0.7 SDs), immediate (~9%, 0.75 SDs) and delayed (19%, 0.6 SDs) recall (both significant at a trend level), forward (~10%, 0.6 SDs) and backward (~15%, 0.6 SDs) digit span, face recognition (~5%, 0.7 SDs), as well as in non-memory tests including spatial (~37%, 0.6 SDs) and non-spatial (~59%, 0.9 SDs) associative learning, verbal fluency (~9%, 0.5 SDs) and the Stroop test for speed of processing (~12%, 0.8 SDs).

Most interestingly, when statistically removing the effect of cannabis use, none of these significant differences remained except the one in the Stroop test for processing speed. Ecstasy use only had a statistical effect on the results in the Stroop test for processing speed. In other words, all but one difference in cognitive tests between the drug using subjects and the controls could be statistically accounted for by cannabis use, while Ecstasy use only accounted for the difference in the Stroop test.

The important message from this study is that concomitant cannabis use may be responsible for much, if not all, of the cognitive differences between Ecstasy users and control subjects that have been reported so far. The study clearly shows the need to adequately control for cannabis use in future studies. In that respect, it adds to the studies of Rodgers and Gouzoulis that already demonstrated an involvement of cannabis in the cognitive deviations found in Ecstasy users. However, an important difference to the latter studies is that Croft found no relative impairment of the Ecstasy users compared to the cannabis users, while Gouzoulis-Mayfrank and Rodgers found worse verbal learning and recall as well as visual recall in Ecstasy-plus-cannabis users compared to cannabis-but-not-Ecstasy users. Thus, although the jury is still out on this, it seems that the putative effects of Ecstasy use on cognitive performance can extend beyond those of cannabis use (given particularly the careful methodology of the Gouzoulis-Mayfrank study). But this still leaves open the possibility that a substantial part of the observed cognitive differences may be the consequence of regular cannabis use.
Overview

Let’s look at a brief overview of the findings: six out of seven studies that tested immediate and delayed recall in some version of the auditory verbal learning test found lower scores in Ecstasy users than controls. Looking at all tests for verbal memory, a total of 13 (if we include Bolla) out of 15 studies found worse performance in Ecstasy users. Visuospatial memory was worse in Ecstasy users in five of six studies: one reported lower scores in immediate recall, two in delayed visual recall, one in face recognition and one in visuospatial memory span and figure recognition.

Gouzoulis-Mayfrank and Semple are the methodologically most sound studies and constitute the firmest basis for conclusions. In particular, they’re the only studies with groups well-matched for education and non-MDMA drug use. Gouzoulis-Mayfrank even nearly eliminated the confounding effect of polydrug use by collecting a sample of Ecstasy users with no other drug use but cannabis. Gouzoulis-Mayfrank found lower scores in immediate verbal and visual recall, word learning and working memory. Comparably lower scores for verbal recall were seen in the studies of Parrott (a) and (b), McCann, Reneman, Rodgers and Krystal. Although these studies are subject to more potentially confounding effects, it is striking that they all point in the same direction and support the more reliable findings of Gouzoulis-Mayfrank.

Semple did not find lower scores in Ecstasy users using the same tests for verbal recall as other studies (Parrott, Gouzoulis-Mayfrank, Reneman) that did find lower scores. The reason for this discrepancy may plausibly be that Semple’s study, though methodologically sound, is too small and thus may have lacked the statistical power to detect differences. Findings of no difference in small studies must be generally regarded as preliminary and need to be reproduced and confirmed independently. Still, it is striking that Semple failed to find alterations in heavy users with an average lifetime consumption of 672 doses which is 7-10 times the doses of Morgan’s, Bolla’s and Gouzoulis-Mayfrank’s studies.

Causality

So what can be said about a possible causal relationship between Ecstasy and lower memory scores?

Allow me to digress briefly: what has been established beyond a reasonable doubt is that in several species of laboratory animals, high or repeated doses of MDMA (the main component of Ecstasy tablets) can produce long-lasting changes in the 5-HT system. There is strong evidence that these changes include damage to serotonergic nerve cells. And so far, we have no reason to believe that human MDMA users should be spared from similar neurotoxic\(^\text{10}\) effects, given an excessive use of the drug. (The question of how ‘excessive’ is defined is still open, but is not important in the present context.) If serotonergic neurotoxicity does occur in Ecstasy users and if there are psychological and cognitive consequences, then we should expect these to show up in mental functions in which the serotonergic system plays a role. Memory, among many others, is one of these functions. Therefore, we have a

\(^{10}\) A working definition of neurotoxicity adopted by the Interagency Committee on Neurotoxicology (ICON), comprised of representatives of the Environmental Protection Agency, the Food and Drug Administration, and others, states: ‘Neurotoxicity is any adverse effect on the structure or function of the central and/or peripheral nervous system by a biological/chemical, or physical agent and may result from direct or indirect actions or reflect permanent or reversible changes in the nervous system’. Two points are important to note: First, this definition not only includes permanent, but also temporary and reversible effects on the nervous system; second, the term neurotoxicity does not necessarily imply adverse functional consequences (e.g., cognitive or emotional deficits).
clear neurobiological rationale to expect and explain memory deficits in Ecstasy users as reported in the presently discussed studies (this is also supported by Reneman’s, McCann’s and Verkes’ studies showing correlations between memory performance and neurobiological variables such as level of 5-HT$_{2A}$ receptors, 5-HIAA, and plasma cortisol, respectively).

That being said, we need to remember that a causal relationship between Ecstasy and memory deficits can’t be proven in the kinds of designs the present studies employ. To come close to such a „proof“ (nothing can ever be proven in a strict sense in science, but this need not worry us here), we would have to do the kind of ethically controversial study outlined at the beginning. So in a strict scientific sense, the issue of causality is still open. But that is not satisfactory. We want to know in which direction the evidence points, whether Ecstasy use is the most likely explanation or whether other, equally convincing alternatives are available.

**Possible explanations**

From the data that lie before us, I think the safe conclusion to draw is that being an Ecstasy user is a risk factor for having worse memory performance. The present studies as a whole seem to me to do a good job in making age, sex, education and the use of non-MDMA drugs (except cannabis) unlikely as the main factors that could explain the observed findings. One study (Gouzoulis-Mayfrank) even makes an admirable effort to exclude interactions of MDMA with other drugs (except cannabis) as an explanation by testing nearly exclusive Ecstasy users.\footnote{Note that even the study of completely exclusive Ecstasy users could not entirely control for MDMA-drug interactions, since Ecstasy tablets often contain MDMA together with some other psychoactive or non-psychoactive compound(s) that may pharmacologically interact with MDMA in the user’s body.}

The remaining, most promising explanations I can see are Ecstasy/MDMA use, (concomitant) cannabis use, lifestyle and/or some pre-existing factor. Ecstasy/MDMA certainly is a very plausible cause: We have a neurobiological rationale that provides the necessary connection between MDMA, serotonergic neurotoxicity and memory impairments. Further, the present studies, apart from showing worse memory in Ecstasy users, also demonstrate correlations between exposure to Ecstasy and memory performance. Four out of seven studies found that increasing exposure to Ecstasy was correlated with decreasing memory function, although whether the critical variable is lifetime exposure, monthly dose, frequency/duration of use or amount of drug per single occasion is as yet unclear.

Four of the present studies (Morgan, Gouzoulis-Mayfrank, Rodgers, Croft) further indicate that the concomitant use of cannabis may amplify memory impairments in Ecstasy users, since it appears that cannabis alone may already have a detrimental effect on memory. It is even possible that this amplification is not simply the sum of the effects of both drugs alone, but the result of a specific interaction of these two drugs in the central nervous system. This question could be addressed to some extent in a study that would manage to find Ecstasy users without concomitant cannabis use, which none of the present studies has (and which is obviously anything but easy).

The recreational use of Ecstasy is typically associated with a certain lifestyle that entails many stress factors that could be detrimental to memory. Hours of dancing at raves during intense sensory stimulation, possibly in conjunction with insufficient fluid intake, present great strain to the organism, especially when such a pace is kept up for two or three days over the weekend. Consequently, sleep and recuperation are greatly reduced during this time, usually paired with an MDMA-
induced malnutrition. The immediate effects of such a weekend episode may be a temporarily disturbed memory function, which could conceivably become permanent if this lifestyle pattern is repeated every weekend. Lifestyle effects may also essentially interact with the pharmacological effects of Ecstasy/MDMA. In animal experiments, it has been established that the hyperthermic and neurotoxic effects of MDMA are amplified when the animal is kept under high ambient temperatures, while they are attenuated in cool environments. When animals in hot environments were additionally deprived of water, MDMA-induced hyperthermia increased even more. If these mechanisms extend to humans, then conditions of hot ambient temperatures and insufficient rehydration at raves may be critical factors in potentiating neurotoxic effects of MDMA intake, and, consequently, lower memory scores.

Such lifestyle effects are certainly among the important remaining factors that have not been adequately controlled for so far in scientific studies. The only effort in this respect has been made by Verkes who recruited control subjects from the same population of club and rave visitors as Ecstasy subjects. He found that the Ecstasy users still performed worse on a number of cognitive tests, indicating little involvement of lifestyle. However, it is necessary to study lifestyle variables in more detail. With regard to the Verkes study, important questions are: Did the controls engage in the same amount of physical exercise (dancing) and sustain the same amount of dehydration, sleep deprivation and malnutrition as the users? You see, it appears likely that the very extent of these stressful effects is specifically related to the consumption of stimulant and appetite suppressing drugs like Ecstasy, amphetamines and maybe cocaine. In other words, party-goers who abstain from stimulant drugs, may on average simply lack the energy to stay up and dance all night for several days, and they will also lack the appetite suppressing effects of these drugs. As a consequence, they will sustain less sleep deprivation and malnutrition. This may have well been the case in the Verkes study, since their control group not only had been Ecstasy-naïve, but had also almost completely abstained from other stimulant drugs such as amphetamines and cocaine (only one control subject had used amphetamine during the three previous months).

In order to completely control for lifestyle effects, one would need a control group that would join Ecstasy users in their clubbing activities and undergo the same amount of sleep and food deprivation so as to be exposed to the same stress factors, without, however, being exposed to Ecstasy. But note that even such a design could not control for interaction effects of MDMA with environmental conditions such as ambient temperature and with levels of bodily fluids. In sum, despite the results of Verkes, lifestyle may be of eminent importance in contributing to worse memory in Ecstasy users. Lifestyle effects need to be evaluated in detail in future studies, although this may prove to be a daunting task.

A further possible explanation I see for the observed memory findings is a pre-existing difference between Ecstasy users and controls. Such a difference could take the form of a (possibly subclinical) psychiatric condition that may involve disturbed mood and memory and predispose its carriers to use Ecstasy for self-medication. Neurobiologically, this condition could be based on some kind of serotonergic hypofunction. In this case, the direction of causality would be inverted not in the sense that Ecstasy use causes memory impairment, but that a pre-existing condition that involves memory impairment causes subsequent Ecstasy use. This is an interesting and not unlikely scenario, but its major disadvantage is that there is not much evidence for it. Finding hard evidence for it would require conducting a rather expensive longitudinal study, i.e., large samples of „pre-Ecstasy“ teenagers would have to be submitted to comprehensive psychiatric and neurobiological testing, and
re-assessed at various later timepoints. This would possibly allow us to isolate a factor that distinguishes those subjects who became Ecstasy users during the course of the study from those who did not. At present, the predisposition/self-medication hypothesis is certainly a possible explanation, but there’s no justification for favoring it over or even using it to discredit other alternatives.

Finally, Parrott offers another interesting possibility connected to those discussed above. In Parrott (a) he writes that “drug users often state that their phenomenological experience becomes more immediate and non-verbal while on MDMA. They become more concerned with direct perception, and do not feel the necessity for labeling thoughts and feelings. If this change towards a more phenomenal and less verbal cognitive style remained afterwards, it might help explain these verbal memory data.” So what Parrott suggests is that frequent Ecstasy use might change a user’s cognitive strategy in direction of a less language-, more perception-based style. This idea conceptualizes the memory findings not as deficits, but as shifts toward other mental capacities. Note that this explanation also works with the notion of a pre-existing difference. Instead of exposure to Ecstasy bringing about the change in cognitive strategy, the latter could have already been different from the start. In this case, it is possible that their different cognitive style would lead future Ecstasy users to seek out more immediate, perception-centered experiences instead of abstract, language-centered experiences.

Again, one problem with the “cognitive style hypothesis” is that there isn’t exactly much evidence in favor of it. One would expect that Ecstasy users, if their mental skills lie more with perception, should fare better (or at least equally well) than controls in tasks requiring sensory processing. But they don’t. We already saw that five of six studies that assessed visual memory found lower scores in Ecstasy users. The same outcome is seen with other, more exclusively perceptual tasks: Ecstasy users perform worse in visual scanning (Parrott (b)), visual attention and audio-visual integration (Gouzoulis-Mayfrank).

Although the cognitive style hypothesis in its present form is too crude to survive scientific scrutiny, it may nevertheless capture something essential. Maybe people who are drawn toward using Ecstasy are indeed somehow different from others in their ways of thinking and experiencing (after all, there is a reason why they use it and not others). Possibly, a future, more specific and fleshed-out version of the cognitive style theory will be able to tell us more about the mental make-up behind people’s different choices regarding drug use or abstinence.

Summed up, available evidence suggests pharmacological effects of Ecstasy/MDMA and cannabis, possibly in conjunction with a stressful lifestyle, as the major candidates for explaining worse memory function in Ecstasy users.

**Consequences for the recreational use of Ecstasy**

Considering the present findings, do Ecstasy users need to worry about their memories? This question connects with issues of the extent of Ecstasy use, the severity of memory reductions and their possible recovery (assuming that lower scores do indeed reflect Ecstasy-induced declines in memory). Those studies that find differences report memory scores 20-50% lower in typical Ecstasy users, corresponding to about 1-2.5 standard deviations. Interestingly, the methodologically most sound study with positive findings (Gouzoulis-Mayfrank) reports differences of 1 standard deviation. Gouzoulis-Mayfrank even explicitly mentions that the scores of their user group lie still within the clinically normal range. Thus, a typical Ecstasy user’s memory performance does not fall into pathological categories. But, of course,
the question of "impairment" is also a subjective one. The extent to which somebody suffers from a cognitive deficit may not correspond to the extent their test scores fall below normal values. In this regard, McCann reports that the Ecstasy users of her study were generally not aware of having cognitive difficulties. Parrott (a) remarks that there are few descriptions or complaints of impaired memory in recreational Ecstasy users. Ricaurte, in the above-mentioned paper on CSF 5-HIAA levels, states that the majority of subjects in his study "... denied any disturbance in sleep, mood, appetite, or in any functional domain in which serotonin has been implicated." Finally, Ecstasy users in Rodgers' study did not perceive themselves as cognitively impaired in any way. Therefore, it certainly does not seem that in the typical case, Ecstasy users are severely restricted by their worse memory in going about their daily business and conducting functioning lives.

A further issue is recovery. If Ecstasy/MDMA is indeed responsible for the observed memory scores, then they are less worrisome if memory turns out to recover after Ecstasy use is stopped. Although recovery is a crucial issue, it has hardly been specifically addressed in current research, since the foremost concern of existing studies was to evaluate memory performance in the first place. Some evidence, however, is available from the studies of Wareing and Morgan. Morgan found that users who were abstinent from Ecstasy for more than six months scored equally well on tests of immediate and delayed verbal recall than control subjects. Only users with less than half a year of abstinence had lower memory scores. Wareing, however, found that previous users of Ecstasy who were abstinent for almost a year showed similar cognitive impairment to current users. Since Morgan's results are more tentative, it would appear that there is not much evidence in favor of a normalization of memory with increasing time of drug abstinence. This issue, however, is far from settled and requires substantial further research. In particular, longitudinal studies that test the same Ecstasy users when they are using it, as well as at various times of abstinence.

If Ecstasy worsens memory, what are the doses that bring about these effects? Based on the present results, we can try to speculate on a no-effect level of Ecstasy use (but the emphasis clearly is on speculation). The non-heavy Ecstasy users in Bolla's study (those consuming less than an estimated 440 mg per month) had scores comparable to the controls. It is therefore possible that taking less than 4.4 tablets of 100 mg each a month leaves memory relatively unaffected or at least that memory changes are too small to be detected and thus probably insignificant. If, however, memory declines linearly with increasing monthly dose, as Bolla's data indicate, then there may not be a no-effect level as such, but only varying degrees of deficits corresponding to varying degrees of Ecstasy use (but also in this case, the memory effects of a few doses will probably both be subjectively and clinically undetectable). To decide between these two possibilities, we would have to know whether the correlation Bolla reports is present only in the subgroup of heavy users or also in the non-heavy users. Unfortunately, this analysis hasn't been done (Bolla, personal communication).

The other study which allows us to compare average monthly doses with the magnitude of memory differences comes from Gouzoulis-Mayfrank. Her subjects had taken an average of 3.36 Ecstasy tablets per month. Thus, if we again assume a 100 mg MDMA per tablet, the use of 336 mg MDMA per month is associated with detectable memory decreases. This dose is less than the estimated 4.4 tablets per month that emerged as the no-effect level in Bolla's study. Unfortunately, we don't know anything about the threshold dose, below which there was no measurable memory decrease. We can only conclude that, according to the Gouzoulis-Mayfrank
study, the no-effect level lies somewhere below 3.36 tablets per month (about 336 mg). However, since this dose does not represent a particularly heavy use of Ecstasy, even typical, not only heavy Ecstasy users must face the possibility that their drug use will lead to a reduction of their ability to memorize or recall. These are not gross reductions according to present findings and they are generally not considered as a subjective impairment. It is possible, however, that they gradually worsen with increasing age. This concern is based on evidence that certain components of the human serotonergic system (e.g., 5-HT receptors) appear to decline with age. Such a decline may add to the presumed Ecstasy-induced damage to the 5-HT system and lead to an amplification of memory impairments. However, until we know more about age-related changes in the human 5-HT system, this possibility remains speculation.

In conclusion, I want to emphasize again that we are on very unfirm ground with considerations of no-effect levels. While these considerations may have relevance in determining dosages for clinical-therapeutic applications of MDMA (see below), they clearly do not warrant the conclusion that the recreational use of less than 3-4 tablets of Ecstasy per month is harmless to memory.

**Consequences for clinical uses of MDMA**

Current and future potential clinical uses of MDMA mainly include MDMA-assisted psychotherapy as well as its use as a pharmacological tool to study the neurochemical regulation of mood and emotion. These clinical applications must be designed for optimal safety from possible harmful effects. We can use the presently reviewed studies to try and derive a maximal monthly dose of MDMA without negative effects on memory that could guide dosing in clinical trials. Combining estimates from Bolla’s and Gouzoulis-Mayfrank’s study we may tentatively assume a no-effect threshold of about 300-400 mg/per month, marking the upper boundary for clinical dose regimens. This dosage corresponds to about 3-4 doses of 100 mg MDMA per month.

But the margin of safety in clinical applications of MDMA is probably increased by the fact that all the adverse effects of the recreational setting are absent in clinical uses: subjects are under continuous medical and psychological care (including, for example, monitoring of body temperature and blood pressure); no physical exercise or excessive sensory stimulation is involved; ambient temperature can be controlled; there are little or no interactions of MDMA with other drugs; and last but not least, subjects are screened for potential medical and psychiatric risk factors before participation. Thus, adverse environmental and psychological conditions that may amplify Ecstasy-induced memory deficits or – in the case of hot ambient temperature – neurotoxicity are absent in clinical settings, so that any no-effect levels derived from studying Ecstasy users will likely be too high for clinical applications.

The margin of safety in clinical applications is probably further increased by the fact that no-effect estimates derived from studies of recreational Ecstasy users assume the use of Ecstasy during one or more years, while clinical application will use MDMA for a much shorter period.

No-effect estimates from the few available controlled studies (mostly from our lab at the University Hospital of Psychiatry in Zurich) indicate that one single dose of 1.5-1.7 mg/kg (about 120 mg) does not have a detectable effect on a variety of psychological and neurophysiological measures including verbal memory recall. Thus, the no-effect level for clinical MDMA use appears to lie somewhere between a
one-time dose of MDMA on one side and 3-4 MDMA doses per month during several years on the other.

The bottom line, however, is that all these considerations are highly speculative and do not bear much weight. At present, we do not have a reliable estimate of the no-effect threshold of MDMA use and what conditions it depends on. We do not clearly know whether MDMA worsens memory and what and how other factors may contribute to this process. For the foreseeable future, we may have to decide on experimental and therapeutic uses of MDMA without reliable knowledge about the potential neurobiological, psychological and behavioral risks involved. We can only try to weigh the potential and real risks against potential and real benefits. Risk-wise, the present studies imply that verbal memory is a major functional domain in which to look for possible alterations and that the memory tests used are sensitive measures to detect these alterations. Therefore, these instruments should also be employed in clinical applications of MDMA to monitor memory performance as an indicator of possible MDMA-induced impairments.

**Conclusion and outlook**

The majority of studies, including the methodologically most sound ones, found worse memory performance in regular Ecstasy users who had typically been exposed to the drug several times per month for over a year. These differences were mostly moderate, with test scores usually in the normal range. Currently the most plausible explanations for these findings are MDMA-induced (potentially neurotoxic) changes in the brain serotonin system (which may be amplified in recreational settings involving hot ambient temperatures and dehydration), and cannabis use. Further, a stressful lifestyle with insufficient sleep, recuperation and food intake may also adversely affect memory. Finally, the possibility of relevant pre-existing, possibly subclinical, differences cannot be excluded. The question of recovery of memory with increasing time of drug abstinence is not settled and represents one of the most pressing issues for future research in this area. Likewise, future studies need to isolate the possibly substantive contribution of lifestyle to the observed memory impairments. Estimates of a no-effect threshold for Ecstasy use may guide dosing in experimental and therapeutic uses of MDMA. The present studies suggest a no-effect level in the range of 300-400 mg MDMA per month or below. However, this estimate is essentially speculative owing to the many confounding adverse effects of the recreational setting, and, more fundamentally, to methodological difficulties in establishing a causal relationship between MDMA and memory alterations.