Psychopharmacology (2001) 153:196–202
DOI 10.1007/s002130000563

ORIGINAL INVESTIGATION

Robbert J. Verkes · Harm J. Gijsman
Monique S.M. Pieters · Rik C. Schoemaker
Saco de Visser · Monique Kuijpers
Ed J.M. Pennings · Dick de Bruin
Govert Van de Wijngaart · Joop M.A. Van Gerven
Adam F. Cohen

Cognitive performance and serotonergic function in users of ecstasy

Received: 28 February 2000 / Accepted: 11 August 2000 / Published online: 26 October 2000

Abstract *Rationale:* (±) 3,4-Methylenedioxymethamphetamine (MDMA or "ecstasy") has been shown to cause long term damage to serotonergic cerebral neurons in animals. The neurotoxic effects in humans are less clear and little is known about the functional consequences, although some studies suggest memory impairment. Given the widespread use of MDMA, our lack of knowledge raises concerns. *Objective:* We investigated, in humans, the relation between past use of ecstasy and cognitive performance as well as serotonergic function. *Methods:* Two groups of 21 males with moderate and heavy recreational use of MDMA, respectively, and a control group of 20 males without use of MDMA were compared. All were from the same subculture. Reaction time, direct recall, and recognition were assessed. Serotonergic function was measured by the neuro-endocrine response to a placebo-controlled, crossover challenge with dexfenfluramine. *Results:* Ecstasy users showed a broad pattern of statistically significant, but clinically small, impairment of memory and prolonged reaction times. Heavy users were affected stronger than moderate users. Release of cortisol but not of prolactin after dexfenfluramine administration was significantly reduced in both groups of ecstasy users compared with the controls. Analyses of covariance showed that likely confounding variables including recent exposure to ecstasy, psychosocial profiles and use of other drugs did not explain the differences found between the groups. *Conclusions:* These results provide further evidence that use of ecstasy may be associated with impairment of memory and of serotonergic function. These findings are compatible with neurotoxicity of ecstasy as shown in animals.

Keywords MDMA · Ecstasy · Serotonin · Memory · Cognition · Neurotoxicity

This study was fully funded by a research grant from the Ministry of Health, Welfare and Sports of the Netherlands. There are no conflict of interest issues for this study

R.J. Verkes (✉) · H.J. Gijsman · M.S.M. Pieters
R.C. Schoemaker · S. de Visser · M. Kuijpers
J.M.A. Van Gerven · A.F. Cohen
Centre for Human Drug Research, Zernikedreef 10,
2333 CL Leiden, The Netherlands
e-mail: r.verkes@czzopsy.azn.nl
Fax: +31-24-3540561

R.J. Verkes
Department of Psychiatry, University Medical Centre Nijmegen,
P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

E.J.M. Pennings
Department of Toxicology,
Leiden University Medical Center L1-39, P.O. Box 9600,
2300 RC Leiden, The Netherlands

D. de Bruin · G. Van de Wijngaart
Addiction Research Institute (CVO), Bijlhouwersstraat 6,
3511 ZC Utrecht, The Netherlands

Introduction

(±) 3,4-Methylenedioxymethamphetamine (MDMA) or "ecstasy" is a recreational drug that is widely used at rave parties. Administration of MDMA to animals in doses comparable to those used by humans results in damage to serotonergic cerebral neurons (Green et al. 1995). Some studies suggest comparable neurotoxic effects in humans (McCann et al. 1998; Semple et al. 1998), but more research in the area is required.

Impairment of the central serotonergic system may result in a blunted rise in the plasma levels of cortisol and prolactin after a serotonergic challenge (Bond et al. 1995; Newman et al. 1998). Challenge with L-tryptophan in ecstasy users showed equivocal results (Price et al. 1989; McCann et al. 1994). Challenge with the indirect serotonin agonist dexfenfluramine showed a blunted cortisol and prolactin response in ecstasy users, but the differences with normal controls could be ascribed to personality and other baseline characteristics (Gerra et al. 1998).

The serotonergic system plays a role in the regulation of mood, impulse control, memory, and in behaviour that involves a high cognitive demand (Buhot 1997). A neurotoxic effect of MDMA could theoretically compromise the serotonergic system to such an extent that this may result in abnormalities in all these areas. Indeed, chronic MDMA use has been associated with impulsiveness on self-report and behavioural measures (Morgan 1998) and electroencephalogram variables (Allen et al. 1993; Dafters et al. 1999). In three previous neuropsychological studies (Krystal et al. 1992; Bolla et al. 1998; Parrott et al. 1998), ecstasy users showed a slightly diminished performance on memory tasks. However, the interpretation of these results is hampered by confounding effects of recent MDMA use, use of other drugs, and psychosocial differences between users and controls. Moreover, users of multiple drugs who also had been using ecstasy showed deficits in memory compared to users of multiple drugs who never used ecstasy (Morgan 1999). Many of these methodological problems could be solved by a large, well-controlled prospective study, but such a study would be impossible with an illicit and potentially toxic substance. The current cross-sectional study attempted to circumvent the methodological difficulties by studying participants from the same subculture with widely varying levels of ecstasy exposure. This makes it possible to rule out the effects of other drugs and to look for relations between exposure and effect. Additionally, we carefully measured a wide range of theoretical confounding variables. The aim of the present study was to investigate the relation between past use of ecstasy and cognitive performance as well as serotonergic function.

Materials and methods

Participants

Healthy male visitors of rave parties aged between 18 and 28 years were recruited by advertisements. Two groups of ecstasy users were recruited, based on the findings of a previous Dutch socio-epidemiologic study (Van de Wijngaart et al. 1998); those who had used ecstasy on 12–48 separate occasions during the past 2 years (n=21); and those who had used it on 48 or more occasions (n=21). These groups were based on recent frequency of use rather than on cumulative use, because in animals damage seemed more strongly associated with the former. A control group consisted of regular rave party visitors who had never used any ecstasy (n=20). To minimise the influence of substances other than ecstasy, exclusionary criteria included: current regular use of more than 3 units of alcohol per day, current regular use of cocaine (more than once per month), amphetamines (more than once per week or more frequently than ecstasy), opiates, or prescribed drugs. A history of alcohol or substance dependence or a major psychiatric disorder during the last year also led to exclusion. Participants were instructed to maintain a regular lifestyle and not to use any psychotropic agents, including all illegal drugs from 1 week before the first test occasion until the last test occasion. This was checked by urine tests at all visits. The study was approved by the Medical Ethics Review Board of Leiden University Medical Center and performed in accordance with the Declaration of Helsinki. After complete written and oral descriptions of the study to the participants, written informed consent was obtained. Participants were paid for their participation.

Recruitment

There were 289 responders, of whom 56 violated entry criteria at first telephone contact (mostly ecstasy use on 1–12 occasions in the past 2 years). After invitation of the first 108 participants into the study, the required numbers in each group were reached and the remaining 125 responders were cancelled. Thirty-four invited participants withdrew before screening, and 74 gave informed consent. Eight participants met exclusion criteria and 66 participants entered the study. Three participants withdrew after adverse events on the first occasion. One participant was excluded after study completion because of sustained hyperprolactinaemia (eight times above the upper normal limit on both occasions; his inclusion in a separate analysis did not affect the main results). Thus, the data from 62 participants were analysed.

Diagnostic procedures

A detailed history of the intake of ecstasy tablets, other illicit drugs, and use of alcohol was assessed by using a structured interview, which was recently used in a large socio-epidemiological study of rave party visitors (Van de Wijngaart et al. 1998). This assessment was performed by two psychiatrists (R.J.V, H.J.G.) after training on the use of the instrument. These investigators used the Structured Clinical Interview for DSM-IV axis I disorders, nonpatient version, to exclude mood, anxiety or psychotic disorders (First et al. 1994). In addition, DSM-IV diagnostic criteria for attention-deficit and hyperactivity disorder (ADHD) in youth were scored retrospectively. ADHD in youth may be a possible confounding variable in our study, because it is often associated with substance use in adolescence (Canbor and Millman 1996) and ADHD may be associated with cognitive underachievement relative to the intellectual potential (Weiss 1996). The level of education was estimated as the highest school grade entered.

The novelty seeking, harm avoidance and reward dependence personality traits were assessed with the Temperament and Character Inventory (TCI) (Svrakic et al. 1993; Duijsens et al. 1997). Assault, verbal hostility, indirect hostility and irritability were determined using the Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957). Cognitive impulsivity, motor impulsivity and non-planning were measured with the Barratt Impulsiveness Scale (BIS-11) (Barratt 1991). Depression was assessed with the Beck Depression Inventory (BDI) (Beck and Beamesderfer 1974; Bouman et al. 1985), and trait anxiety with the Spielberger State-Trait Anxiety Inventory (STAI-DY) (Spielberger et al. 1970; Van der Ploeg et al. 1979).

Cognitive performance

Neuropsychological tests were primarily chosen to assess psychological domains which have been related to serotonergic functions, particularly memory (Buhot 1997). The tests were performed using FePsy, an automated computerised battery of validated neuropsychological tasks (Alphers and Aldenkamp 1994).

The Corsi Block Tapping Test (Milner 1971; Aarts et al. 1983) consists of nine grey buttons on the screen. It starts with three buttons flashing in serial order. The task of the participant is to tap out the same order. If all responses are correct, the number of flashing buttons is increased in increments of one until the participant fails on two consecutive trials. This maximum was defined as the "span". Subsequently, the "superspan" was determined as 24 trials of "span plus one" buttons.

Working memory was assessed following serial and simultaneous presentation of six words and figures (four tests altogether) (Sternberg 1969). After presentation of these items, recognition was tested by presentation of six stimuli: five new items and one previously shown. Participants had to point out the one presented before. Each test consisted of 24 random presentations. For each recognition task the number of correct responses and the mean reaction times of correct responses were determined.

These tests are influenced not only by recall, but also by reaction times [evaluated separately on the non-dominant hand in response

to simple auditive and visual stimuli, and to a Binary Choice Task (Moerland et al. 1986)], and by general information processing. Information processing was studied with a visual searching task and a classification task. In the searching task (Goldstein et al. 1973; DeMita and Johnson 1981), participants had to identify one grid pattern out of 24 as quickly as possible, matching the one shown in the screen centre. After 12 presentations the surrounding grids changed. The number of errors and mean searching time of correct responses were measured. The classification task (Robinson et al. 1980; Anderson et al. 1991) was an adaptation of the original Wisconsin Card Sorting Task, where the participant had to identify the sorting criteria for four stimuli cards, through a trial-and-error process with feedback from the computer program.

Serotonergic function

A double blind, cross over challenge test of 30 mg dexfenfluramine or placebo was performed with a washout-period of at least 5 days. After an overnight fast, participants were collected by taxi and received a glucose drink upon arrival. Participants were excluded if urine was positive for cocaine, amphetamines, benzodiazepines or opiates (using Abuscreen Ontrak, Roche Diagnostic Systems, Mijdrecht, The Netherlands); or for MDMA, MDA or MDEA (using TDx, Abbott, Amstelveen, The Netherlands). Cortisol and prolactin samples were obtained hourly for 7 h and measured as described previously (Gijsman et al. 1998). To check whether differences in dexfenfluramine effects could be related to underlying differences in drug disposition, serum concentrations of dexfenfluramine and of its most important metabolite nor-dexfenfluramine were measured by gas-liquid chromatography with mass selective detection. The detection range was 1–100 ng/ml.

Data analysis

Differences between the three groups in cognitive and psychological parameters were analysed by Student's *t*-test. For significant between-group contrasts, potential confounding variables were entered collectively into an analysis of covariance to investigate whether a change in size of the contrasts could be induced. These variables were: use of alcohol per day; cannabis (lifelong cumulative use, and frequency of use in previous 3 months); amount of time since last use of ecstasy; BDI score; STAI-DY score; retrospective ADHD criteria; school level.

The effects of dexfenfluramine were summarised by subtracting the time-corrected area under the effect curve (AUEC) under placebo from the AUEC under dexfenfluramine. All three possible comparisons between groups were made by two-tailed Student's *t*-tests. For significant between-group contrasts, potential confounding variables were entered into an analysis of covariance, to investigate whether a change in size of the contrasts could be induced. These variables were: body weight, daily use of alcohol, cannabis (lifelong cumulative use, and frequency of use in previous 3 months); time since last use of ecstasy; AUC (nor)dexfenfluramine; TCI subscales reward dependence, harm avoidance and novelty seeking; BDI score; STAI-DY score, retrospective ADHD criteria. Calculations were performed using SPSS for Windows V6.1.2 (SPSS, Inc., Chicago, Ill., USA). All *P*-values are two-tailed and an alpha level of 0.05 was used throughout.

Results

Demographics and substance use

Demographics for the three participant groups are provided in Table 1. There were no significant differences in age, body weight or level of education. On average, the heavy ecstasy user group visited more rave parties in the previous year than the other two groups, but the differences were not statistically significant. Table 2 shows that the difference in mean cumulative lifelong ecstasy use between the

Table 1 Demographics

	Non-users (*n*=20) Mean (SD)	Moderate users (*n*=21) Mean (SD)	Heavy users (*n*=21) Mean (SD)
Age	20.6 (2.2)	22.1 (2.3)	21.7 (2.8)
Body weight	73.8 (11.1)	74.9 (8.4)	71.5 (10.7)
Number of rave parties visited in past 12 months	32.5 (24.9)	33.5 (25.2)	47.0 (31.8)
	Number	Number	Number
Level of education			
Lower general or vocational	1	3	7
Intermediate	6	7	5
At least preuniversity	13	11	9

Table 2 Characteristics of ecstasy use

	Moderate users (*n*=21) Mean (SD)	Heavy users (*n*=21) Mean (SD)
Lifelong cumulative number of ecstasy tablets	169 (252)	741 (678)[a]
Lifelong number of occasions of ecstasy use	73 (68)	230 (170)[a]
Lifelong average number of ecstasy tablets per occasion	2.0 (1.1)	3.1 (1.1)[b]
Duration of use in years	4.4 (2.4)	4.5 (1.8)
Days since last ecstasy use prior to psychometric testing	15.7 (9.5)	9.0 (7.5)[c]
Days since last ecstasy use prior to dexfenfluramine challenge	28.1 (8.8)	19.0 (8.6)[b]

Differences in means between moderate versus heavy users [a]$P<0.001$, [b]$P<0.01$, [c]$P<0.05$

Table 3 Additional drug use patterns

	Non-users (*n*=20) Mean (SD)	Moderate users (*n*=21) Mean (SD)	Heavy users (*n*=21) Mean (SD)
Alcohol (last 3 months, units/day)	1.3 (0.9)	1.4 (1.0)	0.9 (0.6)
Cannabis (lifetime total number of joints)	379 (1190)	1890 (2620)[a]	1850 (2700)[b]
	Number	Number	Number
Cannabis (last 3 months)			
Never	14	3	7
Once per week or less	2	8	7
More than once per week	4	10	7
Amphetamine (last 12 months)			
Never	19	10	0
Once per month or less	1	8	8
Few times per month	0	3	8
Once per week	0	0	5
Cocaine (last 12 months)			
Never	20	7	7
Once per month or less	0	14	14

Differences in means between:
[a]Non-users versus moderate users (t=2.35, df=39, P=0.02)
[b]Non-users versus heavy users (t=2.23, df=39, P=0.03)

Table 4 Psychopathology

	Non-users (*n*=20) Mean (SD)	Moderate users (*n*=21) Mean (SD)	Heavy users (*n*=21) Mean (SD)
Mood inventories (possible range of scores)			
Depressive mood (BDI) (0, 63)	3.0 (3.7)	3.9 (3.3)	7.0 (6.3)
Trait anxiety (STAI-DY) (20, 80)	32.1 (7.0)	33.5 (6.9)	38.8 (10.4)
ADHD before age 15, number of DSM-IV criteria			
Attention deficit disorder (0, 9)	1.7 (1.9)	2.5 (2.4)	2.9 (2.8)
Hyperactivity disorder (0, 9)	2.2 (2.5)	3.0 (2.5)	3.3 (2.2)

two groups of ecstasy users was mainly due to a difference in the number of occasions on which ecstasy was ever used. The average number of ecstasy tablets taken on these occasions was also elevated in heavy users compared to moderate users. Time lapsed since first use of ecstasy did not differ between moderate and heavy ecstasy users.

As shown in Table 3, heavy ecstasy users consumed somewhat less alcohol than moderate users, but this difference was not statistically significant. Ecstasy users consumed more cannabis and cocaine than non-users, but there were no differences between the two groups of ecstasy users. Heavy ecstasy users took more amphetamine than the other two groups, but the use of amphetamines other than ecstasy was limited by the entry criteria of the study.

In order to evaluate whether our participants were representative samples for their peer-group, the data were compared to the results obtained in a large-scale survey among 1121 rave party visitors (Van de Wijngaart et al. 1998). Our study groups were somewhat better educated than rave party visitors in general, but no other differences were found in social background, party visiting behaviour, or use patterns of ecstasy and other drugs. The character, frequency and severity of self-reported transient and prolonged complaints following ecstasy use or rave party visits in the study groups did not differ from those reported in the general population of visitors of rave parties (Van de Wijngaart et al. 1998).

Psychopathology

As shown in Table 4, the mean score for depressive mood was somewhat higher in heavy ecstasy users than in non- and moderate users. The same applied to the mean score for trait anxiety. However, these differences were not significant, when all the likely confounding variables were considered (with school level and hyperactivity in youth as most important confounding variables). The number of criteria for ADHD before the age of 15 years did not differ between the three groups. The psychological profiles determined with the TCI, BIS-11 and BDHI scales were very similar over the three groups, although ecstasy-users scored somewhat higher on novelty seeking.

Cognitive performance

Results of the cognitive tests are provided in Table 5. Reaction times were longest in the heavy user group and lowest in the non-user group, with the moderate group in between. These differences in reaction times diminished

Table 5 Cognitive performance – reaction time (in ms), recall and working memory (total of correct items)

	Non-users (n=20) Mean (SD)	Moderate users (n=21) Mean (SD)	Heavy users (n=21) Mean (SD)
Reaction time			
Simple visual stimuli, ms	246 (27)	258 (37)	273 (39)[b]
Simple auditory stimuli, ms	224 (23)	239 (33)	247 (36)[a]
Binary choice task, ms	326 (42)	347 (64)	364 (72)[a]
Memory span			
Span	6.1 (1.3)	5.2 (1.2)[c]	5.0 (1.1)[b]
Span plus one'	6.4 (1.1)	5.7 (1.0)[c]	5.5 (0.9)[a]
Recognition of words			
Serial	18.8 (2.9)	18.8 (3.2)	16.2 (4.3)[b,e]
Simultaneous	22.1 (1.2)	21.2 (1.8)	19.5 (3.0)[a,e]
Recognition of figures			
Serial	18.8 (2.8)	15.9 (3.6)[d]	15.5 (5.2)[b]
Simultaneous	16.2 (2.9)	13.5 (3.4)[d]	12.5 (3.0)[a]

Differences in means between:
Non-users versus heavy users [a]P<0.05, [b]P<0.01
Non-users versus moderate users [c]P<0.05, [d]P<0.01
Moderate versus heavy users [e]P<0.05

after analyses of covariance, mainly due to school level and BDI score.

Corsi Block memory span in ecstasy users was significantly less than in non-users. The difference between the two groups of ecstasy users was not statistically significant.

Serially presented words were recognised less well by heavy ecstasy users than by non users; a difference of 2.6 words (95%CI 0.3–5.0). Moderate and heavy ecstasy users showed a similar difference of 2.6 (95%CI 0.2–5.0) words. For simultaneous word recognition the differences were even more pronounced. The difference between non-users and moderate ecstasy users just failed to reach statistical significance [0.9 (95%CI 0.1–1.8) words], but the heavy ecstasy user group clearly differed from non-users [2.6 (95%CI 1.1–4.0) words]. Heavy users also performed less well than moderate ecstasy users [a difference of 1.7 (95%CI 0.2–3.3) words]. After serial presentation of figures, non-users recognised 2.8 (95%CI 0.8–4.9) figures more than moderate ecstasy users, and 3.2 (95%CI 0.6–5.9) figures more than heavy users. After simultaneous presentation of figures, non-users recognised 2.7 (95%CI 0.7–4.7) figures more than moderate ecstasy-users, and 3.6 (95%CI 1.8–5.5) figures more than heavy users. Analyses of covariance showed that none of the potential confounders had any relevant impact on the above-mentioned differences between groups in memory span and recognition.

For all tests, the number of missed items and the reaction times for correct or incorrect items were comparable among the three groups.

Serotonergic function

The areas-under-the-concentration-curves (AUCs) of dexfenfluramine did not differ significantly between the three groups. The AUC for dexfenfluramine was 6050 ng.ml^{-1}·min (SD 1390) in non-users, 5360 ng.ml^{-1}·min (SD 1390) in moderate users, and 5280 ng.ml^{-1}·min (SD 1410) in heavy ecstasy users. The AUC for nor-dexfenfluramine was 2780 ng.ml^{-1}·min (SD 540) in non-users, 2450 ng.ml^{-1}·min (SD 460) in moderate users, and 3000 ng.ml^{-1}·min (SD 1040) in heavy ecstasy users. The difference between the latter two groups was significant (t=2.22, df=40, P=0.03).

Table 6 Cortisol and prolactin response to dexfenfluramine

	Non-users (n=20) Mean (SD)	Moderate users (n=21) Mean (SD)	Heavy users (n=21) Mean (SD)
Placebo-corrected area-under-the-effect-curve, time-corrected, ng/ml			
Cortisol	63.3 (41.3)	28.6[a] (33.5)	27.1[b] (58.9)
Prolactin	83.3 (71.3)	63.2 (55.6)	53.5 (75.4)

Differences in means between:
[a]Non-users versus moderate users (t=2.96, df=39, P=0.005)
[b]Non-users versus heavy users (t=2.27, df=39, P=0.03)

Table 6 shows the neuroendocrine effects of the challenge test. For cortisol, the mean placebo-corrected area under the effect curve (AUEC) was significantly higher in the non-user group compared to the moderate user group [difference 34.7 ng/ml (95%CI 11.0–58.4 ng/ml)] and the heavy ecstasy user group [36.2 ng/ml (95%CI 3.9–68.5 ng/ml)]. There were no statistically significant differences between the two ecstasy user groups. After correction for likely confounding variables, including correction for the AUCs of dexfenfluramine and nordexfenfluramine, the differences between ecstasy users and non-users remained significant. The AUEC of cortisol correlated significantly with memory span (with "span" r=0.29, n=62, P=0.02; with "span plus one" r=0.26, n=62, P=0.04), but not with the scores on the recognition tests.

For prolactin, the placebo-corrected AUECs were also highest in the non-user group and lowest in the heavy user group, but the differences between groups failed to reach statistical significance. The placebo responses were highly variable, probably related to diurnal fluctuations and adverse events such as nausea and fatigue. Correction of the prolactin responses for the AUCs of dexfenfluramine and nordexfenfluramine did not have any relevant effect on the results.

Discussion

This study shows significant associations of chronic ecstasy use with diminished memory performance and serotonergic neuroendocrine function. These memory reductions are in line with findings of others in humans (Krystal et al. 1992; Bolla et al. 1998; Parrott and Lasky 1998; Parrott et al. 1998; McCann et al. 1999; Morgan 1999) and animals (Marston et al. 1999).

Neuroendocrine effects were significant for cortisol but not for prolactin, which was partly related to the larger variability of the latter. Gerra et al. also found more pronounced effects of dexfenfluramine on cortisol than on prolactin in ecstasy users (Gerra et al. 1998), and similar findings were obtained in rats (Poland et al. 1997). The findings of our study are compatible with a neurotoxic effect of ecstasy as demonstrated in several animal species (Green et al. 1995), as well as with recent neuro-imaging findings of a decreased number of serotonin transporters in human users of ecstasy (McCann et al. 1998; Semple et al. 1998).

However, this was a cross-sectional study, and other potential explanations or biases should be considered. We minimised the influence of psychosocial factors by taking a control group from the population of rave party visitors. This differs conspicuously from most previous studies, where controls came from a university or general population (Bolla et al. 1998; Gerra et al. 1998; Parrott et al. 1998; McCann et al. 1999). In the current study, self-selection of participants with concerns over physical or psychological complaints does not seem to have occurred, since these complaints were not more frequent in our study group than in the general population of visitors of rave parties. Additionally, none of the psychosocial variables induced a significant change in size of the reductions in memory or neuroendocrine responsiveness.

Acute effects of ecstasy were avoided as much as possible. Urine screening was performed to detect concealed recent ecstasy use. The mean period between the last use of ecstasy and cognitive testing was almost 16 days in moderate ecstasy users and 9 days in heavy users, and never less than 2 days. In addition, the neuroendocrine responsiveness to dexfenfluramine was still reduced after an abstinence period of on average 28 days in moderate users and 19 days in heavy users (at least 1 week). Furthermore, the influence of the time since last use of ecstasy was statistically controlled for, and found to be absent.

Theoretically, the functional deterioration found in this group of ecstasy users could be due to other drugs. However, alcoholics and regular users of cocaine or opiates were excluded. Amphetamine cannot completely be excluded as a cause, but in animals amphetamine damages the dopaminergic system and not the serotonergic system (Ricaurte and McCann 1992). Cannabis was widely used in all three groups and considerably more by ecstasy users than non-users. However, use of cannabis cannot explain the cognitive and neuroendocrine differences between the moderate and heavy ecstasy user groups, since their cumulative cannabis use was equal. Furthermore, it is unlikely that the differences in memory span between users of ecstasy and non-users are related to a more frequent use of cannabis amongst the two groups of ecstasy users compared to controls, since memory appears only impaired in participants with an average weekly use of 7 times or more (Block and Ghoneim 1993). In our group, only four moderate and five heavy ecstasy users reported daily use of cannabis, and the average frequency was no more than a few times per month. Analyses of covariance showed no influence of cumulative or recent use of any drug other than ecstasy. Recently, Rodgers (2000) reported impairment on measures of delayed memory for regular users of ecstasy compared to regular users of cannabis.

It cannot be determined which ecstasy component is responsible for the detrimental effects. In the Netherlands, methylenedioxyamphetamines (MDMA, MDA and MDEA) were found in 76.8–90.2% of these tablets in the period 1993–1996 (Konijn et al. 1997). These substances are therefore the most likely cause of the apparent ecstasy effects found in this study.

Self reported estimates of previous drug use have a considerable degree of inaccuracy, and the exact amounts of long-term previous drug use cannot be determined retrospectively in a cross-sectional study. However, several precautions allowed us to make a semi-quantified assessment of the relationship between drug exposure and effects. Standardised interviews were used to obtain the most reliable indications of previous drug use. In addition, we used wide ranges for the amounts of previous drug use to separate the three groups.

In conclusion, the present study showed significant associations of chronic ecstasy use with impairment of memory and serotonergic neuroendocrine function. The clinical relevance of this impairment cannot be easily determined, but the fact that it is detectable at all in a relatively small cohort should be worrying in itself. A prospective randomised study of the pure substances involved would be necessary to determine the cause of the effects and how long they last after withdrawal. Such a study is obviously impossible. In addition to recent findings, our data provide sufficient grounds for major concerns about the extensive use of ecstasy tablets every weekend in so many Western countries (Saunders 1995).

Acknowledgements We wish to acknowledge the expert assistance of the nursing staff of CHDR, particularly M. ten Hove SRN, and the scientific advice by Miriam Fris MSc, Dr. Bert van Hemert and Professors Freek de Wolff, John Henry and Jan Vandenbroucke. Dexfenfluramine was kindly provided by Les Laboratoires Servier, Neuilly-sur-Seine, France.

References

Aarts JHP, Binnie CD, Smit AM, Wilkens AJ (1983) Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 107:293–308

Allen RP, McCann UD, Ricaurte GA (1993) Persistent effects of 3,4-methylenedioxymetamphetamine (MDMA; "Ecstasy") on human sleep. Sleep 16:560–664

Alphers WCJ, Aldenkamp AP (1994) FePsy, the iron psyche. Manual. 5.0 revised edition edition. Instituut voor Epilepsiebestrijding, Heemstede, The Netherlands

Anderson SW, Damasio H, Jones RD, Tranel D (1991) Wisconsin Card Sorting Test as a measure of frontal lobe damage. J Clin Exp Neuropsychol 13:909–922

Barratt ES (1991) Measuring and predicting aggression within the context of a personality theory. J Neuropsychiatr Clin N Am 3:S35–S39

Beck AT, Beamesderfer A (1974) Assessment of depression: the depression inventory. In: Pichot P (ed) Psychological measurement in psychopharmacology. Modern problems in pharmacopsychiatry. Karger, Basel, pp 151–169

Block RI, Ghoneim MM (1993) Effects of chronic marijuana use on human cognition. Psychopharmacology 110:219–228

Bolla KI, McCann UD, Ricaurte GA (1998) Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology 51:1532–1537

Bond AJ, Feizollah S, Lader MH (1995) The effects of D-fenfluramine on mood and performance, and on neuroendocrine indicators of 5-HT function. J Psychopharmacol 9:1–8

Bouman TK, Luteijn F, Albersnagel FA, Van der Ploeg FAE (1985) Enige ervaringen met de Beck Depression Inventory (BDI). Gedrag 13:13–24

Buhot M (1997) Serotonin receptors in cognitive behaviors. Curr Opinion Neurobiol 7:243–254

Buss AH, Durkee A (1957) An inventory for assessing different kinds of hostility. J Consult Psychol 21:343–349

Canbor RL, Millman RB (1996) Alcohol and drug abuse in adolescents. In: Lewis (ed) Child and adolescent psychiatry, 2nd edn. William and Wilkins, Baltimore, pp 736–763

Dafters RI, Duffy F, O'Donnell PJ, Bouquet C (1999) Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology 145:82–90

DeMita MA, Johnson JH (1981) The validity of a computerized visual searching task as an indicator of brain damage. Behav Res Meth Instr 13:592–594

Duijsens IJ, Goekoop JG, Spinhoven P, Eurelings-Bontekoe EHM (1997) De temperament en karakter vragenlijst (TCI). Nederlands Tijdschrift voor de Psychologie 52:199–202

First, MB, Spitzer, RL, Gibbon, M, Williams, JBW (1994) Structured clinical interview for axis I DSM-IV disorders-non-patient edition (SCID-I/NP, Version 2.0). Biometrics Research Department, New York

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R (1998) Serotonergic function after (±)3,4-methylene-dioxymethamphetamine ("Ecstasy") in humans. Int Clin Psychopharmacol 13:1–9

Gijsman HJ, Van Gerven JMA, Tieleman MC, Schoemaker RC, Pieters MSM, Ferrari MD, Cohen AF, Van Kempen GMJ (1998) Pharmacokinetic and pharmacodynamic profile of oral and intravenous meta-chlorophenylpiperazine in healthy volunteers. J Clin Psychopharmacol 18:289–294

Goldstein G, Welch RB, Rennick PM, Shelly CH (1973) The validity of a visual searching task as an indicator of brain damage. J Consult Clin Psychol 41:434–437

Green AR, Cross AJ, Goodwin GM (1995) Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxy-metamphetamine. Psychopharmacology 119:247–260

Konijn KZ, Pennings EJM, De Wolff FA (1997) XTC – klinische en toxicologische aspecten ("Ecstasy – clinical and toxicological aspects"). Leiden University Medical Center, Leiden

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR (1992) Chronic 3,4-methylenedioxymetamphetamine (MDMA) use: effects on mood and neuropsychological function? Am J Drug Alcohol Abst 18:331–341

Marston HM, Reid ME, Lawrence JA, Olverman HJ, Butcher SP (1999) Behavioural analysis of the acute and chronic effects of MDMA treatment in the rat. Psychopharmacology 144:67–76

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after 3,4-methylenedioxymetamphetamine (MDMA; "Ecstasy"): a controlled study in humans. Neuropsychopharmacology 10:129–138

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA (1998) Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. Lancet 352:1433–1437

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA (1999) Cognitive performance in (±)3,4-metheylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology 143:417–425

Milner B (1971) Interhemispheric differences in the localisation of psychological processes in man. Br Med Bull 27:272–277

Moerland MC, Aldenkamp AP, Alphers WCJ (1986) A neuropsychological test battery for the Apple IIe. Int J Man Mach Stud 25:453–467

Morgan MJ (1998) Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19:252–264

Morgan MJ (1999) Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 141:30–36

Newman ME, Shapira B, Lerer B (1998) Evaluation of central serotonergic function in affective and related disorders by fenfluramine challenge test: a critical review. Int J Neuropsychopharmacol 1:49–69

Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268

Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K (1998) Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. J Psychopharmacol 12: 79–83

Poland RE, Lutchmansignh P, McCracken JT, Zhao J-P, Brammer GL, Grob CS, Boone KB, Pechnik RN (1997) Abnormal ACTH and prolactin responses to fenfluramine in rats exposed to single and multiple doses of MDMA. Psychopharmacology 131:411–419

Price LH, Ricaurte GA, Krystal JH, Heninger GR (1989) Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymetamphetamine (MDMA) users. Preliminary observations. Arch Gen Psychiatry 46:20–22

Ricaurte GA, McCann UD (1992) Neurotoxic amphetamine analogues: effects in monkeys and implications for humans. Ann NY Acad Sci 648:371–382

Robinson AL, Heaton RK, Lehman RA, Stilson D (1980) The utility of the Wisconsin Card Sorting Test in detecting and localising frontal lobe lesions. J Consult Clin Psychol 48:605–614

Rodgers J (2000) Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology 151:19–24

Saunders N (1995) Ecstasy and the dance culture. Neal's Yard Desktop Publishing, London

Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC (1998) Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. Br J Psychiatry 175:63–69

Spielberger CD, Gorsuch RL, Lushene RE (1970) STAI manual for the State Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, Calif.

Sternberg S (1969) Memory scanning; mental processes revealed by reaction time experiments. Am Sci 57:421–457

Svrakic DM, Whitehead C, Przybeck TR, Cloninger CR (1993) Differential diagnosis of personality disorders by the seven-factor model of temperament and character. Arch Gen Psychiatry 50:991–1000

Van de Wijngaart G, Braam R, De Bruin D, Fris M, Maalste N, Verbraeck H (1998) Ecstasy and the Dutch rave scene. A socio-epidemiological study on the nature and extent of, and the risks involved in using ecstasy and other party drugs at dance events. Addiction Research Institute, University of Utrecht, The Netherlands, Utrecht, The Netherlands

Van der Ploeg HM, Defares PB, Spielberger CD (1979) Handleiding bij de Zelf-Beoordelings Vragenlijst (ZBV). Een Nederlandse bewerking van de State-Trait Anxiety Inventory. Swets en Zeitlinger B.V. Lisse, The Netherlands

Weiss G (1996) Attention deficit hyperactivity disorder. In: Lewis (ed) Child and adolescent psychiatry, 2nd edn. William and Wilkins, Baltimore, pp 544–563