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## Original Investigation

# Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users

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### Abstract

*Rationale* Chronic recreational ecstasy (MDMA) use has often been reported to be associated with psychopathology, memory impairments and serotonergic alterations. However, the findings have not been consistent.

*Objectives* To attempt to replicate these findings, to investigate whether such alterations would be reversible and whether they could be predicted by parameters of previous drug use.

*Methods* In a cross-sectional design, 30 current and 31 ex-ecstasy users with ecstasy abstinence of at least 5 months, and 29 polydrug and 30 drug-naive controls were compared on measures of psychopathology, cognitive performance and serotonin transporter availability.

*Results* The groups did not differ significantly in age, gender distribution, education level and premorbid intelligence. The ecstasy groups did not differ significantly from polydrug controls on most of the relevant parameters of concomitant illegal drug use. Reported drug use was confirmed by hair and urine analyses. All three groups of drug users exhibited significantly elevated psychopathology compared with drug-naive controls. Only ex-ecstasy users were significantly impaired on verbal recall. Current ecstasy users showed significantly reduced distribution volume ratios of serotonin transporter availability in the mesencephalon and caudate nucleus. Regression analyses indicated that psychopathology and serotonergic alterations were best predicted by the number of ecstasy tablets taken on a typical event.

*Conclusion* The results indicate that verbal memory impairments were possibly aggravated after prolonged ecstasy abstinence while there was tentative evidence of serotonergic recovery. On the other hand, self-reported elevated psychopathology appeared to be associated with polydrug use in general and not specifically with ecstasy use.

**Keywords**
3-4-Methylenedioxymethamphetamine - MDMA - Ecstasy - Psychopathology - Cognitive performance - Neuroimaging

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# Introduction

The recreational use of the synthetic drug ecstasy has increased considerably over recent years. The lifetime prevalence of ecstasy use in Europe was estimated to be as high as 31–83% within the techno subculture (Tossmann et al. *2001*) and 1–5% in the general population (EMCDDA *2002*). In the US, Strote et al. (*2002*) found that ecstasy use had increased dramatically among college students in the past decade and continued to increase in the year 2000. Approximately 97% of ecstasy users consume additional illegal drugs and up to one in five regular users may develop a dependence syndrome as defined by DSM-IV (Schuster et al. *1998*).

Chemical analyses of confiscated tablets or capsules dealt as ecstasy in Germany in 2001 revealed that the psychoactive agent in ecstasy was predominantly 3-4-methylenedioxymethamphetamine (MDMA). The results indicated that 93% were mono-preparations containing MDMA in 98.4% of the cases (average content: 64 mg). The remaining 7% contained mostly a combination of MDMA and/or methylenedioxyamphetamine (MDA) with amphetamine and/or methamphetamine (Simon et al. *2001*).

In the 1980s, the first animal studies showed MDMA to be a potent and selective serotonergic neurotoxin that can lead to a reduction in serotonin (5-HT) uptake sites and to degeneration of serotonergic axons in certain brain regions (cf. Ricaurte et al. *2000*). Later, it was found that altered serotonergic innervation patterns were still present in the primate brain 7 years after MDMA exposure, suggesting that MDMA-induced serotonergic alterations might not be reversible (Hatzidimitriou et al. *1999*). First evidence of a possible neurotoxic potential of MDMA in humans was presented in the early 1990s. Neurochemical studies showed a significant reduction of 5-HIAA in the CSF of ecstasy users (Ricaurte et al. *1990*; McCann et al. *1994*; Bolla et al. *1998*). Kish et al. (*2000*) reported reduced serotonin levels in the autopsied striatum of a long-term ecstasy user. The user had also consumed cocaine and opiates, but these substances had not been associated with lowered serotonin levels in other cases examined by the same research group (cf. Kish *2002*).

The first neuroimaging study of the possible consequences of ecstasy use was published in the late 1990s. Positron emission tomography (PET) with the specific serotonin transporter (SERT) binding radioligand [$^{11}$C](+)McN5652 revealed global and regional decreases of SERT availability in ecstasy users (McCann et al. *1998*). Although [$^{11}$C](+)McN5652 may be the most suitable tracer available for studying the effects of MDMA on human serotonin transporters (Szabo et al. *2002*), there is controversy about the interpretation of these results, and the study had other limitations (cf. Kish *2002*). Recent findings obtained with glucose (FDG) PET (Obrocki et al. *1999*; Buchert et al. *2001*) as well as ([$^{123}$I] $\beta$-CIT)-SPECT (Semple et al. *1999*; Reneman et al. *2000*) supply

further evidence that recreational use of ecstasy may selectively damage the serotonergic system. Reneman et al. (*2002*) found reduced N-acetylaspartate/creatine; and N-acetylaspartate/choline ratios with single voxel proton MR spectroscopy in the frontal cortex of ectasy users. The N-acetylaspartate/creatine ratios in the prefrontal cortex of ecstasy users were strongly associated with delayed memory function as measured by the Rey Auditory Verbal Learning Test (Reneman et al. *2001c*).

Some, but not all, clinical and neuropsychological studies found persistent use of MDMA to be associated with significantly elevated self-reported symptoms of depression (Gerra et al. *1998*; Gamma et al. *2001*; Morgan et al. *2002*), anxiety (Parrott et al. *2000*; Morgan et al. *2002*), impulsiveness (Gerra et al. *1998*; Parrott et al. *1998*; Tuchtenhagen et al. *2000*) and aggression (Gerra et al. *1998*; Parrott et al. *2000*). Impaired verbal memory has been demonstrated even in subjects with fairly moderate patterns of ecstasy use (Morgan *1999*; Rodgers *2000*; Bhattachary and Powell *2001*). Some authors concluded that ecstasy use may be associated specifically with impairment of cognitive functions related to working memory (McCann et al. *1999*; Gouzoulis-Mayfrank et al. *2000*; Wareing et al. *2000*; Verkes et al. *2001*; Morgan et al. *2002*).

Recent studies have focused on the possible influence of other drugs typically taken by ecstasy users and found an association between cannabis use and psychopathological symptoms in ecstasy users (Gouzoulis-Mayfrank et al. *2000*; Croft et al. *2001*; Morgan et al. *2002*). Impairment of memory performance still appeared to be associated primarily with ecstasy rather than cannabis use (Reneman et al. *2000*; Rodgers *2000*; Zakzanis and Young *2001*; Morgan et al. *2002*). A limitation of many of the above-mentioned studies is a lack of a sufficiently precise, objective, reliable and, in the case of drug use, toxicologically validated, assessment of drug use history and psychopathology of the participants. Due to these methodological flaws, the validity of the evidence of MDMA toxicity to human brain serotonin neurons is questioned by some researchers, such as Kish (*2002*). Overall, ecstasy research has produced inconsistent results (cf. Parrott *2001*), and their interpretation is further complicated by confounding variables such as concomitant use of other drugs or differences between ecstasy users and control participants with respect to psychosocial and biological factors, which were rarely monitored in the earlier studies (for discussion, see Cole et al. *2002*; Morgan *2002*; Parrott *2002*). The aim of this cross-sectional study was to investigate whether elevated psychopathology, cognitive deficits and alterations of serotonergic neurons can be found in ecstasy users, and whether these findings persist after a period of abstinence from ecstasy. For this purpose current and ex-ecstasy users and drug-naive and polydrug control subjects were examined with psychiatric and neuropsychological methods and with positron emission tomography.

In his recent review, Parrott (*2001*, p. 557) concluded that the "psychobiological deficits found in ecstasy users (...) may reflect serotonergic axonal loss" and that the "neuropharmacological damage may be permanent." Following this interpretation, it was predicted that current and former ecstasy users would exhibit elevated psychopathology, selective deficits in cognitive performance (cf. Morgan *2002*, p. 295), particularly memory performance, and reduced SERT availability in certain brain regions, relative to drug-naive and polydrug controls.

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# Material and methods

## Participants

A total of 120 participants were included in the study. The group of current ecstasy users consisted of 30 subjects (15 male, 15 female) who reported a regular consumption of ecstasy for at least 20 weeks prior to participation. The group of ex-ecstasy users included 31 participants (16 male, 15 female) who reported a lifetime exposure of at least 250 ecstasy tablets, and stopped using ecstasy 20 weeks or longer before participation. The 29 polydrug controls (15 male, 14 female) reported a pattern of illegal drug use similar to that of the ecstasy subjects, with the exception of ecstasy. The 30 drug-naive control participants (15 male, 15 female) reported to have never used illegal drugs. Subjects were instructed to abstain from illegal drug use for 6 days prior to testing. On the morning of each day of testing urine screening for drugs and alcohol was performed. In case of positive results subjects were either excluded from the study or given a new appointment. All subjects signed a consent form after they had been informed about the details by the principal investigator (R.T.). The study protocol was approved by the local Ethics Committee, the Health Board and the Federal Authority for Radiation Protection (Bundesamt für Strahlenschutz). The research project was carried out at the University Hospital Hamburg-Eppendorf.

## Recruitment and procedure

Calls for participants were published in local newspapers, magazines and leaflets distributed at techno events and educational institutions in the Hamburg area. Participants were required to be 18–30 years old and were offered payment (EUR 127) and feedback of individual test results. Upon initial phone contact, details relevant for inclusion in the study were obtained from the applicants. Exclusion criteria were acute major medical illness, pregnancy, epilepsy, major depression, schizophrenia and alcohol or opiate dependence. Of the approximately 1500 applicants, 184 received an appointment and 120 completed the testing. The recruitment strategy was first to invite suitable ecstasy users and then to match the control groups by sociodemographic variables. Additionally, the polydrug control group was approximated as closely as possible by the concomitant drug use of the ecstasy groups. The duration of the clinical interviews, neuropsychological tests, PET, drug use history and Addiction Severity Index interviews, neurological examinations, toxicological and blood sampling amounted to approximately 16 h. Testing took place on 2 days, with 1 free day in between whenever possible. Additionally, the participants completed a number of questionnaires at home, which took approximately 3 h.

## Sociodemography, psychopathology and drug histories

Sociodemographic data and an estimate of the severity of problems in seven areas commonly affected by drug use (medical, employment, alcohol, drug, legal, family/social and psychiatric problems) were obtained using the European Addiction Severity Index (McLellan et al. *1992*; Gsellhofer et al. *1994*) interview. The Structured Clinical Interview for DSM-IV (SKID; Wittchen et al. *1997*) was used to establish whether participants met criteria for any mental (axis I) disorders. The subjective perception of psychopathological symptoms was assessed with the Symptom Check List (SCL-90-R, Derogatis *1994*; Franke *1995*). Urine samples were screened for amphetamine, methamphetamine, MDMA, MDA, MDE, barbiturates, benzodiazepines, THC, cocaine metabolites, opiates and alcohol. Hair samples were analyzed for amphetamine, methamphetamine, MDA, MDMA, MDEA and MBDB.

Drug histories were obtained by trained interviewers in detailed semi-structured interviews. Subjects were asked to remember the amount of drugs taken per month, starting with the last month and then going back along the time axis. They were encouraged to recollect the relevant events of each month to support their memory. Additional information, such as the maximum number of exposures to ecstasy on a

single occasion, time of abstinence and ways of application was collected. Secondly, subjects were asked to give a detailed description of their individual drug use pattern in the course of a typical party event. The number of ecstasy tablets taken on such a typical occasion was defined as the *typical ecstasy exposure* for the purpose of this study. Finally, subjects estimated their alcohol, tobacco and medication intake for the past week.

## Neurocognitive test battery

Premorbid intelligence was estimated with a German multiple-choice test of vocabulary knowledge (Mehrfachwahl-Wortschatztest, MWT-B; Lehrl *1985*). Current IQ was assessed from performance on two sub-tests of the German Wilde Intelligence Test (WIT, "observation" and "calculation"; Jäger and Althoff *1994*) and reverse digit recall of the Hamburg-Wechsler Intelligence Test (HAWIE-R; Tewes *1994*). Complex attention skill was tested with the "GoNogo" and "divided attention" sub-tests from a German battery of attention tests (Testbatterie zur Aufmerksamkeitsprüfung, TAP; Zimmermann and Flimm *1993*). The Trail-Making-Test A (TMT-A; Reitan *1992*) was used as a measure of psychomotor speed. Executive function was tested with the Wisconsin Card Sorting Test (WCST; Heaton *1981*) and TMT-B (Reitan *1992*). Learning and memory ability were assessed with two sub-tests from a German test battery, "phone numbers" and "company signs" which require the retention of learned information over a period of 30 min (Lern- und Gedächtnistest, LGT-3; Bäumler *1974*). A brief news story from the Rivermead Behavioral Memory Test (RBMT; Wilson et al. *1985*) was used to test the immediate and 20-min delayed recall of verbal context-bound material. Sequential tests of acquisition, recall and decay of verbal memory were performed with the Auditory Verbal Learning Test (AVLT; Lezak *1983*). This involves learning a list of 15 words read out loud to the subject with immediate reproduction of the learned items in each of five consecutive trials (AVLT 1–5). A second list is presented on the sixth trial (AVLT 6). Interference is measured on a seventh trial by asking the subject to reproduce the original list (AVLT 7). Delayed recall of the first list is tested after 20 min (AVLT 8).

## Positron emission tomography

Positron emission tomography (PET) was performed with the serotonin transporter ligand [$^{11}$C](+)McN5652. This tracer has been demonstrated to provide a highly specific binding to serotonin transporters of the human brain in vivo (Szabo et al. *1995*, *1996*). [$^{11}$C](+)McN5652 was synthesized as described by Suehiro et al. (*1992*, *1993*).

Imaging was performed on a full-ring whole-body system ECAT EXACT 921/47 (Siemens/CTI, Knoxville, Tenn., USA; Wienhard et al. *1992*) in 2D mode. This system covers an axial field-of-view of 16.2 cm by collecting 47 transversal slices with 3.4 mm slice separation.

Head movement was minimized by a thermoplastic mask (Tru-Scan Imaging, Annapolis, Md., USA). A 15-min transmission scan for attenuation correction was obtained before tracer injection using three rotating $^{68}$Ge rod sources, about 70 MBq each. After the transmission scan, 466±76 MBq of [$^{11}$C](+)McN5652 dissolved in 40 ml of 0.9% NaCl was injected through a vein in the left hand at a rate of 600 ml/h. At the beginning of tracer injection, a dynamic scan protocol was initiated including 35 frames with a total acquisition time of 90 min. Subjects were asked to keep their eyes open during the whole time of acquisition. Noise in the acquisition room was kept to a minimum.

The sinograms were corrected for random coincidences, radioactive decay, dead time and varying detector efficiency. Thereafter, the sinograms were 3D-smoothed by

application of a 3 × 3 × 3 binomial kernel. Forty-seven transaxial slices with 64 × 64 voxels were reconstructed using an iterative method. The voxel size was 3.4 × 3.4 × 3.4 $mm^3$, in-plane spatial resolution was about 9 mm full width at half maximum (FWHM). No scatter correction was performed.

In spite of the thermoplastic mask immobilization, there was significant head movement during the acquisition in a number of subjects. This was corrected by application of the Realign tool of the SPM99 software package (Welcome Department of Cognitive Neurology, Institute of Neurology, University College, London; Acton and Friston *1998*). In order to support standardized identification of the volumes of interest (VOIs) in each subject, individual images were stereotactically normalized using the Normalize tool of SPM 99. A [$^{11}$C](+)McN5652 template created earlier served as reference for stereotactic normalization.

In accordance with current literature, the following brain structures were selected for testing the hypothesis of ecstasy-induced alteration of SERT availability (Laruelle et al. *1988*; Buck et al. *2000*; Parsey et al. *2000*): mesencephalon, putamen, caudate and thalamus. White matter served as a control region in which no ecstasy-induced effects were expected due to the absence of SERT. The grey matter of the cerebellum was chosen as the reference region for kinetic modeling.

VOIs for the structures to be examined were predefined in the template. Each VOI was composed of circles of 4.1 mm radius, placed in an appropriate number of transversal slices (Weeks et al. *1997*). No individual adjustment was performed in order to guarantee reproducible results. Kinetic modeling was performed on the level of voxels. Distribution volume ratios (DVRs) were derived by application of the graphic reference tissue method for reversible binding described by Ichise et al. (*1996*, *2001*; Ichise non-invasive plot). The time-activity curve of the reference region was generated using the mean of the cerebellum VOI. The start time for the multilinear regression analysis was fixed at t*=12 min. DVRs for the examined structures were taken to be the mean voxel values within the corresponding VOIs copied to the individual parametric images.

## Statistical analysis

Statistical analysis was performed with SPSS version 10. Group differences were tested for significance with one-way analyses of variance (ANOVA). Analyses of covariance (ANCOVA) were performed to determine whether sex, estimated amount of cannabis, amphetamine, LSD, psilocybin and cocaine taken in the past year or the typical number of exposures to ecstasy were statistically significant covariates and whether they had any effect on the statistical significance of group differences. Planned multiple comparisons were performed with Scheffé tests and in the case of variance inhomogeneity, with Tamhane's $T^2$. All tests of significance were two-tailed.

Stepwise multiple regressions were employed to investigate which parameters of drug use best predicted the dependent variables. The following parameters were entered as predictor variables: the estimated amounts of ecstasy, cannabis, amphetamine, LSD, psilocybin and cocaine taken in the year prior to participation, the maximum and typical number of exposures to ecstasy and the estimated lifetime exposure to ecstasy (cf. Morgan *2002*). The regression coefficients are positive unless otherwise indicated.

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# Results

## Participant details and drug use histories

An overview of relevant sociodemographic and personal characteristics of each group is presented in Table 1. The groups did not differ significantly in gender ratio, mean age, level of education or estimated pre-morbid IQ. There were significant group differences in the use of alcohol [$F(3,116)=4.46$, $P=0.004$] and nicotine [$F(3,116)=16.66$, $P=0.000$] in the week prior to testing. On average, polydrug control participants drank significantly more alcohol than current ecstasy users and drug-naive controls and smoked significantly more cigarettes than the drug-naive controls. The male and female participants in each group did not differ significantly with respect to age, level of education and pre-morbid IQ. On average, current users had last taken ecstasy 23 (SD=16.14) and ex-users 515 (SD=495.07) days before testing, but did not differ significantly on any other parameter of ecstasy use (Table 2).

**Table 1.** Personal characteristics: frequencies, mean±SD

| | Current ecstasy users | Ex-ecstasy users | Polydrug controls | Drug-naive controls |
|---|---|---|---|---|
| *n* (male, female) | 30 (15/15) | 31 (16/15) | 29 (15/14) | 30 (15/15) |
| Age | 24.50±4.00 | 24.13±4.21 | 24.41±4.55 | 23.13±3.67 |
| Education[a] | 8/10/12 | 8/11/12 | 5/13/11 | 7/10/13 |
| IQ[b] | 102.50±9.64 | 106.48±13.94 | 104.28±9.90 | 104.97±13.47 |
| Cigarettes/week | 51.20±57.94 | 94.02±73.44 | 125.31±83.05 | 14.13±35.73 |
| Alcohol g/week | 87.88±96.19 | 137.09±190.63 | 195.42±194.28 | 61.35±73.17 |

[a] *n* basic (9 years)/intermediate (10 years)/college admission level (13 years)

[b] Pre-morbid IQ estimated from MWT-B

**Table 2.** Parameters of ecstasy use in the current and ex-ecstasy users: mean±SD

| | Current ecstasy users | | Ex-ecstasy users | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| ***n*** | **15** | **15** | **16** | **15** |
| Estimated lifetime exposure (tablets) | 1033.77±1702.44 | 600.42±565.28 | 987.31±824.50 | 533.80±317.22 |
| Maximum exposure per session | 12.25±19.93 | 4.77±3.69 | 8.81±6.73 | 7.33±7.28 |
| Typical exposure per session | 4.83±2.85 | 3.07±2.20 | 6.07±6.00 | 1.91±1.61 |
| Tablets taken in previous month | 1.87±2.10 | 1.20±1.42 | 0 | 0 |
| Age of first ecstasy use | 19.47±3.14 | 20.47±4.39 | 19.13±3.30 | 17.13±2.20 |
| Duration of use (months) | 45.50±32.81 | 60.53±32.08 | 56.44±23.77 | 52.47±32.79 |
| Time since last use (days) | 21.60±16.38 | 24.73±16.32 | 485.40±533.09 | 545.13±470.74 |

With respect to all illegal drugs other than ecstasy, the three drug-using groups did not differ significantly in the amount taken in the 30 days prior to testing (Table 3). None of the cocaine or LSD use parameters differed significantly between the groups. However, the polydrug controls had taken significantly less amphetamine relative to the current ecstasy users in the year prior to testing and relative to both ecstasy groups in their lifetime. In contrast, the polydrug controls had taken significantly more psilocybin mushrooms in their lifetime than current ecstasy users, but the number of subjects with psilocybin experience was generally small. The amount of cannabis smoked by current ecstasy users in their lifetime as well as in the 12 months prior to testing was significantly lower

than that of ex-ecstasy users. Eight participants had tried heroin, liquid ecstasy (GHB), poppers or nitrous oxide. The concordance between subjective reports of ecstasy use or abstinence with the hair analyses was 95%. None of the hair samples contained methamphetamine or MBDB.

**Table 3.** Self reported use of other illicit drugs in the three user groups: number of participants (*n*) reporting use; mean±SD

| | Current ecstasy users (CE) | Ex-ecstasy users (EE) | Polydrug controls (PC) | Significant multiple comparisons |
|---|---|---|---|---|
| Cannabis (*n*) | 29 | 31 | 28 | – |
| Grams consumed in past year | 88.22±229.21 | 281.35±411.67 | 141.91±150.76 | CE vs EE |
| Grams consumed in past 30 days | 7.76±18.29 | 18.46±28.57 | 10.70±12.72 | – |
| Duration of use (months) | 59.75±46.78 | 81.77±38.50 | 112.96±75.92 | CE vs PC |
| Lifetime exposure | 566.78±1187.98 | 2132.91±2199.77 | 1247.66±1290.57 | CE vs EE |
| Psilocybin mushrooms (*n*) | 3 | 6 | 10 | – |
| Number consumed in past year | 0.55±1.60 | 2.12±8.40 | 1.47±3.70 | – |
| Number consumed in past 30 days | 0.067±0.37 | 0.31±1.23 | 0.069±0.37 | – |
| Duration of use (months) | 21.88±24.64 | 25.70±29.26 | 17.88±14.90 | – |
| Lifetime exposure | 0.85±3.19 | 5.05±15.98 | 14.41±32.52 | CE vs PC |
| Cocaine (*n*) | 28 | 30 | 22 | – |
| Grams consumed in past year | 6.22±15.11 | 5.33±14.01 | 16.10±36.69 | – |
| Grams consumed in past 30 days | 0.39±0.88 | 0.27±1.01 | 1.83±5.49 | – |
| Duration of use (months) | 29.92±36.30 | 43.07±35.97 | 57.70±44.66 | – |
| Lifetime exposure | 39.10±76.43 | 101.41±218.86 | 254.66±708.53 | – |
| Amphetamine (*n*) | 27 | 27 | 12 | – |
| Grams consumed in past year | 15.15±34.55 | 8.91±45.26 | 0.98±4.64 | CE vs PC |
| Grams consumed in past 30 days | 2.65±10.46 | 0.00±0.00 | 0.07±0.37 | – |
| Duration of use (months) | 34.50±26.15 | 31.72±26.02 | 15.23±18.45 | – |
| Lifetime exposure | 67.90±105.77 | 77.37±115.35 | 4.24±9.07 | CE & EE vs PC |
| LSD (*n*) | 22 | 27 | 11 | – |
| µg consumed in past year | 190.42±809.87 | 19.76±49.77 | 8.62±37.96 | – |

| | Current ecstasy users (CE) | Ex-ecstasy users (EE) | Polydrug controls (PC) | Significant multiple comparisons |
|---|---|---|---|---|
| µg consumed in past 30 days | 17.92±73.96 | 0.00±0.00 | 0.00±0.00 | – |
| Duration of use (month) | 27.70±27.32 | 34.63±26.82 | 25.27±26.86 | – |
| Lifetime exposure | 1608.90±5178.09 | 2436.88±5127.33 | 160.29±375.80 | – |

# Group differences

## Psychopathology

The one-way ANOVA yielded significant group differences for the SCL-90-R Global Severity Index [GSI; $F(3,113)=7.39$, $P=0.000$] and all sub-scales: aggression/hostility [$F(3,113)=4.09$, $P=0.009$], somatisation [$F(3,113)=5.36$, $P=0.002$], obsessive-compulsive [$F(3,113)=9.32$, $P=0.000$], phobic anxiety [$F(3,113)=8.03$, $P=0.000$], interpersonal sensitivity [$F(3,113)=5.17$, $P=0.002$], depression [$F(3,113)=4.73$, $P=0.004$], paranoid ideation [$F(3,113)=2.99$, $P=0.034$], psychoticism [$F(3,113)=4.77$, $P=0.004$] and anxiety [$F(3,113)=3.95$, $P=0.010$]. Planned comparisons showed no significant differences of current and ex-ecstasy users versus polydrug controls. Compared with the drug-naive controls, all drug-using groups had significantly elevated GSI scores. Additionally, the ex-ecstasy users exhibited elevated scores on most and the current ecstasy users and polydrug controls on some of the SCL-90-R sub-scales (Table 4i, Fig. 1). The typical number of exposures to ecstasy (TE) was a significant covariate for GSI [$F(3,106)=3.30$, $P=0.023$, $\eta^2=0.06$; TE: $F=4.70$, $P=0.032$, $\eta^2=0.04$], anxiety [$F(3,106)=3.19$, $P=0.027$, $\eta^2=0.08$; TE: $F=7.32$, $P=0.008$, $\eta^2=0.07$], psychoticism [$F(3,106)=2.14$, $P=0.100$, $\eta^2=0.06$; TE: $F=4.21$, $P=0.043$, $\eta^2=0.04$], and together with sex, for somatisation [$F(3,106)=5.64$, $P=0.001$, $\eta^2=0.14$; TE: $F=4.97$, $P=0.028$, $\eta^2=0.05$; sex: $F=4.97$, $P=0.028$, $\eta^2=0.04$]. The amount of cannabis smoked in the year prior to testing (CY) was a significant covariate for obsessive-compulsive [$F(3,106)=2.69$, $P=0.050$, $\eta^2=0.07$; CY: $F=6.63$, $P=0.011$, $\eta^2=0.06$] and aggression [$F(3,106)=3.37$, $P=0.027$, $\eta^2=0.06$; CY: $F=7.76$, $P=0.006$, $\eta^2=0.07$]. The group differences in psychoticism, obsessive-compulsive and aggression were no longer significant when all measures of drug use were simultaneously treated as covariates.

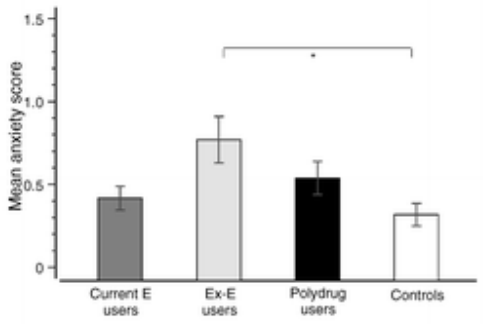
**Table 4.** Statistically significant group differences

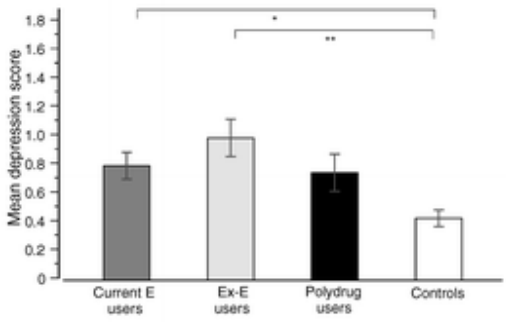
| | Current ecstasy vs drug-naive | Ex–ecstasy vs drug-naive | Current ecstasy vs polydrug | Ex–ecstasy vs polydrug | Polydrug vs drug naive | Current ecstasy vs ex-ecstasy |
|---|---|---|---|---|---|---|
| i) Measures of psychopathology: SCL-90-R | | | | | | |
| Global severity index | **[a] | ***[a] | – | – | *[a] | – |
| Aggression/hostility | – | **[a] | – | – | *[a] | – |
| Somatisation | – | *[a] | – | – | – | – |
| Obsessive-compulsive | ***[a] | ***[a] | – | – | *[a] | – |
| Anxiety | – | *[a] | – | – | – | – |

| | Current ecstasy vs drug-naive | Ex–ecstasy vs drug-naive | Current ecstasy vs polydrug | Ex–ecstasy vs polydrug | Polydrug vs drug naive | Current ecstasy vs ex-ecstasy |
|---|---|---|---|---|---|---|
| Phobic anxiety | – | **[a] | – | – | – | – |
| Inter-personal sensitivity | *[a] | **[a] | – | – | *[a] | – |
| Depression | *[a] | **[a] | – | – | – | – |
| Paranoid ideation | – | *[a] | – | – | – | – |
| Psychoticism | – | **[a] | – | – | – | – |
| ii) Measures of cognitive performance | | | | | | |
| RBMT immediate recall | – | * | – | – | – | – |
| RBMT delayed recall | – | * | – | – | – | – |
| AVLT 1 immediate recall | – | * | – | – | – | – |
| AVLT sum of 5 initial trials | – | * | – | – | – | – |
| AVLT 5–1 | – | – | – | – | – | * |
| AVLT 6 | – | * | – | – | * | – |
| AVLT 8 | – | * | – | – | – | – |
| WCST perseverative errors | – | – | ** | ** | – | – |
| iii) Measures of availability of 5-HT transporters: [$^{11}$C](+)McN5652 distribution volume ratio | | | | | | |
| Midbrain | ** | – | ** | – | – | * |
| Caudate nucleus | – | – | * | – | – | – |

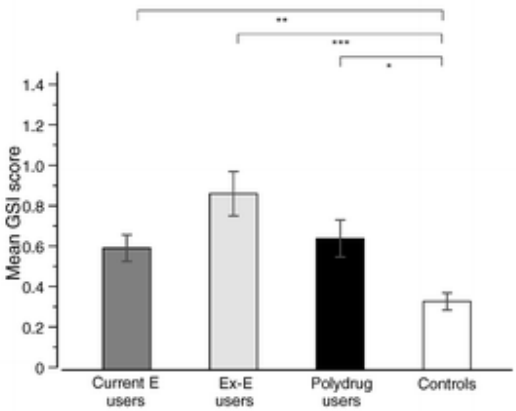
***$P$<0.001, **$P$<0.01, *$P$<0.05

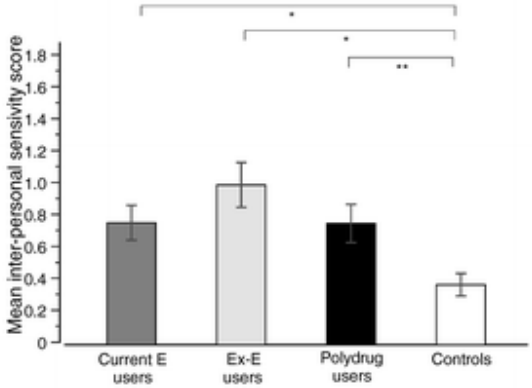
[a]Because of unequal variances Tamhane's $T^2$, otherwise Scheffé tests




**a** **b**



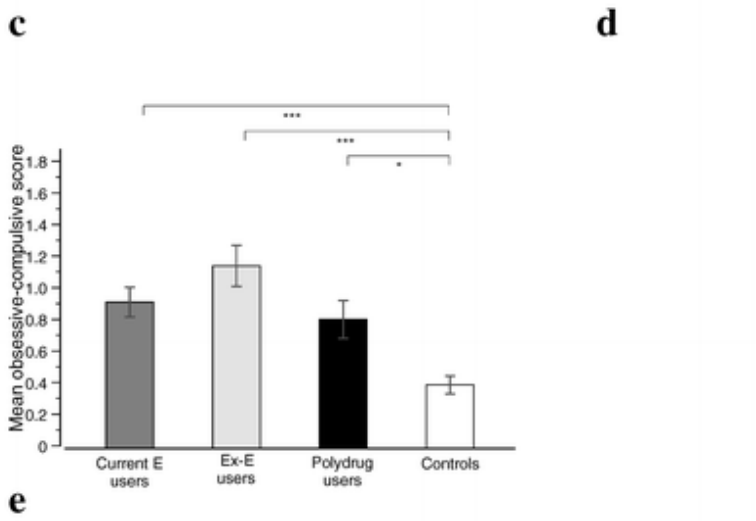
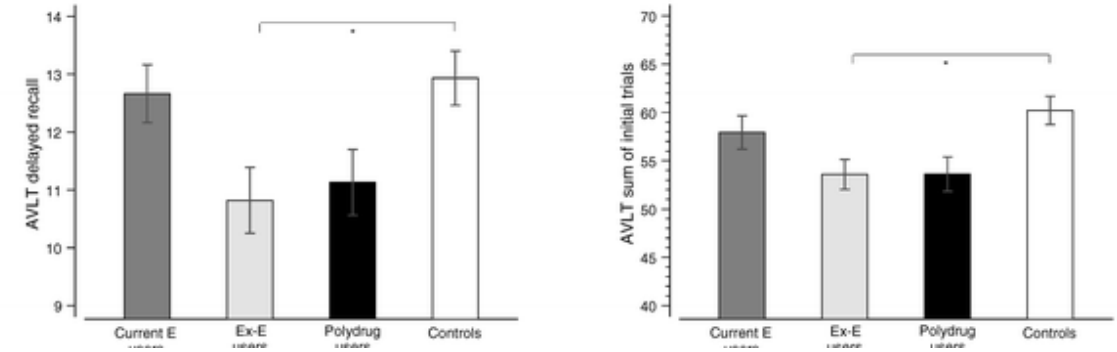



**Fig. 1.** Group differences in SCL-90-R scores (mean±SEM). **a** Anxiety; **b** depression; **c** GSI; **d** interpersonal sensitivity; **e** obsessive-compulsive

## Cognitive performance

One-way ANOVAs revealed no significant group differences in the measure of premorbid intelligence (MWT-B) and current IQ (WIT, HAWIE-R). Similarly, no significant differences were found in the tests of complex attention ability (TAP), psychomotor speed (TMT-A) and executive functioning (TMT-B). In the WCST, only the measure of perseverative errors yielded a significant result [$F(3,111)=7.62$, $P=0.000$]. Planned comparisons indicated that polydrug controls had significantly higher scores than either ecstasy group. Memory and learning ability as measured with the LGT-3, did not differ significantly between the groups. However, significant differences (Table 4, part ii) were found in the performance on immediate [$F(3,115)=2.92$, $P=0.037$; Fig. 2d] and delayed [$F(3,11)=42.94$, $P=0.036$; Fig. 2c] recall of the RBMT brief news story. Ex-ecstasy users performed significantly worse than drug-naive controls on both RBMT measures. Most sub-scales of the AVLT also revealed significant group differences: AVLT 1 [immediate recall on first trial; $F(3,116)=2.82$, $P=0.042$; Fig. 2], AVLT 1–5 [sum of five initial trials; $F(3,115)=4.00$, $P=0.010$], AVLT 5–1 [improvement from trial 1 to 5; $F(3,116)=2.69$, $P=0.050$], AVLT 6 [new list; $F(3,116)=4.67$, $P=0.004$], AVLT 7–5 [interference; $F(3,113)=2.71$, $P=0.049$] and AVLT 8 [delayed reproduction of original list; $F(3,107)=4.11$, $P=0.008$]. Multiple comparisons indicated that current ecstasy users were not significantly impaired on any AVLT measure compared with the control groups. Ex-ecstasy users performed significantly worse on AVLT 1, AVLT sum of initial trials (Fig. 2e), AVLT 6 and AVLT 8 (Fig. 2a) than drug-naive controls. The ex-ecstasy users had significantly higher AVLT 5–1 scores than current ecstasy users. Polydrug controls performed significantly worse on AVLT 6 than drug-naive controls.



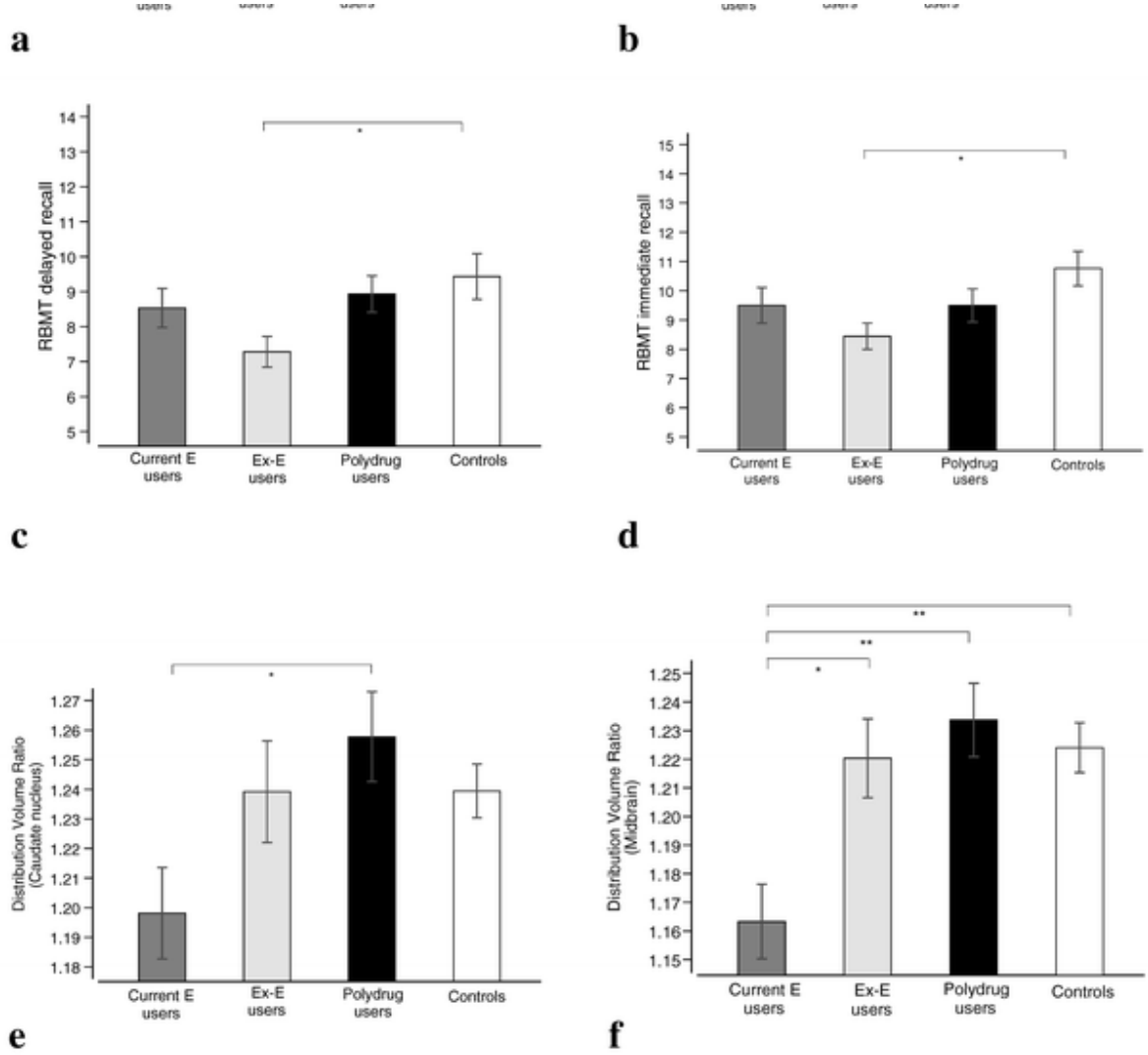



**Fig. 2.** Group differences in memory performance and distribution volume ratios of serotonin transporters (mean±SEM). **a**AVLT delayed recall; **b** AVLT sum of initial five trials; **c** RBMT delayed recall; **d** RBMT immediate recal; **e** distribution volume ratio, caudate nucleus; **f** distribution volume ratio, mesencephalon

The amount of cocaine taken in the past year (CoY) and sex were significant covariates for AVLT sum of initial five trials [$F(3,106)=2.83$, $P=0.042$, $\eta^2=0.08$; sex: $F=4.71$, $P=0.032$, $\eta^2=0.04$; CoY: $F=2.83$, $P=0.042$, $\eta^2=0.08$]. There were no significant covariates for any other measure of cognitive performance that had differentiated between the groups. None of the group differences were affected by using measures of illicit drug use and sex as covariates.

## Measures of neuroimaging

The [$^{11}$C](+)McN5652 DVRs did not differ significantly between the groups in the white matter (control region) and putamen. ANOVAs indicated significant group differences in the mesencephalon [$F(3,113)=6.86$, $P=0.000$], caudate nucleus [$F(3,113)=3.03$, $P=0.032$] and thalamus [$F(3,113)=3.34$, $P=0.022$]. Current ecstasy users exhibited significantly reduced DVRs in the mesencephalon relative to all other groups and in the caudate nucleus only relative to polydrug controls. The typical number of exposures to ecstasy (TE) was a significant covariate for the DVRs of SERT in the caudate nucleus [$F(3,106)=1.61$, $P=0.190$, $\eta^2=0.04$; TE: $F=5.24$, $P=0.024$, $\eta^2=0.05$] and together with the amount of LSD taken in the year prior of testing (LY) and sex, for the thalamus

[$F$(3,106)=3.11, $P$=0.029, $\eta^2$=0.08; TE: $F$ =5.08, $P$=0.026, $\eta^2$=0.05; sex: $F$=6.39, $P$=0.013, $\eta^2$=0.06; LY: $F$=6.13, $P$=0.015, $\eta^2$=0.06]. Sex and amount of LSD taken in the year prior to testing (LY) were also significant covariates for the DVRs in the mesencephalon [$F$(3,106)=5.20, $P$=0.002, $\eta^2$=0.13; sex: $F$=4.84, $P$=0.030, $\eta^2$=0.04; LY: $F$=4.07, $P$=0.046, $\eta^2$=0.04]. The group differences in the caudate nucleus were no longer significant when measures of illicit drug use and sex were treated as covariates simultaneously.

## Stepwise regression analyses

### Measures of psychopathology

Most SCL-90-R scales were best predicted by the typical number of exposures to ecstasy by itself or in combination with other drug use parameters. Only interpersonal sensitivity was best predicted by the amount of cannabis smoked in the year prior to testing ($R^2$=0.04, $P$=0.037). Four scales were best predicted by the typical number of exposures to ecstasy: somatisation ($R^2$=0.10, $P$=0.001), depression ($R^2$=0.10, $P$=0.000), anxiety ($R^2$=0.10, $P$=0.001) and paranoid ideation ($R^2$=0.09, $P$=0.001). Four scales were best predicted by the typical number of exposures to ecstasy in combination with the amount of cannabis smoked in the year prior to testing: GSI ($R^2$=0.18, $P$=0.000), obsessive-compulsive ($R^2$=0.25, $P$=0.000), phobic anxiety ($R^2$=0.12, $P$=0.001) and psychoticism ($R^2$=0.16, $P$=0.000). Aggression was best predicted by the typical number of exposures to ecstasy together with the amount of LSD (negative beta weight) and cannabis taken in the year prior to testing ($R^2$=0.18, $P$=0.000).

### Measures of cognitive performance

AVLT 1 (immediate recall on first trial) was best predicted by the typical number of exposures to ecstasy ($R^2$=0.04, $P$=0.023). The best predictor of AVLT 8 scores was the lifetime exposure to ecstasy ($R^2$=0.05, $P$=0.026). The amount of cannabis smoked in the year prior to testing best predicted AVLT 6 ($R^2$=0.03, $P$=0.023), RBMT immediate ($R^2$=0.05, $P$=0.016) and delayed recall ($R^2$=0.05, $P$=0.019). AVLT 1–5 (sum of five initial trials) was best predicted by the amount of cocaine taken in the year prior to testing ($R^2$=0.07, $P$=0.003). All beta weights were negative.

### Measures of neuroimaging

The DVRs of SERT ligands were best predicted by parameters of ecstasy use. The typical number of exposures to ecstasy was the best predictor of the DVRs in the thalamus ($R^2$=0.12, $P$=0.000) and caudate nucleus ($R^2$=0.07, $P$=0.004) and the number of ecstasy tablets taken in the year prior to testing was the best predictor of the DVRs in the mesencephalon ($R^2$=0.12, $P$=0.000).

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# Discussion

In agreement with the findings of Gamma et al. (*2000*), Gerra et al. (*2000*), Parrott et al. (*2001*), Wareing et al. (*2000*) and Thomasius (*2000*), both groups of ecstasy users reported significantly elevated psychopathology relative to drug-naive controls. In a

similarly designed study, Morgan et al. (*2002*) found elevated psychopathology in current ecstasy users. Their findings of significant differences between current ecstasy users and polydrug controls on all SCL-90-R scales were not replicated in this study.

From the lack of significant group differences in self-reported psychopathology between ecstasy users and polydrug controls, it may be concluded that there was no statistical effect of ecstasy use beyond the use of other illicit drugs. Therefore, this part of the statistical hypothesis was not confirmed by our data. It seems noteworthy, however, to consider in what ways the three groups of drug users differed from drug-naive controls. The elevated scores on the SCL-90-R scales aggression/hostility, obsessive-compulsive and inter-personal sensitivity can be clearly interpreted as an effect of polydrug use per se, since they were present in ecstasy and polydrug users. On the other hand, elevated depression scores were reported by current and ex-ecstasy users but not by polydrug controls. Elevated depression may therefore be considered an ecstasy effect. Only ex-ecstasy users exhibited significantly elevated somatisation, anxiety, phobic anxiety, paranoid ideation and psychoticism scores. This is particularly surprising considering the study by Morgan et al. (*2002*), which found evidence that symptoms of psychopathology might remit with ecstasy abstinence. The different results regarding the ex-ecstasy users might be due to the fact that the ex-ecstasy users in our sample reported a heavier ecstasy exposure and an almost 9 months shorter average abstinence period than the ex-ecstasy users in the study by Morgan et al. (*2002*). The present results are partially compatible with Gerra et al. (*2000*), who found a remission of anger/hostility but persistently elevated depression scores in ecstasy users after approximately 1 year of abstinence.

A possible line of reasoning could be that individuals quitting ecstasy use might often find themselves in a transitional period of their lives, characterized by a loss of their familiar life style and social context such as the rave scene. Thus, from a psychosocial perspective, the impaired psychological well-being of ex-users might reflect a (temporary) disruption in their social integration. However, a cross sectional approach poses limits on assumptions of causality. It is quite possible that inherent psychopathological factors predispose people to use certain drugs (Deykin et al. *1986*, McGuire et al. *1994*, cf. Morgan *2002*). Ecstasy use might be an attempt to self-medicate symptoms of depression, inter-personal sensitivity, anxiety etc. (Khantzian *1997*), which would be an alternative plausible explanation of why ecstasy users exhibit elevated psychopathology after discontinuing ecstasy use. The self reported number of ecstasy tablets taken on a typical occasion, sometimes in combination with other parameters of drug use, best predicted the SCL-90-R scales with the exception of interpersonal sensitivity. This is in contrast to the results presented by Morgan et al. (*2002*), where psychopathology in ecstasy users was associated primarily with the extent of previous cannabis use and not ecstasy use. The present data suggest that the previous cannabis use may play an important, but secondary role for the psychopathology in our sample. However, the proportions of variance accounted for by our regression models were much smaller than those reported by Morgan (*2002*). The role of cannabis in obsessive-compulsive symptoms needs further research because some of our subjects with heavy cannabis use attributed their obsessive-compulsive symptoms to their cannabis use. It should be noted that the elevated SCL-90-R scores of the ecstasy user groups do not necessarily indicate a higher prevalence of psychological disorders of clinical relevance.

Ecstasy users were not significantly impaired on measures of intelligence (MWT-B, WIT, HAWIE-R), complex attention skill (TAP), psychomotor speed (TMT-A) and executive function (WCST, TMT-B).

Current ecstasy users showed no signs of impaired memory ability. The lack of impairment on immediate and delayed prose recall is in contrast to Bolla et al. (*1998*),

Parrott et al. (1998), Morgan (1999) and Rodgers (2000), but in agreement with Fox (2001) and Morgan (2002). Regarding the ability of current ecstasy users to learn AVLT word lists, the present study failed to replicate those of Bolla et al. (1998), Gouzoulis-Mayfrank et al. (2000), Fox et al. (2001) and Reneman et al. (2000, 2001a, 2001b). Ex-ecstasy users performed significantly worse than drug-naive controls on immediate and delayed recall of the RBMT brief news story and AVLT word list. They also had significantly reduced scores on AVLT sum of initial five trials and recalled significantly fewer words from the new ("interference") list (AVLT 6) relative to drug-naive controls. Ex-ecstasy users' scores on AVLT 5–1 were significantly higher than those of current ecstasy users, indicating that they gained more from repeated presentations of the word list, but neither ecstasy group differed significantly from the polydrug or drug-naive control subjects on this measure.

McCann et al. (1999), Wareing et al. (2000) and Gouzoulis-Mayfrank et al. (2000) have concluded that working memory is particularly affected by MDMA neurotoxicity. Data from the present study failed to support this notion, since no impairment could be found on measures believed to tap working memory such as reverse digit recall and the TMT (cf. Morgan et al. 2002).

Previous research has often found ecstasy users to be impaired primarily on memory performance and rarely on other domains of cognitive functioning that do not rely upon memory (e.g. Parrott et al. 1998; McCann et al. 1999; Klugman et al. 1999; Morgan 1999; Semple et al. 1999; Gouzoulis-Mayfrank et al. 2000; Reneman et al. 2000; Rodgers 2000; Fox et al. 2001; Verkes et al. 2001; Morgan et al. 2002). The present study confirmed a selective impairment of verbal memory in ecstasy users. However, it is surprising that only ex- but not current ecstasy users exhibited memory deficits. Previous studies by Morgan et al. (2002), Reneman et al. (2001a) and Wareing et al. (2000) have presented evidence that cognitive deficits in ecstasy users may not be reversed by prolonged abstinence, but the present results suggest that memory deficits may not become apparent before a certain period of abstinence.

Recent publications have proposed that cannabis rather than ecstasy use may be primarily responsible for memory deficits in ecstasy users (Rodgers 2000; Croft et al. 2001). In the present study, measures of drug use explained only small proportions of the variance in memory performance and neither a convincing ecstasy nor cannabis effect was found. Similarly, hardly any of the parameters of drug use were significant covariates of the measures of memory performance.

PET scans revealed that DVRs of SERT were reduced in serotonergic brain regions of current ecstasy users. The reductions were statistically significant in the mesencephalon compared with ex-ecstasy users, polydrug and drug-naive control groups, and significant in the caudate nucleus relative to polydrug controls. Multiple regression analyses indicated that the self reported number of ecstasy tablets taken on a typical occasion or ecstasy exposure in the past year predicted reductions of SERT DVRs.

Our data support the hypothesis that MDMA may cause alterations in SERT availability in the central serotonergic system, but also indicate that these alterations may recover after a period of abstinence. This is in agreement with recent PET or SPECT studies of SERT availability in ecstasy users (Reneman et al. 2000, 2001a, 2001b; McCann et al. 1998). A closer analysis of these studies shows that significant reductions in measures of SERT availability were found in ecstasy user groups with an average abstinence period of up to 4.6 months (Reneman et al. 2000), but that no significant reductions were detectable in ecstasy user groups with 17.2 months (present study) and 29 months (Reneman et al. 2001a) average ecstasy abstinence period. Scheffel et al. (1998) applied the same tracer as the present study and found evidence of SERT DVR reduction in baboons 40 days

following treatment with MDMA, but the reduction was no longer present at nine and 13-month follow-ups. Semple et al. (*1999*) found a positive correlation between duration of abstinence from ecstasy and tracer uptake in several brain regions using ([$^{123}$] $\beta$ -CIT)-SPECT. Altogether, these findings suggest that MDMA-induced reductions of SERT availability may be reversible. However, the evidence of long-lasting abnormal serotonergic re-innervation patterns in non-human primates following MDMA treatment (cf. Ricaurte et al. *2000*), warrant some caution about interpreting our findings as a recovery of MDMA-induced serotonergic alteration. Neuroimaging measures of SERT availability reflect not only the activity and concentration of SERTs but also depend on other factors such as the synaptic serotonin concentration (modified by multiple mechanisms, among others food restriction). Therefore PET or SPECT imaging alone might not be sufficient to exclude the possibility of permanent MDMA-induced serotonergic alterations.

Although the recruitment procedure was designed to gather a sample that would be representative of recreational ecstasy users, specific selection effects cannot be completely ruled out. In the group of current users might have been a large proportion of those who wanted to demonstrate that ecstasy use was not as harmful as generally suggested by the media. Ex-users, on the other hand, may have been especially attracted by the possibility of checking symptoms they attributed to their former ecstasy use. Therefore this group may have contained a disproportionate number of subjects who had discontinued ecstasy use because of the severity of perceived psychiatric or cognitive symptoms. Qualitative data from the psychiatric interviews suggest that most subjects had simply matured out the party scene. The subjects' motivation to participate will be focus of a qualitative evaluation of the psychiatric interviews (results are in preparation).

Another limitation affecting all studies in ecstasy research is the difficulty in obtaining reliable and valid data on drug use from the participants. This is a particularly sensitive issue considering the hypothesis that ecstasy use may be associated with memory problems. This research project developed a standardized, detailed and thorough procedure of obtaining drug use histories with a specific focus on supporting the memory of the subjects. The fact whether a subject had or had not taken ecstasy in the past 5 months was verified with toxicological data, but it was not possible to verify the other important drug use parameters such as the lifetime self reported exposures, exact duration of abstinence or number and content of ecstasy tablets taken on a typical event. Since there is no information on retest reliability and validity of the drug use parameters, all these variables must be regarded as estimates.

In summary, the postulated irreversible ecstasy effects on psychological well-being, cognitive performance and SERT availability were not confirmed by our data. No significant mean differences between the ecstasy user groups and the polydrug controls were found in any of the measures of psychopathology or cognitive performance. Therefore, the theoretical assumption that MDMA serotonergic neurotoxicity would be associated with axonal damage and secondary to that with psychiatric and neurocognitive problems (cf. Parrott *2001*) was not supported by our data.

The essential results of the present study were the significantly reduced availabilty of SERT in the mesencephalon and thalamus of current, but not former ecstasy users, indicating a transient effect of MDMA on the serotonergic system. Only former, but not current ecstasy users exhibited impaired verbal memory, suggesting that memory deficits were not related to SERT availability. The verbal memory impairments found were unique to the ex-ecstasy users, which is in contrast to the results of previous studies, where current users appeared most strongly impaired on verbal memory. Elevated self-reported psychopathology was found in current and former ecstasy users but also in polydrug controls. This might indicate that impaired psychological well-being is associated with

polydrug use and not specifically with ecstasy use.

As the presented data are the baseline of a longitudinal study, the results of the follow-ups promise further insights into possible changes which might take place during ecstasy abstinence or continued ecstasy use.

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