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Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction

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Abstract

Chronic administration of the common club drug 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is associated with long-term depletion of serotonin (5-HT) and loss of 5-HT axons in the brains of rodents and non-human primates, and evidence suggests that recreational MDMA consumption may also affect the human serotonergic system. Moreover, it was consistently shown that abstinent MDMA users have memory deficits. Recently, it was supposed that these deficits are an expression of a temporal or rather hippocampal dysfunction caused by the serotonergic neurotoxicity of MDMA. The aim of this study is to examine the memory deficits of MDMA users neuropsychologically in order to evaluate the role of different brain regions. Nineteen male abstinent MDMA users, 19 male abstinent cannabis users and 19 male drug-naive control subjects were examined with a German version of the Rey Auditory Verbal Learning Test (RAVLT). MDMA users showed widespread and marked verbal memory deficits, compared to drug-naive controls as well as compared to cannabis users, whereas cannabis users did not differ from control subjects in their memory performance. MDMA users revealed impairments in learning, consolidation, recall and recognition. In addition, they also showed a worse recall consistency and strong retroactive interference whereby both measures were previously associated with frontal lobe function. There was a significant correlation between memory performance and the amount of MDMA taken. These results suggest that the memory deficits of MDMA users are not only the result of a temporal or hippocampal dysfunction, but also of a dysfunction of regions within the frontal cortex.

Keywords

MDMA, cannabis, memory, hippocampus, recall consistency, retroactive interference, frontal cortex, serotonin, 5-HT

Introduction

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is an illicit club drug which is widely abused, especially by young people (Christophersen, 2000). In a recent survey by the Federal Centre for Health Education (Bundeszentrale für gesundheitliche Aufklärung; BzgA) in Germany 4% of the interviewed juveniles between 12 and 25 years of age reported having used ecstasy at least once (BzgA, 2004). In Germany, MDMA and its derivatives are therefore the second most popular illicit drug following cannabis (24%) (BzgA, 2004). Even worldwide, MDMA has become one of the most widely used illegal psychoactive drugs, with millions of regular users (Landry, 2002).

Administration of MDMA produces a rapid and marked release of serotonin (5-HT) in animals via inhibition and reversal of the 5-HT transporter (Rudnick and Wall, 1992). Studies in non-human primates provided convincing evidence that MDMA causes a substantial and sustained long-term neurotoxic loss of only 5-HT nerve terminals with an associated depletion of up to 95% of 5-HT in several brain regions, especially in areas of the frontal and the temporal cortex. In contrast, other neurotransmitter systems such as dopamine or norepinephrine remain undamaged (Insel *et al.*, 1989; Wilson *et al.*, 1989; Ali *et al.*, 1993; Scheffel *et al.*, 1998; Hatzidimitriou *et al.*, 1999). Studies of MDMA use in humans have also shown selective decrements in cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) as a

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marker for central serotonergic depletion, which were not accompanied by alterations in CSF homovanillic acid (HVA) or 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolites of dopamine and norepinephrine, respectively (McCann *et al.*, 1994, 1999). Imaging studies with serotonergic radioligands showed reduced 5-HT transporter densities in cortical and subcortical structures of the brains of MDMA users (McCann *et al.*, 1998; Semple *et al.*, 1999; Reneman *et al.*, 2001; Buchert *et al.*, 2003). Moreover, electrophysiological studies suggested alterations of the serotonergic system in regular users of MDMA (Tuchtenhagen *et al.*, 2000; Croft *et al.*, 2001a; Quednow *et al.*, 2004). To summarize, MDMA seems to be a neurotoxin that selectively impairs the serotonergic system in primates including humans.

It has been consistently shown that MDMA users display impairments of verbal and visuo-spatial memory (e.g. Parrott *et al.*, 1998; McCann *et al.*, 1999; Morgan, 1999; Bhattachary and Powell, 2001; Fox *et al.*, 2001b, 2002; Morgan *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2003; Thomasius *et al.*, 2003; Wareing *et al.*, 2004a, 2004b), but little is known about the neuroanatomical basis of these deficits. In view of the neuropsychological profile, Fox *et al.* (2001b) speculated that MDMA users have deficits during storage and/or retrieval of memory information, whereas the capacity per se remains unaffected. Later on, the authors concluded that a dysfunction of the temporal cortex could be responsible for the memory deficits of MDMA users because their neuropsychological profile is similar to patients with temporal lesions (Fox *et al.*, 2002). However, Fox and colleagues (2001b, 2002) did not specify whether temporal association cortices or medial temporal regions could be affected in MDMA users. Gouzoulis-Mayfrank *et al.* (2003) suggested that the memory dysfunction of MDMA users might be related to a hippocampal dysfunction because on the one hand, the hippocampus plays a key role in memory function and on the other hand, the hippocampus and the parahippocampus displayed relatively high rates of serotonergic denervation after MDMA exposure and relatively low rates of recovery after abstinence from MDMA in animal studies. Recent studies using functional magnetic resonance imaging (fMRI) now suggest differences in the activation of the hippocampus between MDMA users and healthy controls during working memory tasks and so supported the view of a hippocampal dysfunction in MDMA users (Daumann *et al.*, 2004b; Jacobson *et al.*, 2004; Moeller *et al.*, 2004). However, two imaging studies did also show abnormalities in the activation of frontal, thalamic and parietal regions of MDMA users during working memory tasks (Daumann *et al.*, 2004a; Moeller *et al.*, 2004).

MDMA users did also show deficits in executive functions and decision-making cognition, and these cognitive functions were associated with frontal rather than with temporal lobe functions (McCann *et al.*, 1999; Wareing *et al.*, 2000; Bhattachary and Powell, 2001; Fox *et al.*, 2001a; Zakzanis and Young, 2001; Alting von Geusau *et al.*, 2004; Fisk *et al.*, 2004; Quednow *et al.*, in press). Furthermore, the frontal cortex is also a major component of the memory system: the dorsolateral prefrontal cortex is being discussed as the substrate of the central executive of working memory (Baddeley, 2003) and it has been shown that dorsolateral and ventrolateral prefrontal areas are also involved in encoding, recall and recognition of declarative and episodic memory information (Ranganath *et al.*, 2003; Ranganath and Knight, 2003). Moreover, in monkeys it has been demonstrated that particularly the frontal regions exhibit a sustained loss of 5-HT axon terminals after MDMA exposure (Fischer *et al.*, 1995; Hatzidimitriou *et al.*, 1999). In addition to that, immunohistochemical studies in rats and monkeys indicate that MDMA appears to cause a selective degeneration of fine-diameter serotonergic axons with small varicosities which arise from the dorsal raphe nucleus and project particularly into the forebrain (O'Hearn *et al.*, 1988; Wilson *et al.*, 1989). Thus, a dysfunction of the frontal cortex could also be responsible for the memory deficits of MDMA users.

The aim of this study is to assess whether memory deficits observed in MDMA users may have an executive component which may be associated with impaired frontal lobe function. Thus, we applied a German version of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) to assess verbal declarative memory function in chronic but recently abstinent MDMA users. Cannabis users and drug-naive participants made up the control groups. The comparison with a control group of cannabis users allowed us to estimate the influence of the common concomitant use of cannabis in MDMA users, which has been previously discussed to be a strong biasing factor in research with MDMA consumers (Croft *et al.*, 2001b; Daumann *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2002). Even though the RAVLT has already been used to assess memory function in MDMA users (Bolla *et al.*, 1998; Fox *et al.*, 2001b; Thomasius *et al.*, 2003; McCardle *et al.*, 2004), none of these previous studies reported measures associated with frontal lobe functions, such as recall consistency and retroactive interference. A low recall consistency reflects the failure to recall a word on a later learning trial when it had been recalled in an earlier trial (Delis *et al.*, 1987). Recall consistency has been found to relate to measures of executive function (Vanderploeg *et al.*, 1994; Beebe *et al.*, 2000) and may represent poor organizational strategies during learning of verbal material (Waters and Waters, 1976; Alexander *et al.*, 2003). Consistent with these findings, recall consistency is impaired after frontal lobe damage (Delis *et al.*, 1994; Alexander *et al.*, 2003). Retroactive interference is defined as the detrimental effect of subsequent learning on the recall of previously learned target material (Postman and Underwood, 1973). Retroactive interference was also associated with executive functions (Torres *et al.*, 2001) and patients with frontal lesions are also excessively susceptible to interference on recall (Shimamura *et al.*, 1995; Baldo *et al.*, 2002). However, due to reports that MDMA users do exhibit executive function deficits, we would expect to observe a decrement in MDMA users' performance in comparison to both control groups particularly in those measures of the RAVLT that have been previously associated with frontal lobe functions. Due to the assumption that the expected mnemonic deficits were caused by MDMA, we anticipate a correlation between MDMA consumption and memory performance.

Methods and materials

Participants

Memory performance was measured in three groups. The first group (MDMA group) included 19 male drug-free chronic users of MDMA; the second group (cannabis group) consisted of 19 male drug-free chronic users of cannabis; and the third group (drug-naive controls) comprised 19 male participants with no history of illicit drug use. MDMA users were recruited by advertisement in a techno-music magazine. Cannabis users and drug-naive controls were recruited by advertisement in a local newspaper. Participants of the MDMA group were required to have consumed MDMA at least 50 times over a period of at least 1 year. In addition, with the exception of cannabis, the use of MDMA clearly had to outweigh the consumption of any other psychotropic drug and participants should especially have no substantial previous use of other amphetamine derivatives or cocaine. To be eligible for inclusion in the cannabis group, participants should not have any substantial previous use of MDMA or any other amphetamine derivatives, cocaine or other illicit drugs. Neuropsychological assessment was carried out when participants were drug free for at least 3 days. Drug-naive controls should have no experience with illicit drugs and were required to have a negative urine drug test. Legitimate use of psychotropic medication, a personal or family history of psychiatric illness or any severe somatic illness were exclusion criteria for all groups. None of the participants had a history of migraine, epilepsy or craniocerebral trauma.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn. After being informed of the aim of the study by written and oral description, all participants gave written informed consent statements.

Procedure

Neuropsychological assessment was carried out after written informed consent was given by all participants. For the estimation of verbal intellectual performance, the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl, 1999) was used. In addition, a SKID-I interview conducted according to Diagnostic and Statistical Manual IV (DSM-IV) procedures was carried out by a trained psychologist in order to ensure the absence of psychiatric disorders in our participants. Drug history and present pattern of psychotropic drug consumption were assessed by a structured interview. Participants who were screened for inclusion in the drug-naive control group were urine-tested for drug use. During the psychiatric and neuropsychological assessment participants were allowed to take a break at any time. In addition to the verbal memory test (see below) the neuropsychological test battery also comprised of two behavioural impulsivity measures and a decision-making task whose results will be published elsewhere (Quednow *et al.*, in press). The whole battery took about 120 min; including breaks as and when needed, and was generally well tolerated by the participants.

Interview for psychotropic drug consumption

A structured interview was developed for the assessment of the use of legal and illicit psychotropic substances. The interview included questions concerning quantity, duration and frequency of present and past consumption of all known psychotropic substances. The quantity of drug consumption was assessed for MDMA in terms of the numbers of tablets consumed. Furthermore, one interview question asked for the highest single MDMA dose ever used (lifetime peak dose). For cannabis, amphetamine and other substances, the quantity was measured in terms of the number of times of use because evaluating and defining the concept of a single dose was difficult. We estimated a cumulative drug dose on the basis of actual and previous substance intake.

Verbal memory assessment

Verbal declarative memory performance was measured by the Verbaler Lern- und Merkfähigkeitstest (VLMT; Helmstaedter *et al.*, 2001) which is a German version of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964). The test examines verbal declarative memory performance with regard to the supraspan, acquisition (learning) performance across five trials, delayed recall, recall after interference and recognition. The instrument comprises of a word list A of 15 nouns (learning list), a second word list B of 15 different nouns (interference list) and a third list C of 50 nouns which includes all words of lists A and B as well as 20 new, but semantically- and phonetically-related words (recognition list). List A was read out by the interviewer five times and immediate recall was tested after each of these five consecutive trials (acquisition trials). Immediately after that, list B was presented and participants needed to recall them (interference trial). Then, list A had to be recalled again (recall after interference trial). After 30 min participants were asked to recall list A once more (delayed recall trial). Then, list C was read out and after each word participants had to decide if the word was new or belonged to list A or B (recognition trial). The correct words were recorded for each individual trial. Errors (such as false positive words, perseverations and intrusions) were not recorded in the recall trials. However, for calculation of the false alarm rate false positive words were collected in the recognition trials.

The dependent variables were: supraspan (trial 1), learning curve (trial 1–5), learning performance (Σ trials 1–5), recall consistency in percent (100/(Σ trials 1–4) * (Σ conjoint recalls of words between trials 1, 2; trials 2, 3; trials 3, 4; trials 4, 5); according to Delis *et al.*, 1987), recall of interference list (list B), recall after interference (trial 6), delayed recall (trial 7 after 30 min), proactive interference (loss between first trial list A and list B; trial 1 minus list B), retroactive interference (loss after interference; trial 5 minus trial 6), loss after consolidation (trial 5 minus trial 7), recognition performance (list C), and recognition performance adjusted by the number of false positive words ($p(A)_{\text{list A}} = (\text{Hits}_A/15 - (\text{false positives}_A + \text{false positives}_B)/20 + 1) * 0, 5$; according to Forrester and Geffen, 1991). *p(A)* is comparable to the discrimination performance (d-prime) of the signal detection theory (Green and Swets, 1966).

Statistical analysis

Before analysing the neuropsychological data, we examined demographic variables. Age, verbal IQ and years of education were analysed using the general linear models (GLM) approach to analysis of variance (ANOVA) across all groups followed by Tukey's HSD *post hoc* tests to determine whether differences existed between experimental groups (SPSS, Chicago, IL). The ratio of smokers and non-smokers between groups was calculated using χ^2-tests.

Neuropsychological data were analysed using the GLM approach to ANOVA across all groups followed by Tukey's HSD *post hoc* tests for single comparisons. The correlation between dependent variables with demographic variables and with parameters of drug use was tested using Pearson's product-moment correlation. Relationships between neuropsychological variables and drug consumption were assessed only across combined drug groups. The confirmatory statistical comparisons of all data across three groups were carried out at a significance level set at $p < 0.05$ (two-tailed). For correction of multiple comparisons within the correlational analyses the Bonferroni procedure was used. Effect sizes d were calculated with GPOWER (Erdfelder *et al.*, 1996).

Results

Demographics and drug use

The demographic data of the groups are shown in Table 1. Overall, the groups did not differ significantly with respect to age, length of education, and verbal intellectual performance as measured by the MWT-B (for statistics, see Table 2). However, because of trends for a different verbal IQ and length of education Tukey's HSD *post hoc* tests were applied. Single comparisons showed that the groups did not significantly differ in these parameters, but there was a trend for a difference between the MDMA group and the cannabis group with respect to verbal intellectual performance [$p = 0.06$; d = 0.75]. In addition, there were significantly fewer smokers in the drug-naive control group compared to the cannabis group [$\chi^2(1) = 6.76$; $p < 0.05$] and the MDMA group [$\chi^2(1) = 10.6$; $p < 0.001$]. Cannabis users and MDMA users did not differ in their smoking habits.

The amount of illicit drug use of the MDMA and the cannabis group is shown in Table 2. Drug-naive controls did not report any experiences with illicit drugs; therefore only the two drug groups were statistically compared. As expected regarding the preselection, MDMA users consumed significantly more MDMA, amphetamine and hallucinogens than cannabis users. Whereas, cannabis users did show only a trend for a more frequent use (times per week) and a significant longer use of cannabis compared to MDMA users. Both groups did not differ with respect to the cumulative cannabis dose and cocaine use. However, it should be noticed that the use of amphetamine and hallucinogens in the MDMA group was not really substantial compared to the use of MDMA (for statistics, see Table 2). Moreover, the previous use of several drugs was highly intercorrelated. After Bonferroni correction (significance level was set at $p < 0.0025$ because of 20 single comparisons) the cumulative MDMA dose was significantly correlated with the cumulative amphetamine [$r = 0.67$] as well as with the cumulative hallucinogen dose [$r = 0.57$]. In addition, there were strong trends for correlations between the cumulative amphetamine dose and the cumulative cannabis dose [$r = 0.45$] as well as between the cumulative amphetamine dose and the cumulative hallucinogen dose [$r = 0.39$]. The weekly doses and the duration of use of these drugs did show similar patterns (data not shown).

Memory

The RAVLT memory performance of the three experimental groups is shown in Fig. 1 for each trial.

A repeated measurements ANOVA (group × trial) with the first five learning trials revealed a significant main effect for the factor trial [$F(4, 216) = 179.1$; $p < 0.001$], reflecting the expected increase of memory performance over the five trials, and a significant between-subject effect [$F(2, 54) = 10.09$; $p < 0.001$], indicating different learning performances between the groups. The interaction of the factors trial and group was not significant, suggesting that the gradient of the learning curve was not different between the groups. *Post hoc* tests revealed that the MDMA group had a significantly worse learning performance compared to drug-naive controls [$p < 0.001$; d = 1.09] as well as compared to cannabis users [$p < 0.001$; d = 1.11]. Cannabis users and drug-naive controls did not differ in their learning performance.

ANOVAs over all groups of the first trial (supraspan) [$F(2, 54) = 2.68$; $p = 0.08$] and the list B [$F(2, 54) = 2.45$; $p = 0.10$] did show only trends for a group effect. *Post hoc* tests revealed only a

Table 1 Demographic data (means and standard deviations in parentheses)

	Total ($n = 57$, ♂)	MDMA ($n = 19$, ♂)	Cannabis ($n = 19$, ♂)	Controls ($n = 19$, ♂)	Value[a]	df/df_{err}[a]	p[a]
Age	24.35 (4.81)	24.21 (5.77)	25.42 (4.26)	23.42 (4.30)	$F = 0.83$	2/54	0.44
Smoker/non-smoker	31/26	15/4	11/8	5/14	$\chi^2 = 10.75$	2	**<0.01**
Verbal IQ	105.3 (12.09)	100.6 (11.67)	109.7 (9.47)	105.7 (13.53)	$F = 2.81$	2/54	*0.07*
Years of education	12.67 (1.41)	12.32 (1.70)	13.21 (0.63)	12.47 (1.54)	$F = 2.29$	2/54	0.11

[a]ANOVA (over all groups) or Chi²-test (over all groups) for frequency data.

Table 2 Pattern and amount of illicit drug use: Results of the psychotropic drug interview (means and standard deviations in brackets)[a]

	Drug and characteristic	MDMA ($n = 19$, ♂)	Cannabis ($n = 19$, ♂)	F	df/df_{err}	p
MDMA	Tablets per week	1.97 (2.73)	0.01 (0.05)	9.82	1/36	<**0.01**
	Years of use	3.66 (1.95)	0.11 (0.46)	59.7	1/36	<**0.001**
	Cumulative dose (tablets)	457.9 (433.9)	6.7 (24.0)	20.5	1/36	<**0.001**
	Lifetime peak dose (tablets)	6.1 (4.7)	0.32 (0.82)	27.7	1/36	<**0.001**
	Last consumption (days)	17.4 (14.6); *n = 19*	504.7 (810.4); *n = 3*	9.34	1/20	<**0.01**
Cannabis	Times per week	1.63 (1.62)	3.89 (4.72)	3.86	1/36	*0.06*
	Years of use	3.95 (3.11)	6.55 (3.67)	5.61	1/36	<**0.05**
	Cumulative dose (times)	547.1 (502.7)	1033.4 (1348.6)	2.17	1/36	0.15
	Last consumption (days)	11.1 (21.6); *n = 16*	7.1 (4.7); *n = 19*	0.62	1/33	0.44
Amphetamine	Times per week	0.82 (1.31)	0.04 (0.16)	6.62	1/36	<**0.05**
	Years of use	3.37 (2.05)	0.63 (1.89)	18.3	1/36	<**0.001**
	Cumulative dose (times)	208.5 (279.5)	14.5 (59.6)	8.75	1/36	<**0.01**
	Last consumption (days)	38.1 (89.9); *n = 17*	240.0 (169.7); *n = 2*	7.84	1/17	<**0.05**
Cocaine	Times per week	0.04 (0.10)	0.02 (0.06)	0.79	1/36	0.38
	Years of use	0.66 (1.70)	0.26 (0.81)	0.84	1/36	0.37
	Cumulative dose (times)	4.87 (12.51)	2.49 (9.04)	0.45	1/36	0.51
	Last consumption (days)	34.5 (17.2); *n = 4*	17.5 (5.0); *n = 2*	1.68	1/4	0.26
Hallucinogens	Cumulative dose (times)	23.4 (38.8)	1.95 (4.24)	5.75	1/36	<**0.05**
	Last consumption (month)	7.86 (9.37); *n = 14*	7.20 (4.60); *n = 5*	0.02	1/17	0.88

[a]Consumption per week, duration of use, and cumulative dose are averaged within the total group. Last consumption is averaged only for persons who used the drug. In this case, sample size, *n*, is shown.

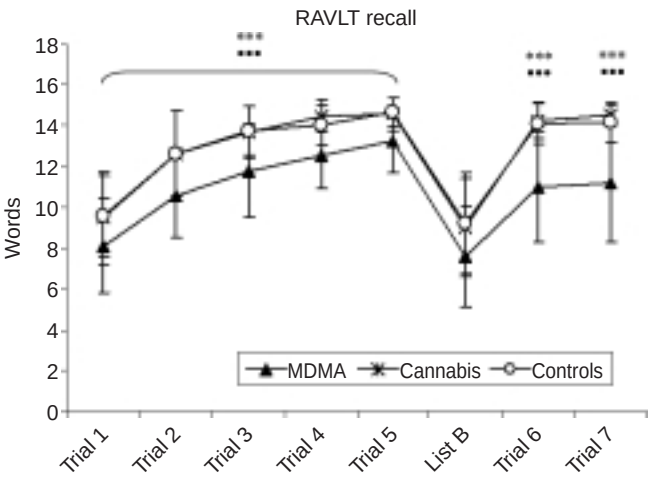

Figure 1 Performance on the first five learning trials, the interference list B, the recall after interference trial (trial 6) and the delayed recall trial after 30 min (trial 7) of the RAVLT of MDMA users, cannabis users and healthy controls (means and standard deviations). Learning performance was analysed with repeated measurements ANOVA across the five first trials, whereas the other trials where tested with univariate ANOVAs. Tukey's *post hoc* tests: MDMA vs. healthy controls, ***$p < 0.001$; MDMA vs. cannabis, •••$p < 0.001$.

weak trend for a worse performance on the first trial of the MDMA group compared to drug-naive controls [$p = 0.10$; $d = 0.65$].

Moreover, ANOVAs performed over all groups revealed significant main effects for the factor group in recall after interference (trial 6) [$F(2, 54) = 21.25$; $p < 0.001$] and in delayed recall (trial 7) [$F(2, 54) = 19.65$; $p < 0.001$]. *Post hoc* tests showed that MDMA users had a significantly worse memory performance on trials 6 and 7 compared to drug-naive controls [trial 6: $p < 0.001$; $d = 1.36$/trial 7: $p < 0.001$; $d = 1.28$] as well as compared to cannabis users [trial 6: $p < 0.001$; $d = 1.43$/trial 7: $p < 0.001$; $d = 1.44$]. Cannabis users and drug-naive controls did not differ in their performance on these trials.

The recognition performance of all groups is shown in Fig. 2. ANOVAs performed over all groups showed a significant main effect for the factor group in the hit rate of list A [$F(2, 54) = 7.02$; $p < 0.01$]. *Post hoc* tests revealed a significantly lower hit rate of list A of the MDMA group in comparison to the drug-naive controls [$p < 0.01$; $d = 0.89$] and to the cannabis users [$p < 0.01$; $d = 1.01$]. Furthermore, there were trends for a group effect in the hit rate [$F(2, 54) = 2.87$; $p = 0.07$] and the false alarm rate of list B [$F(2, 54) = 2.44$; $p = 0.10$]. In *post hoc* tests, the MDMA group did show only trends for fewer hits [$p = 0.07$; $d = 0.72$] and more false alarms on list B [$p = 0.08$; $d = 0.70$] than the cannabis group. Cannabis users and drug-naive controls did not differ in their recognition performance.

Table 3 Composite measures of the RAVLT of MDMA users, cannabis users and healthy controls (means and standard deviations in brackets)

	MDMA ($n = 19$, ♂)	Cannabis ($n = 19$, ♂)	Controls ($n = 19$, ♂)	F	df/df_{err}	p
Learning performance *Σ trials 1–5*	56.2 (8.16)	64.8 (6.21)	64.7 (5.72)	10.09	2/54	<**0.001**
Recall consistency, trials 1–5 *in percent*	86.6 (8.61)	94.8 (3.94)	95.1 (4.8)	11.85	2/54	<**0.001**
Proactive interference *trial 1 minus list B*	0.53 (2.46)	0.47 (2.29)	0.37 (1.83)	0.03	2/54	0.975
Retroactive interference *trial 5 minus trial 6*	2.26 (2.47)	0.32 (0.89)	0.58 (0.90)	8.28	2/54	<**0.001**
Loss after consolidation *trial 5 minus trial 7*	2.05 (2.04)	0.05 (0.85)	0.52 (1.02)	10.51	2/54	<**0.001**
Adjusted recognition list A *p(A) list A*	0.85 (0.10)	0.93 (0.05)	0.90 (0.08)	4.60	2/54	<**0.05**
Adjusted recognition list B *p(A) list B*	0.74 (0.03)	0.84 (0.02)	0.81 (0.03)	4.64	2/54	<**0.05**

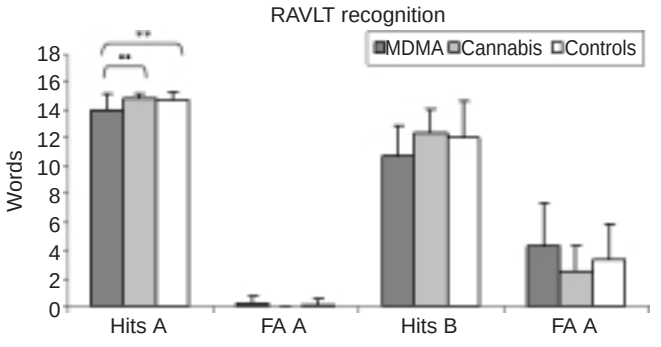

Figure 2 Hits and false alarms (FA) of lists A and B of the RAVLT of MDMA users, cannabis users and healthy controls (means and standard deviations). Tukey's *post hoc* tests: MDMA vs. healthy controls, $^{**}p < 0.01$; MDMA vs. cannabis, $^{\bullet\bullet}p < 0.01$.

Table 3 shows several composite measures of memory performance of the RAVLT. ANOVAs over all groups revealed significant main effects in all of these parameters, with exception of the proactive interference (for statistics, see Table 3).

In *post hoc* tests, MDMA users showed a significantly worse learning performance [$p < 0.001$; d = 1.09], a significantly lower recall consistency [$p < 0.001$; d = 1.18], a significantly stronger retroactive interference [$p < 0.01$; d = 0.94] and a significantly higher loss after consolidation [$p < 0.01$; d = 0.94] compared to drug-naive controls. MDMA users and drug-naive controls did not differ in adjusted recognition performance in list A and list B. Compared to the cannabis group, MDMA users revealed significant deficits in learning performance [$p < 0.001$; d = 1.11], recall consistency [$p < 0.001$; d = 1.14], retroactive interference [$p < 0.01$; d = 1.08], loss after consolidation [$p < 0.001$; d = 1.23] and adjusted recognition performance in list A [$p < 0.05$; d = 0.91] and list B [$p < 0.05$; d = 0.92]. Cannabis users and drug-naive controls did not differ in their performance in any of the composite memory measures.

Age, years of education and verbal IQ were not significantly correlated with the different parameters of memory performance.

Cannabis use and verbal IQ as covariates

Since it was assumed that the concomitant cannabis use of MDMA users is responsible for their cognitive deficits (Croft *et al.*, 2001b; Simon and Mattick, 2002) we introduced the cumulative cannabis dose as a covariate in an analysis of covariance (ANCOVA) to examine if the above shown group differences are maintained. Furthermore, in the analysis of the demographic data slight differences within the verbal IQ occurred. Thus, we introduced verbal IQ as a covariate in a separate ANCOVA analysis. However, both procedures did not change our main results: repeated measurements ANCOVAs (group × trial) with the first five learning trials still showed significant between-subject effects [covariate cannabis (CC): $F(2, 53) = 6.40$; $p < 0.01$/covariate age (CA): $F(2, 53) = 9.50$; $p < 0.001$] and *post hoc* tests showed that the learning performance of the MDMA group remained significantly worse compared to drug-naive controls [CC: $p < 0.01$/CA: $p < 0.001$] as well as compared to cannabis users [CC: $p < 0.001$/CA: $p < 0.001$]. ANCOVAs of the supraspan and of list B did not reveal significant group effects. The group effects within the analyses of trial 6 [CC: $F(2, 53) = 16.06$; $p < 0.001$/CA: $F(2, 53) = 18.20$; $p < 0.001$] and 7 [CC: $F(2, 54) = 14.62$; $p < 0.001$/CA: $F(2, 53) = 17.12$; $p < 0.001$] remained also highly significant and *post hoc* tests still showed that MDMA users had a significantly worse memory performance on both trials compared to drug-naive controls [CC: trial 6: $p < 0.001$; trial 7: $p < 0.001$/CA: trial 6: $p < 0.001$; trial 7: $p < 0.001$] as well as com-

pared to cannabis users [CC: trial 6: $p < 0.001$; trial 7: $p < 0.001$/CA: trial 6: $p < 0.001$; trial 7: $p < 0.001$]. ANCOVAs with the hit rate of list A showed also significant group effects [CC: $F(2, 53) = 6.07$; $p < 0.01$/CA: $F(2, 53) = 6.76$; $p < 0.01$] and *post hoc* tests showed a significantly lower hit rate of list A of the MDMA group in comparison to the drug-naive controls [CC: $p < 0.01$/CA: $p < 0.01$] and to the cannabis users [CC: $p < 0.01$/CA: $p < 0.001$].

Furthermore, there were still significant group effects regarding the sum of trials 1–5 (learning performance) [CC: $F(2, 53) = 6.40$; $p < 0.01$/CA: $F(2, 53) = 9.50$; $p < 0.001$] and *post hoc* tests revealed significant deficits in learning performance of the MDMA group compared to drug-naive controls [CC: $p < 0.01$/CA: $p < 0.001$] and to the cannabis group [CC: $p < 0.001$/CA: $p < 0.001$]. The group effects with regard to retroactive interference also remained significant [CC: $F(2, 53) = 6.50$; $p < 0.01$/CA: $F(2, 53) = 6.49$; $p < 0.01$] and *post hoc* tests revealed a significant stronger retroactive interference within the MDMA group compared to drug-naive controls [CC: $p < 0.01$/CA: $p < 0.01$] and to the cannabis group [CC: $p < 0.001$/CA: $p < 0.01$]. Moreover, the group effect regarding the recall consistency was still significant [CC: $F(2, 53) = 7.25$; $p < 0.01$/CA: $F(2, 53) = 9.93$; $p < 0.001$] and *post hoc* tests showed a significant lower recall consistency within the MDMA group compared to drug-naive controls [CC: $p < 0.01$/CA: $p < 0.001$] and to the cannabis group [CC: $p < 0.001$/CA: $p < 0.001$]. The group effects within the analysis of adjusted recognition performance of list A [CC: $F(2, 53) = 3.83$; $p < 0.05$/CA: $F(2, 53) = 4.73$; $p < 0.05$] and B [CC: $F(2, 53) = 4.16$; $p < 0.05$/CA: $F(2, 53) = 4.06$; $p < 0.05$] remained also significant and *post hoc* tests showed that MDMA users had a significantly worse recognition performance on both measures compared to cannabis users [CC: p(A): $p < 0.01$; p(B): $p < 0.01$/CA: p(A): $p < 0.01$; p(B): $p < 0.01$]. MDMA users and drug-naive controls still did not significantly differ in these recognition measures, but there were strong trends towards a worse performance of the MDMA user after correcting for verbal IQ [CC: p(A): $p = 0.15$; p(B): $p = 0.10$/CA: p(A): $p = 0.06$; p(B): $p = 0.08$]. Finally, in the ANCOVAs cannabis users and drug-naive controls did not differ in their memory performance in any variable.

To check on the validity of ANCOVA results we have tested for homogeneity of covariate regression coefficients by examining the interaction between the independent variable and both covariates separately (Tabachnick and Fidell, 2001). There were no significant interactions between the group factor and the covariates in any of the dependent variables. This indicates that the slopes of the regression lines are the same for each group formed by the categorical variables and measured on the dependents. Therefore, the assumption of homogeneity of covariate regression coefficients was not violated.

Consequently, neither the concomitant cannabis use nor the slight differences in the verbal IQ seem to account for the shown group defences between MDMA users and both control groups.

An ANCOVA with amphetamine and hallucinogen use as covariates was not appropriate because the use of these drugs was highly correlated with the MDMA use and 'controlling' for these variables would remove meaningful variance and as a result, produce statistical artefacts (Miller and Chapman, 2001). When cocaine was used as a co-variable, the results remained unchanged (data not shown).

Correlation between drug intake and memory performance

After Bonferroni correction (significance level was set at $p < 0.0004$ because of 140 single comparisons) only parameters of MDMA use were significantly correlated with memory scores: years of MDMA use were significantly correlated with learning performance [$r = -0.56$], delayed recall [$r = -0.70$], loss after consolidation [$r = 0.63$] and adjusted recognition list A [$r = -0.62$]. The cumulative MDMA dose was significantly correlated with recall after interference [$r = -0.55$], and delayed recall [$r = -0.61$]. The peak dose MDMA was significantly correlated with recall after interference [$r = -0.66$], delayed recall [$r = -0.65$], retroactive interference [$r = 0.57$] and loss after consolidation [$r = 0.65$]. In all cases a higher or longer MDMA intake was associated with worse memory performance. Due to high interrelations within the drug consumption variables, the use of multiple regression models was not suitable to analyse the interrelations of drug use and memory performance. The period of abstinence from any illicit drug did not correlate with the memory parameters.

Discussion

The aim of this study was to investigate whether the memory deficits of MDMA users arose only from a temporal dysfunction or whether frontal brain regions could also be involved. MDMA users showed widespread and marked verbal memory deficits compared to drug-naive controls as well as to cannabis users. MDMA users revealed impairments in learning, consolidation, recall and recognition. In addition to that, they have also displayed a worse organization of memory information which is reflected in a high inconsistency of recall, and a diminished retroactive interference which is expressed by a high loss after interference. The MDMA users did also show slightly worse performance in the supraspan, which may indicate a moderate deficit in working memory. Moreover, memory performance was significantly correlated with the amount of MDMA intake. Cannabis users did not differ from drug-naive controls in their memory performance. Finally, ANCOVAs controlling for cannabis use and verbal IQ did not change the results.

Due to the lack of any clear dissociation between the different performance measures of the RAVLT, it is not easily concluded whether the memory deficits from MDMA users are primarily caused by insufficient encoding, storage or retrieval processes. Similar global deficits in verbal memory performance have been shown in patients with diffuse brain injury and non-specific brain damage (Bigler *et al.*, 1989; Geffen *et al.*, 1994; Leathem and Body, 1997) as well as in patients with left temporal and left medial temporal lesions (Helmstaedter and Elger, 1996;

Helmstaedter *et al.*, 1997). However, the strongest effects occurred in delayed recall and in the loss after consolidation indicating an impairment of long-term memory or rather recall from long-term memory and are therefore possibly reflecting a dysfunction of medial temporal structures (Helmstaedter *et al.*, 2001). The effects seen in recall consistency and retroactive interference were however also pronounced.

In previous studies recall consistency was significantly correlated with other measures of executive functioning (Vanderploeg *et al.*, 1994; Beebe *et al.*, 2000). It was supposed that worse recall consistency could have two reasons: either a decreased capacity of working memory per se (Alexander *et al.*, 2003) or a poor organization of memory information during learning (Waters and Waters, 1976; Sternberg and Tulving, 1977). Whereas, Alexander and colleagues (2003) put forward that the organization of memory information during learning could also be a function of working memory, because it requires the maintenance of information. Interestingly, in our study recall consistency was highly correlated with the supraspan [$r = 0.50$; $n = 57$; $p < 0.001$] which supports the assumption of an interrelation of working memory and recall consistency. It has been shown that patients with focal frontal lesions have deficits in their recall consistency as well as in the organization of verbal memory information (Stuss *et al.*, 1994; Alexander *et al.*, 2003). In addition, frontal lobe atrophy measures were the most consistent predictors for recall consistency in patients with multiple sclerosis (Benedict *et al.*, 2005).

Moreover, retroactive inhibition was also previously related to executive functions (Torres *et al.*, 2001) and patients with focal frontal lesions have also shown a decreased recall of interfering word lists (like the list B in our test) and a strong retroactive interference (Baldo *et al.*, 2002). It is striking that our MDMA users have shown a significantly stronger retroactive interference but a normal proactive interference compared to both control groups. On this, Torres *et al.* (2001) have demonstrated that only the retroactive interference but not the proactive interference in the RAVLT was strongly associated with executive functions. Recently, Anderson (2003) conceptualized retroactive interference as a consequence of executive inhibitory mechanisms which have evolved to allow organisms to override prepotent responses and not as a passive effect of new learning.

Taken together, the strong retroactive inhibition and the worse retroactive inhibition in our MDMA users could be interpreted as a deficit in executive functioning (additionally, both measures were significantly correlated: $r = -0.39$; $n = 57$; $p = 0.003$). Furthermore, data from patients with frontal lesions, showing increased susceptibility to retroactive interference as well as a decreased recall consistency, suggest that these measures could be related to the functionality of the frontal cortex. In addition, especially the frontal cortex appears to display a particularly strong denervation after MDMA exposure and a relatively low rate of recovery after drug withdrawal in animal studies (Fischer *et al.*, 1995; Hatzidimitriou *et al.*, 1999). Thus, the neuropsychological profile of our MDMA users suggests that their memory deficits could be the consequence of a combined temporal and frontal dysfunction.

In our study, the working memory (supraspan) of the MDMA users was decreased, but less impaired relative to most other memory measures and the difference did not reach a significant level. Some previous studies reported more pronounced and significant verbal working memory deficits in MDMA users (Wareing *et al.*, 2004b), especially in the supraspan of the RAVLT (Fox *et al.*, 2001b). However, other studies reported unimpaired performance in immediate recall of verbal material (Simon and Mattick, 2002) and in the supraspan of the RAVLT in users of MDMA (McCardle *et al.*, 2004). Thus, further studies are needed to elucidate the impact of MDMA use on verbal working memory.

Moreover, MDMA users revealed a significantly worse recognition performance as shown in the hit rate of list A, but the effect sizes were not so strong either, compared to most other memory measures. In fact MDMA users differed significantly from cannabis users in the adjusted recognition measures, but not from drug-naive controls. However, the weaker effect in recognition could possibly be explained by a ceiling effect because most control participants recognized correctly all 15 words. As a result, the recognition performance of the MDMA users could have been overestimated.

The deficits in verbal declarative memory of our MDMA users – especially with respect to immediate and delayed recall – are consistent with many previous studies (Parrott *et al.*, 1998; Parrott and Lasky, 1998; Gouzoulis-Mayfrank *et al.*, 2000; Rodgers, 2000; Fox *et al.*, 2001b; Morgan *et al.*, 2002; Thomasius *et al.*, 2003). It should be noted that our group of MDMA users showed a relatively heavy MDMA use with more than 450 tablets per lifetime. Studies showing no (Croft *et al.*, 2001b; Simon and Mattick, 2002; Back-Madruga *et al.*, 2003) or only weak impairment (Gouzoulis-Mayfrank *et al.*, 2000; McCardle *et al.*, 2004) in verbal memory performance of MDMA users examined mostly users with a lifetime dose lower than 100 tablets (only in the study of Simon and Mattick had the users a somewhat higher dose of 258 tablets). This supports the assumption that especially heavy MDMA use impairs verbal memory.

The conclusion of Fox *et al.* (2001b) that the memory deficits of MDMA users could be primarily the consequence of storage and/or retrieval problems which in turn arise from a selective dysfunction of temporal structures (Fox *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2003), is – in this exclusiveness – not supported by our data. The present neuropsychological analysis of the memory performance of MDMA users suggests that a fronto-temporal dysfunction may underlie the deficits shown here. This view is supported by previous studies demonstrating that MDMA users show also disturbances in executive functions which were mainly linked to the frontal cortex (McCann *et al.*, 1999; Wareing *et al.*, 2000; Bhattachary and Powell, 2001; Fox *et al.*, 2001a; Zakzanis and Young, 2001; Alting von Geusau *et al.*, 2004; Fisk *et al.*, 2004; Quednow *et al.*, in press). However, it should be noted that executive functions are not a unitary construct but that various cognitive processes were involved (Funahashi, 2001). Thus, attributing executive functions only to the functionality of the frontal cortex is over-simplistic (Alexander and Stuss, 2000) and further research should elucidate whether other brain regions than frontal and temporal areas could be implicated in the memory deficits of MDMA users.

Due to the use of cannabis users as a 'clinical' control group and due to the introduction of cannabis use as a covariate in an ANCOVA we could largely rule out cannabis use as potential confound of our results because MDMA users revealed memory deficits also in comparison to the cannabis users, whereas cannabis users did not differ in their memory performance from drug-naive controls. This seems to be in contrast to some previous studies reporting detrimental effects of heavy cannabis use on memory performance even after withdrawal of cannabis use for 7 days (Pope *et al.*, 2001, 2002). Whereas, after longer periods of abstinence no or only subtle and clinically irrelevant effects on cognitive function could be observed (Lyketsos *et al.*, 1999; Pope *et al.*, 2001, 2002; Lyons *et al.*, 2004; Fried *et al.*, 2005). However, in our study the cannabis users had indeed a mean duration of cannabis abstinence of about 7 days (median 6 days) but they smoked cannabis only less than four times the week in the mean. This is not very much compared to previous studies which found memory impairment in cannabis users. In these studies the cannabis users had a much heavier use of the drug with mostly at least one exposure a day. Thus, we think that the moderate use of cannabis in our group of cannabis users has not had any effect on memory function.

Acute MDMA effects were relatively unlikely to account for the memory deficits of MDMA users because the mean period of abstinence of MDMA was 17.4 days (median 14 days), and more than 75% of our MDMA users reported an abstinence of MDMA for at least 1 week, whereas the elimination half-life of MDMA in humans is relatively short, at about 8–9 h (de la Torre *et al.*, 2000). In addition to that, no correlation between memory measures and period of abstinence was found. These facts suggest that the memory deficits of MDMA users probably cannot be explained by an acute or post-acute pharmacological effect of MDMA. In the MDMA and the cannabis group, the duration of abstinence from cannabis was considerably shorter (11.1 and 7.1 days respectively), and the plasma elimination half-life of Δ^9-tetrahydrocannabinol (THC), one of the main active components of cannabis, ranged between 18 and 50 h after radio-labelled THC administration (Huestis and Cone, 1998). An elimination of 95% of a substance takes about five half-lives; therefore, THC takes 3.8 to 10.4 days to be almost fully eliminated. Moreover, it is known that acute oral THC administration could impair learning and episodic memory (Curran *et al.*, 2002). However, it is also unlikely that acute or post-acute cannabis effects explain the memory deficits of our MDMA group because we found no alterations in memory performance in the cannabis group, although they had a smaller mean duration of cannabis abstinence than the MDMA group as well as a more intensive cannabis consumption. This assumption is further supported by the lack of a correlation between the duration of abstinence of cannabis and the different variables of memory performance. However, one limitation of this study is that the history of drug consumption was assessed only by means of subjective reports. A drug-usage screening would be desirable to control more reliably for acute and post-acute drug effects within a few days of the assessment. A related and so far unsolved problem is that the exact consumption pattern of drugs across an individual's lifetime is not objectively calculable (Curran, 2000). Nevertheless, Stuerenburg *et al.* (2002) found a concordance of 91.3% between the self-reported drug intake and toxicological analyses of hair specimens in a sample of German MDMA users.

We found a strong correlation between parameters of MDMA consumption and memory performance, but not between other illicit drugs and memory measures. These dose–response relationships support the view that the memory deficits of MDMA users were caused by a selective neurotoxic effect of MDMA on the 5-HT system (Parrott, 2002; Gouzoulis-Mayfrank *et al.*, 2003) because first, it is well known that MDMA selectively damages 5-HT nerve terminals in animal studies (Insel *et al.*, 1989; Wilson *et al.*, 1989; Ali *et al.*, 1993; Scheffel *et al.*, 1998; Hatzidimitriou *et al.*, 1999) and second, it was shown that the 5-HT system plays a predominant role in mnemonic processes (Park *et al.*, 1994; Riedel *et al.*, 1999, 2002). Furthermore, the correlation with the MDMA peak dose is in line with animal data that high or high frequent doses of MDMA might be required to produce neurotoxic damage (O'Shea *et al.*, 1998).

To summarize, our results provide evidence that the memory deficits of MDMA users are caused by a fronto-temporal dysfunction. Associations with the amount of MDMA consumption and the fact that MDMA is a neurotoxin selective for the 5-HT system suggest that these cognitive deficits were acquired via MDMA use. Furthermore, the concomitant cannabis use of the MDMA users could not account for the shown memory deficits because cannabis users did not show changes in memory performance and cannabis use was not statistically correlated with mnemonic measures.

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