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ORIGINAL INVESTIGATION

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Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy")

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Abstract *Rationale:* In animal studies, the common club drug 3,4-methylendioxymethamphetamine (MDMA, "Ecstasy") consistently caused a prolonged loss of presynaptic serotonergic neurons, and evidence suggests that MDMA consumption may also affect the human serotonergic system. Serotonin (5-HT) has been implicated in the regulation of impulsivity and such executive functions as decision-making cognition. In fact, MDMA users have shown elevated impulsivity in two studies, but little is known about decision making in drug-free MDMA consumers. *Objective:* The aim of this study was to examine the cognitive neurotoxicity of MDMA with regard to behavioral impulsivity and decision-making cognition. *Methods:* Nineteen male, abstinent, heavy MDMA users; 19 male, abstinent cannabis users; and 19 male, drug-naïve controls were examined with the Matching Familiar Figures Test (MFFT) as well as with a Go/No-Go Task (GNG) for impulsivity and with a Gambling Task (GT) for executive functioning. *Results:* MDMA users showed significantly elevated impulsivity in the MFFT Impulsivity score (I-score), but not in commission errors of the GNG, compared with controls. Cannabis users did not yield altered impulsivity compared with controls. In the GT, MDMA users performed significantly worse than cannabis consumers and controls, whereas cannabis users exhibited the same decision-making capacity as controls. In addition, the I-score as well as the decision-making performance was correlated with measures of MDMA intake. The I-score and the decision-making performance were also correlated. *Conclusion:* These results suggest that heavy use of MDMA may elevate behavioral impulsivity and impair decision-making cognition possibly mediated by a selective impairment of the 5-HT system.

Keywords MDMA · Cannabis · Impulsivity · Decision-making cognition · Matching Familiar Figures Test · Go/No-Go Task · Gambling Task · Serotonin · 5-HT

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "Ecstasy") is an illicit club drug that is widely abused, especially by young people (Christophersen 2000). In a recent survey from the Federal Centre for Health Education (BZgA) in Germany, 4% of the interviewed juveniles between 12 and 25 years of age reported having used Ecstasy at least once (BZgA 2004). Therewith, after cannabis (24%), MDMA and derivatives rank second of the most popular illicit drugs in Germany (BZgA 2004). Even worldwide, MDMA has become one of the most widely used illegal psychoactive drugs, with millions of regular users (Landry 2002).

In animals, administration of MDMA produces a rapid and marked release of serotonin (5-HT) via inhibition and reversal of the 5-HT transporter (Rudnick and Wall 1992). Studies in nonhuman primates provided convincing evidence that MDMA causes a substantial and sustained long-term neurotoxic loss only of 5-HT nerve terminals, with an associated depletion of up to 95% of 5-HT in several brain regions, whereas 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; Taffe et al. 2002). Studies of MDMA use in humans have also shown selective dec-

rements in cerebrospinal fluid (CSF) concentrations of 5-hydroxy indoleacetic acid (5-HIAA) as a marker for central serotonergic depletion, with no 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 exhibited 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). Furthermore, 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). In summary, MDMA seems to be a neurotoxin that selectively impairs the serotonergic system in primates, including humans.

An important physiological role of the neurotransmitter 5-HT is behavioral inhibition. Previous animal and human studies demonstrated that increasing central 5-HT function inhibits aggression (Soubrié 1986; Morand et al. 1983); conversely, low 5-HT neurotransmission is associated with impulsive aggressive behavior in rodents, primates, and humans (Soubrié 1986; Linnoila et al. 1983; Coccaro et al. 1989; Virkkunen et al. 1994). Indeed, evidence of low 5-HT neurotransmission was reported to be involved in the etiology of several disorders characterized by behavioral disinhibition, including alcohol dependence, suicide, bulimia, personality disorders, conduct disorder, and aggression (LeMarquand et al. 1999). In addition, lowering serotonin via tryptophan depletion increases impulsive behavior in rats (Harrison et al. 1999; Winstanley et al. 2004) and healthy individuals (Rogers et al. 1999a; Walderhaug et al. 2002). Behavioral inhibition has been proposed as a critical component of decision-making cognition (Monterosso and Ainslie 1999; Cardinal et al. 2004; Deakin et al. 2004). Moreover, behavioral inhibition as well as decision making has been conceptualized as elements of executive functioning, and both were therefore linked to the functions of the prefrontal cortex (Smith and Jonides 1999; Funahashi 2001; Elliott 2003). It has been postulated previously that prefrontal 5-HT further plays a crucial role in executive functions and especially decision making because patients with focal prefrontal lesions as well as tryptophan-depleted healthy volunteers demonstrated impaired decision-making cognition (Rogers et al. 1999a,b, 2003).

It has been shown previously that MDMA users display an elevated behavioral impulsivity in the Matching Familiar Figures Test (MFFT) (Morgan 1998; Morgan et al. 2002). Because of the correlation of MDMA intake with the MFFT Impulsivity score (I-score), it was suggested that the serotonergic neurotoxicity of MDMA caused these behavioral deficits (Morgan 1998; Morgan et al. 2002). This assumption is supported by animal data showing that repeated MDMA administration leads to an increase in inappropriate responses, indicating an elevation of impulsivity (Taylor and Jentsch 2001). Studies with MDMA users applying self-reported measures of impulsivity were not discussed here because self-report inventories were not suitable for measuring the state-dependent behavioral neurotoxicity induced by illicit drugs (Dougherty et al. 2004).

There is evidence that MDMA use impairs 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). It was proposed that MDMA users also showed impaired executive functions (McCann et al. 1999; Bhattachary and Powell 2001; Fox et al. 2001a; Zakzanis and Young 2001; Alting von Geusau et al. 2004). In most of the aforementioned studies, memory deficits and executive dysfunction in MDMA users were assumed to be a consequence of the serotonergic neurotoxicity of MDMA. As of yet, only one study has assessed the decision-making cognition of MDMA users, although decision-making tasks involve primarily the 5-HT system, whereas classical executive function tasks (e.g., working memory tasks, Tower of London, extradimensional shift) implicate instead the dopaminergic or noradrenergic system (Robbins 2000). However, Fox et al. (2002) did not find changes in the Decision-Making Task of Rogers et al. (1999a) in MDMA users.

The aim of this study was to further investigate the behavioral neurotoxicity of MDMA use with regard to different aspects of impulsivity and decision-making cognition. Thus, we applied two common behavioral impulsivity measures, the MFFT (Kagan et al. 1964) and the Go/No-Go Task (GNG) (Newman and Kosson 1986), as well as a Gambling Task (GT) (Bechara et al. 1994), for decision-making cognition in chronic but recently abstinent MDMA users compared with those attributes of a clinical control group of cannabis users and healthy control sub jects with no history of drug abuse. 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 is discussed in previous works as being a strong biasing factor in research with MDMA consumers (Croft et al. 2001b; Daumann et al. 2001; Gouzoulis-Mayfrank et al. 2002). Although the GNG according to Newman and Kosson (1986) and the GT according to Bechara et al. (1994) are well-established measures for impulsivity and decision-making performance, they have not been used to examine MDMA users so far. Because of the serotonergic neurotoxicity of MDMA and the postulated involvement of 5-HT in impulsivity and decision-making cognition, we expected elevated levels of impulsivity and a decision-making deficit in MDMA users in comparison with both control groups. Due to the assumption that the supposed behavioral deficits were caused by MDMA, we anticipated correlations of MDMA consumption with impulsivity and decision-making measures.

Materials and methods

Participants

Impulsivity and decision-making cognition were 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-naïve control subjects) 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-naïve control subjects were recruited by advertisement in a local newspaper. Subjects of the MDMA group were required to have used MDMA at least 50 times over a period of at least 1 year. In addition, the use of MDMA clearly had to outweigh the consumption of any other psychotropic drug. To be eligible for inclusion in the cannabis group, participants should have no substantial previous use of amphetamine derivatives like MDMA and no substantial previous use of cocaine. Neuropsychological assessment was carried out when participants were drug-free for at least 3 days. Inclusion criteria for the drug-naïve control subjects included negative urine drug test results. Legitimate use of psychotropic medication; a present psychiatric illness; a family history of a severe psychiatry illness, such as schizophrenia and bipolar disorder; as well as a 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 the Diagnostic and Statistical Manual IV (DSM-IV) procedures was carried out by a psychologist trained in the use of this instrument to ensure the absence of present psychiatric disorders in our participants. Drug history and present pattern of psychotropic drug consumption were assessed by a structured interview. Subjects who were screened for inclusion in the drug-naïve control group were urine-tested for drug use. In addition to the impulsivity and decision-making measures (see below), the neuropsychological test battery also comprised a verbal memory task the results of which will be published elsewhere (Quednow et al. in press). The whole battery took about 120 min, including breaks as needed, and was generally well tolerated by the participants. During the psychiatric and neuropsychological assessment, the subjects could ask for a break at any time.

Interview for psychotropic drug consumption

For the assessment of the use of legal and illegal psychotropic substances, a structured interview was developed that comprised 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. In addition, 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. On the basis of the actual and former substance intake, we estimated a cumulative drug dose. The data for pattern and amount of drug consumption of the groups are shown in Table 1.

Neuropsychological assessment

Go/No-Go Task First, participants were administered a computerized version of the Go/No-Go Task (Go/No-Go version 1.2; Hiloma Software Development, Montreal, Canada) in accordance to Newman and Kosson (1986) and Newman et al. (1990). Participants learned by trial and error to press a button for "active" stimuli and not to press for "passive" stimuli. Stimuli, consisting of eight two-digit numbers (four active, four passive, which ranged from 3 to 99) were repeated ten times in different, randomly assigned sequences for a total of 80 trials. Two different sets of eight numbers were employed (one per condition). Correct responses were rewarded with a high-pitched tone, presentation of the word "Richtig" (correct) on the computer screen, and the addition of 10 "Pfennig" (cents) to an on-screen running tally of the participant's earnings. Incorrect responses were punished with a low-pitched tone, presentation of the word "Falsch" (wrong), and subtraction of 10 Pfennig from the participant's earnings.

All participants completed two conditions. In the reward–punishment condition, participants began with 1.00 DM (Deutsche Mark). Responses to active numbers were reinforced, and responses to passive numbers were punished. In the punishment–reward condition, participants began with 1.00 DM; nonresponses to active numbers were punished, and nonresponses to passive numbers were rewarded. Each condition was preceded by a 12-trial reward pretreatment in which the ratio of active to passive numbers was 2:1. This pretreatment served to establish hypothetically a dominant response set for reward (Newman et al. 1990; LeMarquand et al. 1999).

Participants were given instructions for the GNG, the reinforcement contingencies, and the process of trial-and-error learning. With the experimenter present, participants

Table 1 Pattern and amount of illegal drug use: results of the psychotropic drug interview

Drug and characteristic	MDMA (n=19, ♂)	Cannabis (n=19, ♂)	Controls (n=19, ♂)
MDMA			
Tablets per week	1.97 (2.73)	0.01 (0.05)	0.00 (0.00)
Years of use	3.66 (1.95)	0.11 (0.46)	0.00 (0.00)
Cumulative dose (tablets)	457.9 (433.9)	6.7 (24.0)	0.00 (0.00)
Lifetime peak dose[a] (tablets)	6.1 (4.7)	0.32 (0.82)	0.00 (0.00)
Last consumption (days)	17.4 (14.6); n=19	504.7 (810.4); n=3	0.00 (0.00)
Cannabis			
Times per week	1.63 (1.62)	3.89 (4.72)	0.00 (0.00)
Years of use	3.95 (3.11)	6.55 (3.67)	0.00 (0.00)
Cumulative dose (times)	547.1 (502.7)	1033.4 (1348.6)	0.00 (0.00)
Last consumption (days)	11.1 (21.6); n=16	7.1 (4.7); n=19	0.00 (0.00)
Amphetamine			
Times per week	0.82 (1.31)	0.04 (0.16)	0.00 (0.00)
Years of use	3.37 (2.05)	0.63 (1.89)	0.00 (0.00)
Cumulative dose (times)	208.5 (279.5)	14.5 (59.6)	0.00 (0.00)
Last consumption (days)	38.1 (89.9); n=17	240.0 (169.7); n=2	0.00 (0.00)
Cocaine			
Times per week	0.04 (0.10)	0.02 (0.06)	0.00 (0.00)
Years of use	0.66 (1.70)	0.26 (0.81)	0.00 (0.00)
Cumulative dose (times)	4.87 (12.51)	2.49 (9.04)	0.00 (0.00)
Last consumption (days)	34.5 (17.2); n=4	17.5 (5.0); n=2	0.00 (0.00)
Hallucinogens[b]			
Cumulative dose (times)	23.4 (38.8)	1.95 (4.24)	0.00 (0.00)
Last consumption (month)	7.86 (9.37); n=14	7.20 (4.60); n=5	0.00 (0.00)

Means and standard deviations in parentheses. 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
[a]Highest single MDMA dose ever used
[b]Primarily LSD and psilocybin were used

completed eight practice trials that involved four presentations of each of the two practice stimuli (one as an active number and two as a passive number). The experimenter was not present during the actual testing. The order of presentation of the two conditions was the same for all participants. The experimenter reentered the room between conditions to explain the expectations for the next condition.

Dependent measures for this task included commission errors (failures to inhibit responses to passive numbers) and omission errors (failures to respond to active numbers) and total gain in DM. According to the motivational theory of Gray et al. (1983), impulsive persons make more commission errors because they are less sensitive to punishment and more sensitive to reward, whereas omission errors are not related to impulsivity (Newman 1987).

Matching Familiar Figures Test Participants were administered a paper-and-pencil version of the 12-item MFFT (Kagan et al. 1964; Kagan 1966). The format of the MFFT involves simultaneous presentation of a stimulus figure and an array of eight alternatives, all except one differing in one or more details. The participants were then asked to select as quickly as possible from the alternatives the figure that exactly matched the standard. Each participant was given two practice items followed by 12 test items. If their initial selection was incorrect, they were told that they were wrong and were asked to try again. For each subject, the 12 items were scored according to the time to first response and the number of errors made before the correct match. Four dependent variables were analyzed: (1) the mean latency to first response, (2) the total number of errors committed, (3) an Impulsivity score (I-score), and (4) an Efficiency score (E-score). The I-score is a composite index of impulsivity, whereas the E-score reflects the self-explanatory dimension "fast and accurate" vs "slow and inaccurate." Both scores were originally derived by Salkind and Wright (1977) and later validated by Messer and Brodzinky (1981). The I-score is calculated by subtracting the standard score of the mean latency to first response from the standard score of the total number of errors committed (I-score=$Z_{error} - Z_{latency}$), and the E-score is calculated by summing the standard score of the mean latency to first response with the standard score of the total number of errors committed and a following multiplication with -1 [E-score = -($Z_{error} + Z_{latency}$)]. The error and latency values of all participants were standardized to the means and standard deviations of the control group.

Decision-making Task After the GNG, participants were administered a computerized and modified version of the Iowa GT (Bechara et al. 1994, 1997). The task was pro-

grammed in Turbo Pascal for Windows 95 and Windows 98 by coauthor Christian Hoppe. The GT is a virtual card game in which participants are told to accumulate as much play money as possible by picking one card at a time from any of the four decks (A, B, C, and D) until 100 cards have been selected. The decks (40 cards each) differ in representation of both the level of immediate gain and the level of penalty risk. In contrast to the original Iowa GT, the cards had either a gain or a penalty (in the original version, each card yields a gain, and some cards had an additional penalty). Gain cards from decks A and B yield 200 points, compared with 100 points for every gain card from decks C and D. Some cards in each deck carry penalties, such that the accumulated penalties exceed the accumulated gains in decks A and B, and the accumulated penalties are smaller than the accumulated gains in decks C and D. Thus, continued choice from decks C or D leads to a net gain (1,600 points per deck), whereas continued choice from decks A or B leads to a net loss (-1,600 points per deck). The optimal strategy is to avoid the short-term appeal of the "disadvantageous" decks A and B in favor of the slower gain from the "advantageous" decks C and D.

Performance on the GT is scored by a global outcome score (net score) and a score for each consecutive block of 25 cards. These scores correspond to the number of cards chosen from the advantageous decks (C and D) minus the number of cards chosen from the disadvantageous decks (A and B). The analysis of the GT performance by blocks of 25 cards provides information about the learning capacity and strategy used by participants (Bechara 2001).

Statistical analysis

Before analyzing the neuropsychological data, we examined demographic variables. Age, verbal IQ, and years of education were analyzed using the general linear models (GLM) approach to analysis of variance (ANOVA) across all groups as well as *t* tests for independent samples for single comparisons to determine whether differences existed between experimental groups (SPSS, Chicago, IL). The ratio of smokers and nonsmokers between groups was analyzed using χ^2 tests.

Neuropsychological data were initially analyzed using the GLM approach to ANOVA across all groups and *t* tests for independent samples for single comparisons. In addition, GT blocks were analyzed using the GLM approach to repeated-measures ANOVA with GT blocks as dependent variables (fourfold) and group as a between-subjects fixed factor (threefold across all groups or twofold for single comparisons).

Correlations of dependent variables with each other, with demographic variables, and with drug use were tested using Pearson's product-moment correlation. Relationships between neuropsychological variables and drug consumption were analyzed only across combined drug groups. The confirmatory statistical comparisons of all data across three groups were carried out at a significance level set at $p < .05$ (two-tailed). Because of the directional hypothesis of an elevated impulsivity and disturbed decision making in MDMA users, single comparisons between MDMA users and drug-naïve control subjects as well as between MDMA users and cannabis users were carried out at a significance level set at $p < .05$ (one-tailed).

Results

Demographics

The demographic data of the groups are shown in Table 2. Overall, the three groups did not significantly differ 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, post hoc *t* tests were applied. Single comparisons showed that, compared with drug-naïve control subjects, neither the MDMA nor the cannabis group differed in length of education and intellectual functioning. However, the MDMA group and the cannabis group differed significantly with respect to length of education [$t(36) = 2.15$, $p < .05$] and verbal intellectual performance [$t(36) = 2.59$, $p < .05$]. In addition, there were significantly fewer smokers in the drug-naïve control group compared with the cannabis group [$\chi^2(1) = 6.76$, $p < .05$] and the MDMA group [$\chi^2(1) = 10.6$, $p < .001$]. Cannabis users and MDMA users did not differ in their smoking habits.

Table 2 Demographic data

	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	.44
Smoker/nonsmoker[b]	31/26	15/4	11/8	5/14	χ^2=10.75	2	.005
Verbal IQ[c]	105.3 (12.09)	100.6 (11.67)	109.7 (9.47)	105.7 (13.53)	F=2.81	2/54	.07
Years of education[c]	12.67 (1.41)	12.32 (1.70)	13.21 (0.63)	12.47 (1.54)	F=2.29	2/54	.11

Means and standard deviations in parentheses
[a] ANOVA (over all groups) or χ^2 test (over all groups) for frequency data
[b] χ^2 test (two-tailed) MDMA vs controls, p<.001; cannabis vs controls, p<.05
[c] t test (two-tailed) MDMA vs cannabis, p<.05

Go/No-Go Task

Initial inspection of the data revealed that several subjects failed to understand the task instructions because they performed at a chance level [according to the signal detection theory of Green and Swets (1966), we used a criterion of $d'<0.25$, which is equivalent to 56.5% correct responses]. Thus, data for 18 MDMA users, 17 cannabis users, and 15 drug-naïve control subjects were available for the final analysis.

Omission and commission errors as well as gain in each condition were also summed into total scores (Table 3). Errors within the 12-trial, reward-pretreatment phase were not included because participants had to be exposed to the stimuli at least once in order to learn which were active and passive.

An initial ANOVA did not reveal any significant main effect between the groups in the dependent variables (for statistics, see Table 3). Single comparisons with the *t* test for independent samples (one-tailed) showed a significantly elevated commission error rate [punishment-reward condition: $t(33)=1.74$, $p<.05$; summed conditions: $t(33)=1.73$, $p<.05$] as well as a lower gain [punishment-reward condition: $t(33)=-1.67$, $p<.05$; summed conditions: $t(33)<-1.87$, $p<.05$] in MDMA users in comparison with cannabis users. MDMA users and drug-naïve controls, as well as cannabis users and drug-naïve control subjects, did not differ significantly in the dependent variables of the GNG. The GNG variables were not correlated with age, years of education, or verbal IQ.

Variables from the single GNG conditions were not correlated with drug consumption separately because the analysis would suffer either from capitalization on chance or from the overly conservative alpha levels that would be needed to correct for test multiplicity. Across drug groups, the summed gain was correlated with years of amphetamine use ($r=-.44$, $n=35$, $p<.01$), years of MDMA use ($r=-.35$, $n=35$, $p<.05$), cocaine use per week ($r=-.38$, $n=35$, $p<.05$), and years of cocaine use ($r=-.35$, $n=35$, $p<.05$). Summed commission errors were correlated with the cumulative cannabis dose ($r=.36$, $n=35$, $p<.05$), years of amphetamine use ($r=.44$, $n=35$, $p<.01$), cocaine use per week ($r=.45$, $n=35$, $p<.01$), years of cocaine use ($r=.59$, $n=35$, $p<.001$), and the cumulative cocaine dose ($r=.42$, $n=35$, $p<.05$). Summed omission errors were not correlated with drug consumption. In both groups, only 19 participants reported an instance of amphetamine use, and only six participants reported an instance of cocaine use. Thus, statistical correlations with these substances should be interpreted with caution. The period of abstinence of any illegal drug did not correlate with the variables of the GNG.

In summary, MDMA users made significantly more commission errors than did cannabis users. However, this difference could be explained by an increased performance of the cannabis group rather than by an elevated impulsivity of the MDMA group because MDMA users and drug-naïve control subjects show a comparable performance in this task.

Matching Familiar Figures Test

Data for 19 MDMA users, 19 cannabis users, and 19 drug-naïve control subjects were available for this analysis. The I-score ($r=-.28$, $n=57$, $p<.05$) as well as mean latency to first response ($r=.38$, $n=57$, $p<.01$) were significantly correlated with age (i.e., impulsivity decreases and reaction time slows down as age increases). This relationship of age and impulsivity is a well-known phenomenon with regard to the MFFT (Kirchner-Nebot and Amador-Campos 1998). Thus, analyses of these variables had to be corrected for age.

An initial ANOVA (reaction time and I-score corrected for age) revealed no significant main effect between the groups in the dependent variables (for statistics, see Table 4). Yet because we wanted to test a directional hypothesis, we've also done single comparisons with the *t*

Table 3 Scores on the Go/No-Go Task of MDMA users, cannabis users, and drug-naïve controls

Condition	MDMA (n=18, ♂)	Cannabis (n=17, ♂)	Controls (n=15, ♂)	F^a	$df/df_{err}{}^a$	p^a
Reward-punishment						
Omission errors	3.06 (3.25)	4.00 (5.31)	3.53 (3.66)	0.22	2/47	.81
Commission errors	12.83 (6.50)	11.00 (5.91)	11.26 (5.96)	0.45	2/47	.64
Gain	3.70 (0.73)	3.96 (0.73)	3.86 (0.93)	0.47	2/47	.63
Punishment-reward						
Omission errors	6.94 (4.75)	6.12 (4.94)	6.97 (5.60)	0.12	2/47	.89
Commission errors[b]	9.28 (4.80)	6.29 (5.36)	9.60 (8.16)	1.46	2/47	.24
Gain[b]	3.16 (0.87)	3.65 (0.87)	3.25 (1.41)	1.04	2/47	.36
Summed conditions						
Σ omission errors	10.94 (6.83)	9.18 (5.69)	10.20 (7.70)	0.30	2/47	.74
Σ commission errors[b]	22.11 (9.44)	17.29 (6.75)	20.87(12.87)	1.12	2/47	.34
Σ gain[b]	6.86 (1.26)	7.61 (1.12)	7.11 (2.12)	1.09	2/47	.35

Means and standard deviations in parentheses
[a]ANOVA (over all groups)
[b]*t* test (one-tailed) MDMA vs cannabis, $p<.05$

Table 4 Scores on Matching Familiar Figures Task of MDMA users, cannabis users, and drug-naïve controls

	MDMA (n=19, ♂)	Cannabis (n=19, ♂)	Controls (n=19, ♂)	F^a	$df/df_{err}{}^a$	p^a
Σ errors (number)	8.16 (4.09)	5.95 (4.36)	6.47 (4.23)	1.42	2/54	.25
Mean latency to first response[b] (s)	49.5 (19.3)	53.3 (21.7)	60.5 (29.9)	1.81	2/53	.17
Impulsivity score[b,c] (z-score)	0.76 (1.43)	0.12 (1.49)	0.00 (1.77)	1.49	2/53	.23
Efficiency score (z-score)	−0.03 (0.82)	0.36 (0.99)	0.00 (0.93)	1.10	2/54	.34

Means and standard deviations in parentheses
[a]ANOVA (over all groups)
[b]The mean latency to first response and the Impulsivity score were significantly correlated with age; therefore, ANOVAs were corrected for age in these variables
[c]t test (one-tailed, raw values corrected for age) MDMA vs controls, $p<.05$; MDMA vs cannabis, $p=.12$

test for independent samples (one-tailed) with respect to the I-score. After correcting the raw values for age, this analysis did show a significantly increased I-score [$t(36)=1.66$, $p<.05$] in MDMA users in comparison with drug-naïve control subjects. However, MDMA users and the cannabis users did not significantly differ in the I-score [$t(36)=1.21$, $p=.12$ (one-tailed)], and cannabis users did not show a significant elevation of the I-score compared with controls [$t(36)=0.71$, $p=.48$ (two-tailed)].

Across drug groups, the mean latency to first response ($r=-.48$, $n=22$, $p<.05$) as well as the I-score ($r=.48$, $n=22$, $p<.05$) was significantly correlated with the lifetime peak dose of MDMA, indicating that high single doses of MDMA were associated with a faster reaction time and an elevated impulsivity in the MFFT. In addition, cumulative amphetamine doses correlated with the number of errors ($r=.33$, $n=38$, $p<.05$), and the years of cannabis use were associated with reaction time ($r=.36$, $n=38$, $p<.05$). Finally, the cumulative hallucinogen dose was correlated with the E-score ($r=-.38$, $n=38$, $p<.05$). The period of abstinence of any illegal drug also did not correlate with the MFFT variables. Thus, acute drug effects are unlikely to account for the elevated impulsivity of the MDMA users.

In summary, MDMA users showed an elevated impulsivity in the MFFT compared with drug-naïve control subjects, whereas cannabis users and control subjects had comparable I-scores. In addition, high single doses of MDMA were associated with higher I-scores and a faster reaction time.

Decision-making Task

One MDMA user had previously executed the GT and was therefore excluded from this analysis. Thus, data for 18 MDMA users, 19 cannabis users, and 19 drug-naïve control subjects were available for analysis. Performance of the experimental groups on the GT is shown in Fig. 1. An ANOVA of the GT net score across all groups showed a significant main effect of the factor group [$F(2,53)=4.78$, $p<.01$]. Single comparisons (one-tailed) of the net score revealed that the MDMA users performed significantly worse compared to drug-naïve controls [$t(35)=-2.04$, $p<.05$] as well as compared with the cannabis group [$t(35)=-3.28$, $p<.001$]. Cannabis users and control subjects did not differ in terms of the net score. An ANOVA [block × group, with repeated measures at factor block (fourfold)] with GT blocks across all groups revealed a significant main effect of the factor block [$F(3,159)=22.8$, $p<.001$], reflecting the strategy shift across blocks and a significant interaction of factor blocks and group [$F(6,159)=2.21$, $p<.05$], indicating differences in deck preferences across blocks between the groups. There was also a significant between-subject effect [$F(2,53)=4.78$, $p<.01$], indicating different preferences of decks in total between the groups.

Single comparisons with ANOVA [block × group, with repeated measures at factor block (fourfold)] showed a significant between-subject effect [$F(1,35)=4.17$, $p<.05$] and a significant interaction of both factors [$F(3,105)=2.87$, $p<.05$] between MDMA users and drug-naïve control subjects. In addition, the analysis revealed a significant between-subject effect between MDMA users and cannabis users [$F(1,35)=10.7$, $p<.01$], but in this comparison, the interaction of both factors was not significant [$F(3,105)=2.05$, $p=.11$]. Cannabis users and drug-naïve control subjects did not differ in repeated-measures ANOVA. In all single comparisons, the main effect of the factor block was significant to a level of at least $p<.01$. Performance on the GT was not correlated with age, years of education, or verbal IQ.

In the fourth block, the ratios of good and bad decks converge in all groups (Fig. 1). The explanation for this

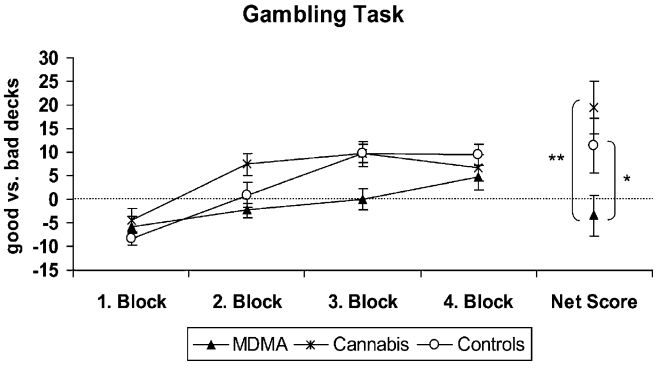

Fig. 1 Performance on the Gambling Task of MDMA users. Cannabis users and drug-naïve controls scored by a global outcome score (*net score*) and a score for each consecutive block of 25 cards (means±standard error of means). *t test (one-tailed) $p<.05$, **t test (one-tailed) $p<.001$

Table 5 Pearson's product-moment correlations between impulsivity measures (MFFT, Go/No-Go Task) and the Decision-Making Task (Gambling Task)

n=57[a]	MFFT errors	MFFT reaction time	MFFT I-score	MFFT E-score	Gambling Task net score
Gambling Task, net score	**−.42**	.29	**−.42**		–
Go/No-Go Task, total gain	**−.38**		−.33	.28	**.42**
Go/No-Go Task, commission errors	**.36**		**.34**		**−.49**

The table shows only the task pairs with correlation coefficients falling below a significance level of $p < .05$. Correlation coefficients falling below a significance level of $p<.01$ are bold
[a]MFFT n=57, Gambling Task n=56, Go/No-Go Task n=50

effect is that both advantageous and both disadvantageous decks have a maximum of 80 cards in total. Thus, if subjects demonstrated an early preference for only one of the two deck types, they had to draw cards from the remaining decks at the end. Thus, a good decision-making strategy will be punished and a bad strategy rewarded in the last block. A repeated-measures ANOVA across only the first three blocks reveals, therefore, stronger interaction effects between factor blocks and group despite lower statistical power due to fewer degrees of freedom [all groups: $F(4,106) = 2.96$, $p = .02$; MDMA vs controls: $F(2,70) = 5.41$, $p = .007$; MDMA vs cannabis: $F(2,70) = 2.69$, $p = .08$; cannabis vs controls: $F(2,72) = 1.26$, $p = .29$].

Across drug groups, the GT net score was correlated only with years of MDMA use ($r = -.34$, $n = 37$, $p < .05$), indicating that a long period of MDMA use was associated with impaired decision-making performance in the GT. Other illegal drug use patterns did not significantly correlate with the GT performance. Furthermore, the period of abstinence from any illegal drug did not correlate with the GT performance. Thus, acute drug effects are unlikely to account for the impaired decision-making cognition of the MDMA users.

In summary, MDMA users performed significantly worse in the GT compared with both cannabis users and drug-naïve control subjects. However, cannabis users and control subjects did not differ in their decision-making performance. In addition, a longer duration of MDMA use was associated with a worse decision-making performance.

Correlations between impulsivity and decision-making tasks

Table 5 shows the Pearson's product-moment correlations between the two impulsivity tasks and the decision-making task. The GT net score was highly correlated with the I-score of the MFFT as well as with the commission errors in the GNG, supporting the mutual interdigitation of the impulsivity and decision-making concepts. Furthermore, GNG commission errors were also highly correlated with the MFFT I-score, suggesting that these measures tap into similar cognitive mechanisms. It also appears that the MFFT error score, rather than the reaction time, was related to GNG commission errors and to the GT net score.

Discussion

The aim of this study was to analyze the effect of MDMA use on impulsivity and decision-making cognition. MDMA users showed significantly higher impulsivity in the MFFT I-score but not in commission errors made on the GNG compared with drug-naïve control subjects. Cannabis users and drug-naïve control subjects did not differ in impulsivity measures. In the GT, MDMA users showed a significantly lower decision-making performance than cannabis consumers or drug-naïve control subjects, whereas the decision-making performance of cannabis users was similar to that of drug-naïve control subjects. To the best of our knowledge, our study is the first to highlight decision-making deficits in MDMA users. Furthermore, the MFFT performance was correlated with a lifetime peak dose of MDMA, and the decision-making performance was correlated with years of MDMA intake. These associations suggest that the elevated impulsivity and the disrupted decision-making performance are a consequence of the MDMA intake. In addition, the I-score and the decision-making performance were correlated, indicating that the decision-making deficit of MDMA users may be attributed to an acquired lack of inhibitory control. It has to be emphasized that the MDMA users examined in the present study were mostly heavy users (at least 50 times of use, with an apparent mean of over 450 lifetime uses).

Impulsivity

MDMA users showed a significantly increased impulsivity in the MFFT but not in the GNG. This dissociation indicates that these tasks reflect different aspects of cognitive impulsivity. It was proposed that several behavioral impulsivity paradigms describe different facets of impulsivity (Monterosso and Ainslie 1999; Moeller et al. 2001; Swann et al. 2002). According to the taxonomy of Moeller et al. (2001), the MFFT is among the response disinhibition/attentional paradigms, whereas passive avoidance learning tasks like the GNG according to Newman and Kosson (1986) would be assigned to the punishment and/or extinction paradigms. This concept is of special interest because it was previously shown that only the response disinhibition/attentional paradigms, but not the punishment and/or

extinction paradigms, were associated with 5-HT function (Puumala and Sirviö 1998; Evenden 1999; Harrison et al. 1999; Moeller et al. 2001). Thus, a selective serotonergic neurotoxicity of MDMA could have manifested only in the MFFT but not in the GNG performance. However, both tasks indeed seem to measure facets of the same construct because the MFFT I-score and the GNG commission errors were positively correlated.

This study replicates previous findings of elevated cognitive impulsivity in the MFFT in MDMA users (Morgan 1998; Morgan et al. 2002), and in accordance with the findings of Fox et al. (2002) [who used the Cambridge Neuropsychological Test Automated Battery (CANTAB) Go/No-Go Task], we could not demonstrate changes in the MDMA users' GNG commission error rate. Thus, also across previous studies, the dissociation of both impulsivity measures appeared. It should be noticed that the effect sizes of the MFFT I-score in our study were smaller (d=0.49) than in the study conducted by Morgan (1998) (d=0.66). This finding may be explained by the fact that Morgan (1998) and Morgan et al. (2002) used the longer 20-item version of the MFFT of Cairns and Cammock (1978). The 12-item MFFT used here is in fact valid (Arizmendi et al. 1981; van den Broek et al. 1987), but it is less reliable than the 20-item version (Loper and Hallahan 1980). The lower reliability of the 12-item version could explain the different effect sizes. Future studies should therefore use the longer 20-item version.

Functional imaging studies suggested that several brain regions are involved in behavioral inhibition. In these studies, the prefrontal, the inferior parietal, and the cingulate cortices were consistently activated during inhibition of reactions (Liddle et al. 2001; Lee et al. 2001; Rubia et al. 2001, 2003; Garavan et al. 2002; Watanabe et al. 2002; Horn et al. 2003). Furthermore, patients with wide frontal lesions exhibit an increase in impulsive behavior (Miller and Milner 1985; Miller 1985, 1992), and it was recently shown that patients with selective orbitofrontal lesions revealed an increased impulsivity as measured with the MFFT (Berlin et al. 2004). Thus, the elevated impulsivity of MDMA users may be ascribed to an impairment of frontal, inferior parietal, or cingulate regions. This view is supported by results of animal studies showing that the frontal regions in particular exhibit a sustained loss of 5-HT axon terminals after MDMA exposure (Fischer et al. 1995; Hatzidimitriou et al. 1999). In addition, immunohistochemical studies indicate that MDMA appears to cause a selective degeneration of fine-diameter serotonergic axons with small varicosities that arise from the dorsal raphe nucleus and that project particularly into the forebrain. In contrast, 5-HT-containing axons with large round varicosities and small intervaricose segments that arise predominantly from the median raphe nuclei appear to be unaffected by MDMA (O'Hearn et al. 1988; Wilson et al. 1989).

Acute drug effects were unlikely to account for the elevated impulsivity of MDMA users because the mean period of abstinence of MDMA was 17.4 days (median= 14 days) and the elimination half-life of MDMA in humans is relatively short, with about 8–9 h (de la Torre et al. 2000). In addition, no correlation between impulsivity measures and period of abstinence was found.

Furthermore, we found no alteration of impulsivity in chronic but presently abstinent cannabis users. To the best of our knowledge, this is the first published study involving cannabis users and behavioral measures of impulsivity. Acute administration of Δ^9-tetrahydrocannabinol (THC)-one of the psychoactive components of cannabis-increased impulsive responding on the Stop Task but did not affect other impulsivity measures such as the GNG (McDonald et al. 2003). However, it is unlikely that the elevated impulsivity of MDMA users is caused by postacute cannabis effects because we found no increased impulsivity in the cannabis group, although that group had a smaller mean duration of cannabis abstinence as well as a more intensive cannabis consumption than the MDMA group.

Decision-making cognition

In contrast to the findings of Fox et al. (2002), we could demonstrate decision-making deficits in MDMA users. However, there are some differences between the studies: In this study, the cumulative MDMA dose of the users was 2.5-fold larger than that of the MDMA users described by Fox et al.; thus, a behavioral neurotoxic effect was possibly more penetrating in our study. Otherwise, the decision-making tasks in both studies were very different. The Decision-Making Task of Rogers et al. (1999a) is more complex and requires a higher intellectual performance level than the GT according to Bechara et al. (1994). In a previous study analyzing three decision-making tasks, the Rogers task was strongly correlated with IQ, whereas no association of the Bechara task with IQ was found (Monterosso et al. 2001). We also could not determine a correlation between GT performance and verbal IQ. Another difference is that no learning of reinforcement contingencies by trial-and-error is needed in the Rogers task; thus, the Rogers task rather measures risk-taking behavior in association with analytical skills and less so the ability for long-term maximization of profit as the Bechara task does. In addition, Monterosso et al. (2001) could show in cocaine-dependent subjects that both tasks did not correlate. In summary, the Rogers task measures "cognitive" or "executive" components, whereas the Bechara focuses on "impulsive" and "emotional" components of decision-making performance (Monterosso et al. 2001). This assumption is partly supported by the correlation of the MFFT I-score with the GT performance results reported here.

A comparable finding was reported by Paulus et al. (2002, 2003): Users of methamphetamine, which has serotonergic as well as dopaminergic neurotoxic effects, have also shown decision-making deficits.

On the basis of lesion studies, the orbitofrontal/ventromedial (Eslinger and Damasio 1984; Damasio et al. 1991; Shallice and Burgess 1991; Bechara et al. 1994; Rogers et al. 1999b) and the dorsolateral/dorsomedial prefrontal cortices (Ernst et al. 2002; Manes et al. 2002) were suggested as key structures for decision-making cognition.

Paulus et al. (2002) demonstrated in an fMRI study that methamphetamine users showed significantly less activation of the orbitofrontal/ventromedial prefrontal cortex during a decision-making task than controls. The authors interpreted their findings as a consequence of methamphetamine neurotoxicity. Accumulating evidence suggests that several amphetamine derivates can cause decision-making deficits by sustained modulation of serotonergic and dopaminergic projections in frontolimbic and frontostriatal circuits (Jentsch and Taylor 1999; Rogers et al. 1999b, Paulus et al. 2002). Because of these previous findings, we propose that the decision-making deficits of MDMA users are based on alterations of their orbitofrontal/ventromedial and/or dorsolateral/dorsomedial prefrontal cortex caused by MDMA.

To accomplish a gambling task, multiple cognitive and emotional processes are involved, including remembering past outcomes, learning long-term contingencies, evaluating immediate wins relative to long-term losses and, finally, choice mechanisms regulating the decision maker's impulsiveness and recklessness (Busemeyer and Stout 2002). A decrease in inhibitory control would therefore lead to an impaired decision-making performance. We confirmed this relationship in the correlation of GT performance with MFFT I-score as well as with commission errors made in the GNG. Thus, the decision-making deficit of MDMA users is probably because of the loss of inhibitory control.

Again, acute drug effects were unlikely to account for the decision-making deficits of MDMA users because the mean period of abstinence of MDMA and other drugs was too long (see above) and we found no correlation between the GT performance and the period of drug abstinence.

In contrast to a previous study (Whitlow et al. 2004), we could not find decision-making deficits with the GT in cannabis users. However, the heavy cannabis users described by Whitlow et al. (2004) had to abstain from cannabis use only for at least 12 h before testing, which is a very short period of time, because THC plasma elimination half-lives are known to range from 18 to 50 h (Huestis and Cone 1998). As described above, acute THC can increase some aspects of impulsivity (McDonald et al. 2003); thus, the decision-making deficit of the cannabis users in the study conducted by Whitlow et al. was probably caused by acute drug effects. However, it is unlikely that postacute cannabis effects influenced the decision-making cognition of our MDMA group because (1) our participants had to abstain from cannabis use for at least 3 days before testing and (2) we found no alterations in decision-making performance in the cannabis group, although they had a smaller mean duration (7.1 days) of cannabis abstinence than the MDMA group (11.1 days) as well as a more intensive cannabis consumption.

Neurotoxicity or predisposition?

Cognitive functions have been proposed as sensitive markers of neurotoxicity (Paule 1995). A fundamental concept of toxicology is the dose-response relationship, which states that there is a direct relationship between the amount of a toxic noxa to which an individual or a group is exposed and a toxic (behavioral) effect (Rosenberg 1995). Thereby, the dose of a toxic drug can be measured in different ways, e.g., peak, weekly or cumulative dose, but also in frequency or length of use. In this study, it was demonstrated that the significantly elevated impulsivity of MDMA users and the significantly disturbed decision-making cognition were associated with the lifetime peak dose of MDMA and the years of MDMA intake, respectively. These dose-response relationships suggest that the cognitive deficits are a consequence rather than a predisposition. Furthermore, the correlation with the MDMA peak dose is in line with animal data that high or frequent doses of MDMA might be required to produce neurotoxic damage (O'Shea et al. 1998).

It was plausibly argued that people may start and continue to abuse drugs just because they are more impulsive, are risk seekers, and are bad decision makers. Thus, higher impulsivity and worse decision-making cognition would be vulnerability factors for every type of drug abuse (Bechara et al. 2001; Bechara and Damasio 2002; Ernst et al. 2003). However, we could not show impulsivity and decision-making deficits in regular cannabis users, a finding that disproves the assumption that drug abuse in general had to be associated with higher levels of impulsivity or dysfunctional decision making. Our data, instead, support the notion that an increase in impulsivity and a decline in decision-making cognition in amphetamine derivate users resulted from the serotonergic or dopaminergic neurotoxicity of these substances (Jentsch and Taylor 1999; Rogers et al. 1999b; Paulus et al. 2002). With respect to cocaine, Bolla et al. (1998, 1999) pointed out that both the predisposition of a cognitive style and the neurotoxicity of the substance may have an interactive strengthening effect. Maybe this applies also for the amphetamine derivates. However, cross-sectional designs, such as the one used in this study, are less suitable to prove both assumptions adequately. Longitudinal designs measuring behavioral impulsivity and decision-making cognition in MDMA users (ideally before the onset of stimulant use or after long-term abstinence) are required to determine whether impulsive behavior leads to stimulant use or vice versa. Furthermore, cross-sectional designs cannot answer the question regarding the reversibility of the neurotoxic effects of MDMA. Again, only longitudinal designs can enlighten this issue.

In contrast to the findings in MDMA users, nonhuman primates exposed to high-dose repeated regimens of MDMA surprisingly do not exhibit cognitive deficits under normal conditions, although 5-HT markers in several neocortical brain regions were decreased by 50–90% (Frederick et al. 1998; Taffe et al. 2001; Winsauer et al. 2002). However, Taffe et al. (2001, 2003) reported that the brains of MDMA-treated monkeys were not functionally intact because alterations in brainstem auditory evoked potentials (BSAEP) persisted up to 13 weeks following MDMA exposure. In addition, it was shown that MDMA-treated monkeys revealed strong behavioral deficits under an additional challenge to the 5-HT system (Frederick et al.

1998; Taffe et al. 2002, 2003). But how can the discrepancy between the dramatic decrease in 5-HT brain levels and the lack of behavioral consequences under normal conditions be explained? Frederick and Paule (1997) summarized some possible difficulties in detection of behavioral neurotoxicity of MDMA in laboratory animals: "the treatment regimens used did not sufficiently damage the 5-HT system enough to alter the observed behaviors; other brain regions functionally compensate for any damage that is induced; the behaviors that were monitored were not subserved by the 5-HT system; or, the behavioral tasks used were not sensitive to changes in the 5-HT system" (p. 72). Thus, further animal studies on cognitive neurotoxicity of MDMA should apply cognitive test batteries which are more similar to the tests with which cognitive deficits in MDMA users have been shown.

One limitation of this study is that the history of drug consumption was assessed using only subjective reports. A drug-usage screening would be desirable to better control for acute and postacute 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). However, 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.

Due to the use of cannabis users as a "clinical" control group, we could largely rule out cannabis use as potential confound of our results. Nevertheless, our MDMA users also reported some use of amphetamine. However, the amount of amphetamine use was relatively small (~3.5 times per month) compared to the MDMA use (~8.5 tablets per month) especially because every single "line" of sniffed amphetamine (which is a very small quantity) was documented as one time of use. Furthermore, the MFFT I-score as well as the performance in the GT was not correlated with indicators of amphetamine use but only with MDMA use, although MDMA use and amphetamine use were highly intercorrelated in our MDMA users (cumulative doses: r=.57, n=19, p<.01; weekly doses: r=.80, n=19, p<.001). Thus, we think that MDMA and not amphetamine is the denominator with respect to the shown deficits in impulsivity and decision-making cognition. However, it should also be noticed that possible drug-drug interactions could not completely be excluded in such study design based on "real-life conditions".

In summary, our results provide, to the best of our knowledge, the first evidence of a decision-making deficit on the basis of an increased behavioral impulsivity in heavy but presently abstinent users of MDMA. Associations with the amount of MDMA consumption and the fact that MDMA is a neurotoxin selective for the 5-HT system suggest that these behavioral deficits were acquired via MDMA use. Furthermore, the concomitant cannabis use of the MDMA users could not account for the behavioral deficits because (1) cannabis users did not show changes in impulsivity or decision-making performance and (2) parameters of cannabis use were not statistically correlated with impulsivity and decision-making measures. Our data also suggest that the elevated impulsivity and the decision-making deficits of MDMA users could likely be attributed to a dysfunction of regions within the frontal cortex. Thus, the cognitive deficits of MDMA users could not be explained exclusively because of an impairment of temporal regions, as has been proposed by some researchers (Fox et al. 2002; Gouzoulis-Mayfrank et al. 2003; Daumann et al. 2004; Jacobsen et al. 2004).

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