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Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users

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Abstract

Previous studies have consistently shown impairments of memory and learning in regular users of the neurotoxic drug ecstasy (3,4-methylenedioxymethamphetamine [MDMA]). In addition, deficits in working memory, planning ability and central executive control, as well as high cognitive impulsivity, were also reported in some studies. Hence, the memory decrements may be secondary due to other cognitive failures. The purpose of this study was to analyze the nature of the cognitive deficits of ecstasy users. Tests of memory, working memory, central executive function and cognitive impulsivity were administered to 60 currently abstinent ecstasy users and to 30 nonusers. Heavy ecstasy users ($n=30$, lifetime dose ≥ 80 ecstasy tablets) had lower memory performance than both nonusers and moderate users ($n=30$, lifetime dose <80 ecstasy tablets). In contrast, we found no group differences in central executive function, working memory, planning ability and cognitive impulsivity between ecstasy users and controls. Poorer memory and working memory performance was associated with a heavier pattern of ecstasy use. Low working memory, planning ability and central executive control and high cognitive impulsivity did not predict poor memory performance. Our results indicate primary memory dysfunction in heavy ecstasy users, which may be related to a particularly high vulnerability of the hippocampus to the neurotoxic effects of MDMA. Hippocampal dysfunction after ecstasy use may be a risk factor for earlier onset and/or more severe age-related memory decline in later years.

Keywords: Cognition; Ecstasy; Hippocampus; MDMA; Memory; Neurotoxicity; Serotonin

1. Introduction

The popular recreational drug ecstasy (MDMA = 3,4-methylenedioxymethamphetamine and other congeners) has a well-recognized neurotoxic potential upon central serotonergic systems in animal studies (Ricaurte et al., 1992, 2000). There is growing evidence that these toxic effects can be very long lasting or even permanent (Fischer et al., 1995; Hatzidimitriou et al., 1999) and may also occur in humans (McCann et al., 1998, 2000; Reneman et al., 2001b). A recent study with nonhuman primates suggests that central dopaminergic systems may also be affected by the neurotoxic effects of ecstasy (Ricaurte et al., 2002). Dopamine and serotonin are involved in numerous functions including regulation of mood, vegetative functions, neuroendocrine secretion and cognition. Recent studies indicate that diminished serotonergic neurotransmission may cause cognitive impulsivity with higher rates of anticipatory responses in reaction time (RT) tasks and may interfere with memory and learning processes (Richter-Levin and Segal, 1996; Poulos et al., 1996; Riedel et al., 1999; Buhot et al., 2000), while intact dopaminergic function is thought to be essential for short-term or working

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CR, correct responses; 5-HT, serotonin; LGT-3, *Lern-und Gedächtnistest* (learning and memory test); LPS, Leistungsprüfsystem (system for the assessment of cognitive performance); LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; *n*, number of subjects in the group; PAD, Plan-A-Day; RT, reaction time; RWTH, *Rheinisch Westfälische Technische Hochschule* (University of Technology of Rheinland-Westfalen); TAP, *Testbatterie zur Aufmerksamkeitsprüfung* (battery for the assessment of attentional functions); WAIS-R, Wechsler Adult Intelligence Scale—Revised.

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memory performance (Luciana et al., 1998; Durstewitz et al., 1999).

During the last years, evidence has accumulated in favor of dose-related impairments of learning and memory performance in abstinent ecstasy users (Krystal and Price, 1992; Bolla et al., 1998; Parrott and Lasky, 1998; Morgan, 1999; Gouzoulis-Mayfrank et al., 2000; Rodgers, 2001; Bhattachary and Powell, 2001; Zakzanis and Young, 2001a). In addition, deficits of central executive control, working memory and selective attention, as well as elevated impulsivity and poor problem solving, have also been demonstrated, although these results were less consistent (Curran and Travill, 1997; Morgan, 1998; McCann et al., 1999; Dafters et al., 1999; Wareing et al., 2000; Gouzoulis-Mayfrank et al., 2000; Verkes et al., 2001; Zakzanis and Young, 2001b; Zakzanis et al., 2002). Open trial studies with user populations suffer from inherent methodological problems and confounding variables such as polydrug use patterns and different motivational levels, lifestyles, cognitive strategies and premorbid performance levels. Despite these problems, the accumulating evidence does suggest an association of ecstasy use with residual neurotoxic effects resulting in subtle cognitive decline.

However, the nature of the emerging ecstasy-related cognitive disturbance remains to be elucidated. One possibility is that there are several impairments in distinct cognitive domains, which are independent from each other. This might be related to a widespread pattern of MDMA-related neurotoxicity all over the brain, thus leading to disturbances in several functional circuitries. This model is in line with the recognized widespread pattern of MDMA-related neurotoxicity in animal studies (Ricaurte et al., 1992, 2000; Fischer et al., 1995; Hatzidimitriou et al., 1999). Alternatively, it is conceivable that one common core deficit underlies or contributes to impairments in several cognitive domains. Reduced cortical inhibition, elevated levels of cognitive and behavioral impulsivity or low executive control and short-term or working memory deficits might lead to secondary impairments of memory and learning performance. Therefore, these functions are considered candidates for the hypothetical underlying core cognitive disturbance of ecstasy users (Parrott, 2000; Parrott and Lasky, 1998; Gouzoulis-Mayfrank et al., 2000). The purpose of this study was to analyze the nature of the cognitive deficits of ecstasy users and provide clues about which functional brain systems might be more affected in humans after MDMA use.

2. Methods

2.1. Subjects

Sixty MDMA users (inclusion criterion: use of ecstasy on at least 20 occasions) were recruited directly in the dance scene by students who were involved in the study, via word-of-mouth and via the Internet. Because most ecstasy users tend to experiment also with other typical club drugs, subjects who reported use of amphetamines, cocaine, cannabis or LSD were not excluded. However, subjects were excluded if they reported substantial use of alcohol (defined as drunkenness occurring at a frequency of at least twice per month over 6 months or longer within the last 2 years), or regular use of other legal or illegal psychotropic drugs such as opiates and benzodiazepines (defined as use once per month or more frequently over 6 months or longer within the last 2 years). The control group consisted of 30 healthy persons who were matched for age, sex and level of education with the MDMA users and had no previous or current history of alcohol or drug use other than moderate use of cannabis. All ecstasy users agreed to abstain from drug use for at least 7 days prior to the study with the exception of cannabis. Because daily moderate cannabis use was part of the lifestyle of many subjects and because cannabis screens may remain positive for several weeks after the last use (thus making it impossible to verify reported abstinence), we tolerated that most subjects agreed to abstain from cannabis only on the study day. Exclusion criteria for all participants were: (1) a positive drug screen on the study day except for cannabis; (2) any current or previous Axis I psychiatric diagnosis except for drug abuse in the user group; and (3) any organic brain disorder or relevant general medical condition requiring pharmacological treatment.

2.2. Procedures

All subjects underwent a structured interview according to the Diagnostic and Statistical Manual of Mental Disorders IV (APA, 1994). In addition, we took a medical history and detailed history of drug use. Drug screens were performed on the study day with urine samples for stimulant amphetamines, methylenedioxyamphetamines (ecstasy), cocaine and its metabolite, marijuana, benzodiazepines, barbiturates and opiates. After detailed description of the study to the subjects, written informed consent was obtained and subjects were paid for their participation. The study was in accordance with the 1975 Declaration of Helsinki and was approved by the local ethics committee at the RWTH Aachen.

2.3. Neuropsychological test battery

2.3.1. General intelligence

- *General Knowledge* (from the Wechsler Adult Intelligence Scale—Revised [WAIS-R], German version; Tewes, 1991): Subjects answered 24 questions of general knowledge (crystallized intelligence, remains unaffected for a relatively long period of time after the onset of any organic cognitive decline). We employed this test in order to control for accidental preexisting differences in general cognitive capacity or education between groups.

2.3.2. Tests of executive control, planning ability and cognitive impulsivity

- *Go/NoGo* (from the computerized battery for the assessment of attentional functions TAP; Zimmermann and Fimm, 1995): A task of selective visual attention requiring target selection and response inhibition (executive control). Two visual patterns are presented on the computer screen and one of them is defined as the critical target. Subjects have to respond to the critical target as quickly as possible by pressing a computer key and by ignoring the noncritical target.
- *Visual Scanning* (from the TAP; Zimmermann and Fimm, 1995): Subjects are scanning a matrix of 5×5 similar graphic elements for a predefined target, which may or may not be included in the matrix (critical vs. noncritical trials). Subjects are instructed to scan the matrix row by row and from left to right. A high correlation between target position within the matrix and RT is expected if a subject is working systematically in this task, whereas a low correlation is suggestive of a more impulsive cognitive style.
- *Plan-A-Day* (PAD; Funke and Krüger, 1995): A computerized test for assessing planning competencies. Subjects have to plan a working day and try to solve as many tasks as possible within a given time period. In order to achieve this, they have to "go" to different locations and they have to consider different distances between the locations and different levels of priority of the goals. In order to shorten the time needed to go from one place to the other, a "joker" (taxi) may be used only once. If a subject is not satisfied with his solution he may delete single "actions" (key hits) or longer sequences of actions and try a different strategy. The tasks are presented on the screen at the beginning of each trial. However, subjects can get an overview of the tasks at any time during the trial by pressing the function key F2 (low demand on memory). The PAD is available with different levels of difficulty. We used a demanding version with a large number of tasks.

2.3.3. Tests of working memory

- *Digit Span backwards* (from the WAIS-R, German version; Tewes, 1991): Subjects repeat a list of orally presented digits backwards.
- *2-back* (from the TAP; Zimmermann and Fimm, 1995): A task consisting of the sequential visual presentation of single digits or simple figures. Subjects have to press a button when the presented digit or figure is the same as the one presented two trials earlier.

2.3.4. Tests of memory

• *LGT-3* (*Lern-und Gedächtnistest*, learning and memory test; Bäumler, 1974)*:* In each of the four subtests of this paper-and-pencil test, the material to be learned is presented visually for 1 min. Memory performance is assessed immediately after the learning phase and again after one hour.

– *LGT-3—logos*: Subjects have to memorize 20 logo-like figures each consisting of a central icon and a frame. In the retrieval phase, they have to identify the correct frame corresponding to each central icon out of an array of four similar frames.
– *LGT-3—city map*: Subjects have to memorize a line which is drawn in the free space between small rectangles and other irregularly shaped figures. This array looks like a route on a city map. In the retrieval phase, subjects are presented with the map only, and they have to draw the route in it. Deviations from the previously presented line are scored according to standardized criteria.
– *LGT-3—German–Turkish*: Subjects have to memorize 20 word pairs consisting of a Turkish word and its German translation. In the retrieval phase, they have to identify the correct Turkish word corresponding to each German word out of a list consisting of five Turkish words.
– *LGT-3—construction of a library:* Subjects are given a text consisting of 10 sentences and containing information about the construction of a library (name of the architect, address, number and size of the different rooms, costs of construction, etc). In the retrieval phase, subjects have to answer a list of 21 questions on these items.

2.4. Data analysis

For the purpose of statistical analyses, we employed the median split procedure to build two subgroups of MDMA (30 heavy users: lifetime dose ≥ 80 ecstasy tablets, and 30 moderate users: lifetime dose < 80 ecstasy tablets, respectively) Thus, we compared 30 heavy with 30 moderate MDMA users and 30 healthy nonusers. Sociodemographic data were analyzed by means of ANOVA (age) and χ^2 test

Table 1
Demographic data of ecstasy users and controls ($n = 30$ in each group)

	Heavy users	Moderate users	Controls
Mean age in years (mean ± S.D.)	25.1 ± 4.65	24.0 ± 3.14	25.37 ± 2.72
Men/women	21:9	21:9	21:9
Level of education			
1. Basic school-leaving exam after form 9 (*Hauptschulabschluß*)	4	2	3
2. Intermediate school-leaving exam after form 10 (*Realschule/mittlere Reife*)	12	8	10
3. Highest school-leaving exam qualifying for admission to college/university after form 12 or 13 (*Fachabitur/Abitur*)	12	20	17
4. University degree (*Hochschulabschluß*)	2	–	–

Table 2
Patterns of lifetime drug use in ecstasy users and controls ($n = 30$ in each group, mean values and S.D.)

	Ecstasy		Cannabis			Amphetamine		LSD	
	Heavy users	Moderate users	Heavy users	Moderate users	Controls	Heavy users	Moderate users	Heavy users	Moderate users
Subjects reporting use	30	30	23	22	8	24	21	10	7
Estimated lifetime dose	503.2 ± 555.5 pills***	39.5 ± 18.0 pills***	x	x	x	233.7 ± 473.5 g*	40.9 ± 94.9 g*	74.0 ± 194.4 trips	15.3 ± 42.5 trips
Duration of regular use (months)	40.9 ± 35.2***	16.0 ± 14.7***	62.8 ± 52.0^{++}	50.4 ± 42.0^{+}	20.4 ± 38.7	32.1 ± 33.2*	16.53 ± 20.4*	17.2 ± 46.8	6.8 ± 16.3
Average frequency of use (days per month)	4.5 ± 3.2***	1.8 ± 1.3***	17.9 ± 12.6^{+++}	16.0 ± 13.4^{+++}	4.3 ± 9.1	7.6 ± 9.1*	3.7 ± 5.7*	1.02 ± 1.94	0.38 ± 0.89
Average daily or one night dose	2.6 ± 1.8 pills **	1.4 ± 0.7 pills **	730.5 ± 695.8 mg^{+++}	535.5 ± 479.5 mg^{+}	182.2 ± 421.9 mg	483.3 ± 526.9 mg	309.4 ± 346.7 mg	0.72 ± 1.33 trips$^{(*)}$	0.26 ± 0.52 trips$^{(*)}$
Age at onset of use	19.6 ± 4.4	20.0 ± 2.8	15.6 ± 2.6^{+}	15.8 ± 1.9$^{(+)}$	18.1 ± 2.4	18.9 ± 3.8	19.0 ± 3.0	19.1 ± 18.0	18.0 ± 4.3
Time since last dose in days (median [range])	194.8 ± 351.8 (23 [7–1440])	242.3 ± 401.4 (30 [7–1440])	37.2 ± 112.5 (1 [1–540])	2.78 ± 2.7 (1 [1–8])	16.7 ± 19.6 (7 [1–60])	182.2 ± 384.8 (16 [7–1800])	245.4 ± 369.8 (30 [7–1200])	664.4 ± 756.8 (270 [14–2160])	708.7 ± 670.0 (722.5 [10–1600])
THC-screen in urine sample on study day	–	–	18 positive/ 12 negative	13 positive/ 17 negative	4 positive/ 26 negative	–	–	–	–

THC = tetrahydrocannabinol (Cannabis); x = subjects felt that they were unable to give a reliable estimate.
$^{(*)}$ $P < .05$ (differences between heavy and moderate ecstasy users, two-tailed t test).
* $P < .1$ (differences between heavy and moderate ecstasy users, two-tailed t test).
** $P < .01$ (differences between heavy and moderate ecstasy users, two-tailed t test).
*** $P < .001$ (differences between heavy and moderate ecstasy users, two-tailed t test).
$^{(+)}$ $P < .1$ (differences between heavy ecstasy users and controls or moderate ecstasy users and controls, ANOVA and post hoc Scheffé test).
$^{+}$ $P < .05$ (differences between heavy ecstasy users and controls or moderate ecstasy users and controls, ANOVA and post hoc Scheffé test).
$^{++}$ $P < .01$ (differences between heavy ecstasy users and controls or moderate ecstasy users and controls, ANOVA and post hoc Scheffé test).
$^{+++}$ $P < .001$ (differences between heavy ecstasy users and controls or moderate ecstasy users and controls, ANOVA and post hoc Scheffé test).

(educational levels). The patterns of drug use were analyzed by means of independent *t* tests (heavy/moderate users) except for the pattern of cannabis use, which was analyzed by means of ANOVA (heavy/moderate users/controls). Cognitive performance scores of the three groups were analyzed by means of ANOVA and Scheffé post hoc tests. In order to avoid excessive Type II error accumulation, we did not employ a Type I error correction for multiple testing. In case of significant group differences, we ran additional analyses of covariance (ANCOVA) using the General Knowledge score as a covariate. This applied for the LGT-3 test only. The various aspects of the pattern of use of ecstasy, amphetamines, cannabis and LSD (duration of use, lifetime dose, daily dose, frequency of use, time since last dose) were entered in a linear stepwise regression analysis in order to study the relations between LGT-3 performance of the entire sample of ecstasy users and their previous use of ecstasy and other drugs. Potential predictor variables were included if they explained variance at a threshold of $P \leq .05$. In a separate multiple linear regression analysis, we explored the possible influences of other cognitive functions on memory performance (LGT-3—logos, immediate and delayed recall) of the entire sample of ecstasy users (enter and remove methods of regression analysis; potential predictor variables: Digit Span score; 2-back RTs; Go/NoGo RTs; Visual Scanning: correlation between target position and RT; PAD: peak score, number of deletions of single actions, frequency of use of the F2 key). All procedures were performed using SPSS software version 10.0 (SPSS, Chicago, IL); *P* values $\leq .05$ were considered significant.

3. Results

3.1. Sociodemographic data and drug histories

Sociodemographic data are presented in Table 1. The three groups were identical in terms of sex distribution and they were similar in terms of age (ANOVA: $F = 1.21$, $df = 2$, $P = .30$) and level of education (χ^2 test: $\chi^2 = 1.57$, $df = 2$, $P = .46$, educational levels 1–2 and 3–4 were pooled together for testing). The patterns of drug use are presented in Table 2. Most ecstasy users reported concomitant amphet-

Table 3
Neuropsychological test battery scores of ecstasy users and controls (group means ± standard deviation, $n = 30$ in each group) and results of ANOVA, ANCOVA with General Knowledge as a covariate (in parentheses) and post hoc group comparisons ($df = 2$)

		Scores			ANOVA (ANCOVA)		Scheffé (*P*)		
		Heavy users (H)	Moderate users (M)	Controls (C)	*F*	P	H/C	M/C	H/M
General Knowledge	WAIS-R score	**14.6 ± 4.6**	**17.4 ± 3.0**	**17.1 ± 3.73**	4.847	.01	.043	.965	.022
Go/NoGo	Correct responses (CR)	19.7 ± 0.5	19.5 ± 0.7	19.4 ± 0.9	1.300	.278	–	–	–
	Reaction times (RT, ms)	398.0 ± 66.1	403.8 ± 75.0	382.6 ± 54.8	0.823	.442	–	–	–
Visual Scanning	Noncritical trials CR	48.2 ± 1.1	48.1 ± 1.0	48.5 ± 1.0	0.792	.456	–	–	–
	Noncritical trials RT (ms)	4992.6 ± 1191.8	4764.5 ± 1753.3	4367.7 ± 1268.5	1.474	.235	–	–	–
	Critical trials CR	44.8 ± 4.1	44.8 ± 3.5	45.5 ± 3.2	0.318	.728	–	–	–
	Critical trials RT (ms)	2756.0 ± 778.2	2541.5 ± 840.7	2444.9 ± 729.8	1.237	.295	–	–	–
	Correlation RT/target position (*Z*-transformed)	0.913 ± 0.502	1.039 ± 0.465	1.119 ± 0.579	1.093	.340	–	–	–
Plan-A-Day	Peak score	26.9 ± 4.3	28.5 ± 3.6	27.8 ± 3.9	1.218	.301	–	–	–
	End score	24.0 ± 7.1	25.1 ± 7.6	25.8 ± 7.7	0.396	.674	–	–	–
	Peak – end score	2.9 ± 6.5	3.5 ± 7.1	1.9 ± 4.7	0.716	.492	–	–	–
	Single deletions	20.6 ± 13.7	24.1 ± 19.1	19.1 ± 15.3	0.642	.529	–	–	–
	Sequences of deletions	10.8 ± 7.4	12.2 ± 7.9	8.4 ± 5.2	1.840	.166	–	–	–
	Use of F2 key	21.1 ± 9.1	21.6 ± 10.6	19.3 ± 6.1	0.432	.651	–	–	–
Digit Span backward	Score	8.0 ± 2.3	8.8 ± 2.0	8.8 ± 2.3	1.249	.292	–	–	–
2-back letters	CR	11.9 ± 2.7	12.9 ± 1.7	12.3 ± 3.2	1.135	.326	–	–	–
	RT (ms)	641.8 ± 149.4	630.1 ± 153.9	622.2 ± 140.9	0.133	.876	–	–	–
2-back figures	CR	8.9 ± 3.1	8.7 ± 2.8	9.7 ± 3.0	0.863	.425	–	–	–
	RT (ms)	695.2 ± 146.5	723.4 ± 153.3	742.5 ± 131.6	0.786	.459	–	–	–
LGT-3 memory test									
• Logos	Immediate recall score	**10.6 ± 3.9**	**13.2 ± 3.1**	**13.5 ± 4.0**	5.556 (3.439)	.005 (.037)	.012	.939	.031
	Delayed recall score	**9.1 ± 4.1**	**12.1 ± 3.2**	**12.5 ± 4.6**	6.623 (3.973)	.002 (.022)	.005	.917	.017
• City map	Immediate recall score	**17.0 ± 4.7**	17.1 ± 5.4	**20.1 ± 5.3**	3.587 (3.084)	.032 (.051)	.066	.082	.995
	Delayed recall score	**16.4 ± 3.7**	16.5 ± 5.4	**18.9 ± 4.7**	2.717 (2.372)	.072 (.099)	.126	.148	.997
• German–Turkish	Immediate recall score	10.7 ± 3.6	11.6 ± 3.7	12.2 ± 4.0	1.109	.335	.338	.832	.680
	Delayed recall score	**9.0 ± 3.2**	10.4 ± 4.4	**11.6 ± 3.6**	3.462 (2.262)	.036 (.110)	.036	.507	.346
• Library	Immediate recall score	**11.9 ± 4.1**	**14.5 ± 3.9**	14.0 ± 4.22	3.358 (0.457)	.039 (.635)	.150	.893	.056
	Delayed recall score	**1.1 ± 3.8**	**13.8 ± 3.9**	13.0 ± 4.5	3.511 (0.554)	.034 (.577)	.196	.753	.041

H/C: heavy ecstasy users/controls, M/C: moderate ecstasy users/controls, H/M: heavy/moderate ecstasy users.
Significant ($P < .05$) or marginal ($P < .1$) group differences are indicated by bold characters.

amine and cannabis use, about one third of users reported LSD use. Only two moderate and two heavy ecstasy users reported sporadic cocaine use (data on cocaine use are not included in Table 2). In general, a higher extent of ecstasy use was associated with a higher extent of amphetamine and cannabis use, although correlations were not particularly high (range of significant Pearson's correlation coefficients from r=.335 to r=.699, data not shown). However, only the difference in the extent of concomitant amphetamine use between the two user groups reached statistical significance. The control group denied regular drug use except for mild cannabis use in eight subjects.

3.2. Cognitive performance

Descriptive and inferential statistics are presented in Table 3.

- General intelligence: Heavy ecstasy users performed poorer than both nonusers and moderate users in the WAIS-R General Knowledge test.
- Executive control, cognitive impulsivity, planning ability: There were no performance differences between the three groups in the Go/NoGo, Visual Scanning and the PAD task.
- Working memory: There were no performance differences between the three groups in the Digit Span and 2-back scores.
- Memory: Heavy users recalled less items than controls and partly also less items than moderate users in most subtests of the LGT-3. Moderate users did not differ significantly from controls. In the ANCOVA, using the General Knowledge score as the covariate, group differences were still significant for the logos test and approached significance for the city map test.

3.3. Memory performance and extent of previous drug use

We found a significant influence of the frequency of ecstasy use on both the immediate and delayed recall score in the logos test ($\beta = -0.400$, S.E. = 0.180, $T = -2.931$, df=45, P=.005, and $\beta = -0.351$, S.E. = 0.197, $T = -2.512$, df=45, P=.016, respectively) and on the immediate recall score in the library test ($\beta = -0.314$, S.E. = 211, $T = -2.217$, df=45, P=.032). Otherwise, the various aspects of the pattern of use of ecstasy, amphetamines, cannabis and LSD had no significant effects on memory performance.

3.4. Memory performance and other cognitive functions

None of the chosen variables from the tests of working memory, executive control, cognitive impulsivity and planning ability was found to be a significant predictor for the immediate and delayed recall performance in the LGT-3—logos test (all P values $>.3$).

4. Discussion

4.1. Primary memory disturbance

The aim of the present study was to analyze the nature of the cognitive deficits of currently abstinent ecstasy users. A battery including tests of memory, working memory, planning ability, cognitive impulsivity and central executive control was administered to 30 heavy and 30 moderate ecstasy users and to 30 nonusers, who were matched for age, sex and level of education. Ecstasy users did not differ from controls in terms of working memory, executive control, cognitive impulsivity and planning ability. Heavy ecstasy users with an average estimated lifetime dose of 500 ecstasy pills over the last 3–4 years performed poorer in the memory tasks and in a general knowledge test, which is thought to reflect general intelligence. The group difference between heavy users and controls remained significant in one memory test after correcting for lower general knowledge. Moderate users with an average estimated lifetime dose of 40 ecstasy pills over the last 1–2 years did not differ from controls. Poorer memory performance in ecstasy users was associated only with heavier ecstasy use, but not with the extent of use of other drugs.

Our data are in line with the view that substantial ecstasy use over a period of months or few years may cause long-term impairment of memory performance. Other cognitive functions such as working memory, executive control, planning ability and cognitive impulsivity were not clearly affected by ecstasy use. In consequence, our data contradict the hypothesis that problems of working memory or central executive control and cognitive impulsivity might underlie the memory and learning deficits of ecstasy users (Gouzoulis-Mayfrank et al., 2000; Parrott, 2000; Wareing et al., 2000). The cognitive performance pattern of ecstasy users in our study rather suggests a primary memory disturbance, which may be associated with neurotoxic effects of MDMA upon central serotonergic systems. Notably, this result is in agreement with a well-designed recent study (Fox et al., 2002), which used a different comprehensive cognitive test battery. Fox et al. (2002) also reported decrements in learning and memory performance, but relatively normal behavioral measures of impulsivity, planning ability and inhibitory mechanisms in ecstasy users compared to polydrug controls.

4.2. Is the hippocampus particularly vulnerable to the neurotoxic effects of ecstasy upon serotonergic systems?

The pattern of cognitive performance in ecstasy users is compatible with the view that the function of the hippocampus, a region which is linked especially to memory processes, might be more profoundly affected from the neurotoxic effects of ecstasy compared with the neocortex,

which serves other higher cortical functions such as central executive control, working memory and planning ability. This interpretation is in line with the conclusion by Fox et al. (2002) that their sample of ecstasy users "displayed cognitive deficits in tasks that were predominantly sensitive to temporal lobe dysfunction," but no deficits in most tasks sensitive to prefrontal functioning (Fox et al., 2002). This dissociation might be related to a predominant physiological role of the serotonin system for mnemonic processes, as has been suggested by both human and animal experimental studies (Park et al., 1994; Riedel et al., 1999; Cassaday et al., 2003). However, it may also be related to a particular vulnerability of the hippocampus and parahippocampal regions to the neurotoxic effects of ecstasy. Indeed, although MDMA-related neurotoxicity appears to be widespread all over the brain, the extent of neurotoxic damage and the rate of recovery after abstinence vary across different brain regions. In particular, the hippocampus and the parahippocampus display relatively high rates of serotonergic denervation after MDMA exposure and relatively low rates of recovery after abstinence from MDMA in animal studies (Ricaurte et al., 1992; Fischer et al., 1995; Hatzidimitriou et al., 1999). Of all the brain regions examined in a recent study with nonhuman primates, the subiculum, a part of the hippocampal formation with important connections to the mamillar bodies and the anterior nucleus of the thalamus, showed the largest reduction in the density of serotonin (5-HT) immunoreactive axons 7 years after treatment with MDMA (Hatzidimitriou et al., 1999).

Moreover, an additional issue should be considered, which might contribute to a particularly high susceptibility of the hippocampus to the MDMA-related serotonergic damage: Serotonin is not only a neurotransmitter, but it has additional important neurotrophic functions during brain development and maturation (Azmitia, 1999). Recent evidence suggests that the hippocampus is an exception from a general rule regarding the timing of the production and migration of neuronal cells: Although the adult brain retains a high grade of plasticity in terms of synaptogenesis and changes of synaptic connectivity, neurogenesis (i.e. the production of new neuronal cells) is already completed at birth in almost all brain regions. However, the hippocampus still displays neurogenesis throughout life, and stimulation of 5-HT_{1A} receptors by endogenous serotonin stimulates hippocampal neurogenesis throughout adulthood (Gould, 1999). Adult-generated hippocampal neurons are thought to be specifically important for learning and memory processes (Gould, 1999). This may be another reason why hippocampal systems might be more sensitive to serotonin depletion than neocortical brain regions and it might explain the pattern of cognitive performance in ecstasy users with more consistent decrements in memory and learning performance compared to other cognitive domains which are dependent only on neocortical function.

4.3. Clinical significance

In general, the memory disturbance of ecstasy users is subtle. In most cases, it develops after substantial ecstasy use, but even very heavy users are not necessarily impaired to a clinically relevant degree. This may challenge the practical relevance of our data and similar data from the literature. However, this same fact may bear the biggest danger because the subtle cognitive decline may not be noticed by the individuals themselves over a prolonged period of time. Therefore, subjects are likely to continue using ecstasy and put themselves at substantial risk for further deterioration over the years. Theoretically, it is possible that the impairment becomes more apparent only after many years when the effects of normal aging add to the possible neurotoxic damage (McCann et al., 2000; Curran, 2000). In this context, ecstasy use in young years may become a serious risk factor for earlier manifesting and/or more severe age-related memory problems in later life (Morgan, 2000; Morgan et al., 2002). Important questions concerning individual differences in susceptibility to the neurotoxic effects of ecstasy and the reversibility or permanence of the adverse cognitive effects after longer periods of abstinence are still unanswered.

4.4. Methodological limitations

Our study has methodological limitations which are inherent to open trial studies with user populations. In line with the results from previous studies, heavy ecstasy users performed poorer in a test of crystallized intelligence (Gouzoulis-Mayfrank et al., 2000). Therefore, we cannot entirely rule out the possibility that the poorer memory performance of heavy ecstasy users was only due to accidental preexisting differences in general cognitive capacity or education. However, we do not think that this was the case, because there was a significant association of poorer memory performance with heavier previous ecstasy use and because group differences in nonverbal memory performance remained significant after statistical control for the possible influence of general intelligence.

Another methodological problem is related to the widespread and still increasing frequency of polydrug use among ecstasy users. While a few years ago we were able to recruit a reasonable number of ecstasy users with concomitant use of cannabis only (Gouzoulis-Mayfrank et al., 2000), this was impossible in our present study. Most subjects reported regular concomitant use of cannabis and stimulant amphetamines and about one-third reported regular concomitant use of LSD. Hence, it might be problematic to relate the cognitive performance data to the use of one specific drug. Nevertheless, memory performance was associated only with the extent of previous ecstasy use, but not with the extent or recency of previous

use of cannabis, amphetamine or LSD. Cannabis is known to impair neuropsychological function up to one week after the last use (Fletcher et al., 1996; Pope et al., 2001) and many users in our study had used cannabis one day before they were examined. However, cognitive impairment after cannabis seems to apply for heavy cannabis users, whereas the subjects in our study displayed a pattern of frequent, but otherwise relatively mild, cannabis use. For example, none of our subjects would have suited the inclusion criteria of at least 5000 episodes of marijuana smoking, as it was defined in the study by Pope et al. (2001). Moreover, in a previous study of our group using similar cognitive tests, mild cannabis use up to one day before testing did not impair the cognitive performance of subjects to a significant degree (Gouzoulis-Mayfrank et al., 2000). Finally, only heavy ecstasy users showed relative impairments in memory performance, whereas the two user groups were similar with respect to the extent and recency of their cannabis use.

Needless to say, studies of this type have additional inherent methodological problems that simply cannot be solved perfectly (e.g. unprecise recall of the details of previous drug use, uncertain chemical composition of illegally purchased drugs). Despite these limitations, it is very unlikely that the concomitant use of other drugs fully accounts for the poorer memory performance of heavy ecstasy users. Based both on our own results and converging data from the literature (Bolla et al., 1998; Parrott and Lasky, 1998; Morgan, 1999; Reneman et al., 2000; Rodgers, 2001; Zakzanis and Young, 2001a; Reneman et al., 2001a), the memory disturbance in our sample of heavy ecstasy users is likely to be related to the well-recognized neurotoxic potential of ecstasy upon serotonergic systems. Given the popularity of ecstasy among young people, further investigations are clearly needed. In our view, research strategies should now combine prospective and longitudinal designs with cognitive assessments and modern neuroimaging techniques in order to shed more light onto the course of the adverse cognitive effects of ecstasy use.

5. Conclusion

Previous studies have shown cognitive deficits in currently abstinent ecstasy (MDMA) users compared to controls. The most consistent findings have been decrements in memory and learning performance. However, deficits in working memory, planning ability and central executive control, as well as high cognitive impulsivity, were also reported. This study was intended to analyze the nature of the cognitive deficits in a large group of currently abstinent ecstasy users. Our findings indicate that ecstasy use is associated with primary memory dysfunction, but no clear deficits of central executive function and working memory or elevated cognitive impulsivity. The memory dysfunction may well be related to the neurotoxic effects of ecstasy upon central serotonergic systems.

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