Psychopharmacology (2004) 173:418–424
DOI 10.1007/s00213-003-1729-y

ORIGINAL INVESTIGATION

Karsten Heekeren · Jörg Daumann · Mark A. Geyer · Euphrosyne Gouzoulis-Mayfrank

Plasticity of the acoustic startle reflex in currently abstinent ecstasy (MDMA) users

Received: 11 September 2003 / Accepted: 18 November 2003 / Published online: 14 January 2004

Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is neurotoxic upon central serotonin systems in experimental animals and probably also in humans. Serotonin is involved in the habituation, sensitization and prepulse inhibition (PPI) of the startle reflex. *Objectives:* To study the plasticity of startle reflex in currently abstinent MDMA users. *Methods:* Electromyographic responses to acoustic startle stimuli (pulse alone and prepulse-pulse trials) were recorded in 23 currently abstinent ecstasy users and 20 matched control subjects. Depending on the extent of their previous drug use ecstasy users were divided into two groups [life-time dose <90 (n=11) and ≥90 pills (n=12), respectively]. *Results:* There were no significant differences in habituation, sensitization or PPI of the startle reflex between the entire group of ecstasy users and controls. However, sensitization of the startle reflex was stronger in the ≥90 compared with either the <90 MDMA pills or the control group. Correlations between patterns of drug use and startle parameters did not reach the level of significance, although users with a younger age at the onset of MDMA (and other drug) use tended to present with higher sensitization of the startle reflex. *Conclusions:* Heavy users of MDMA (and other recreational drugs) present with strong sensitization of the startle reflex. Nevertheless, it is unclear whether this finding is secondary to the use of MDMA and its well-recognized neurotoxic potential. Alternatively, strong sensitization might reflect a pre-existing trait predisposing to drug use. A clearer picture of the impact of ecstasy on startle plasticity may be obtained from longitudinal investigations.

Keywords MDMA (3,4-methylenedioxymethamphetamine) · Startle reflex · Neurotoxicity · Sensitization · Habituation · Prepulse Inhibition

K. Heekeren
Department of Psychiatry and Psychotherapy,
University of Technology (RWTH),
Pauwelsstrasse 30, 52074 Aachen, Germany

M. A. Geyer
Department of Psychiatry,
University of California San Diego,
9500 Gilman Drive, La Jolla, CA 92093-0804, USA

J. Daumann · E. Gouzoulis-Mayfrank (✉)
Department of Psychiatry and Psychotherapy,
University of Cologne,
Joseph-Stelzmann Strasse 9, 50924 Cologne, Germany
e-mail: e.gouzoulis@uni-koeln.de
Tel.: +49-221-4784001
Fax: +49-221-4783738

Introduction

Ecstasy (MDMA: 3,4-methylenedioxymethamphetamine and other congeners) is a popular recreational drug with well recognized neurotoxic potential upon central serotonergic systems (Ricaurte et al. 1992, 2000). Ecstasy use leads to widespread degeneration of presynaptic serotonergic axon terminals and serotonin depletion in brain tissue. These effects can be very long-lasting or even permanent in animal studies (Fischer et al. 1995; Hatzidimitriou et al. 1999), and may also occur in humans (McCann et al. 1998, 2000; Reneman et al. 2001). Serotonin is involved in numerous functions, including regulation of mood, vegetative functions, neuroendocrine secretion, processing of sensory stimuli and cognition. Several reports suggest that ecstasy users exhibit abnormalities in most of these functional domains (reviews in McCann et al. 2000; Gouzoulis-Mayfrank et al. 2002). To date, the most consistent findings have been dose-related impairments of learning and memory performance (Krystal et al. 1992; Bolla et al. 1998; Parrott and Lasky 1998; Morgan 1999; Gouzoulis-Mayfrank et al. 2000, 2003; Rodgers 2000; Bhattachary and Powell 2001; Zakzanis and Young 2001; Daumann et al. 2003).

With regard to sensory processing, findings have been inconsistent, with one study reporting an association of the extent of previous ecstasy use with the intensity dependence of acoustic evoked potentials and another study reporting an increase of intensity dependence per se but no association with the extent of previous ecstasy use

(Tuchtenhagen et al. 2000; Croft et al. 2001). The term intensity dependence of acoustic evoked potentials refers to the usual increase of amplitude of evoked potentials with increasing intensity of the sensory stimulus (review in Carrillo-de-la-Penna 1992). To our knowledge, there have as yet been no published reports on the plasticity of startle reflex in ecstasy users.

The startle reflex is a primitive response to sudden intense sensory stimuli with the primary reflex pathway located in the brain stem. However, the reflex exhibits a high degree of plasticity, is influenced by the activity of higher brain areas, and is modulated by both attentional and emotional states (Filion et al. 1998; Koch 1999; Braff et al. 2001b). Although the role of serotonin in startle modulation is not entirely understood, it is involved in three fundamental phenomena: habituation, sensitization and prepulse inhibition (PPI) (Sipes and Geyer 1994, 1996; Kehne et al. 1996; review in Geyer et al. 2001). PPI is a robust inhibition of the reflex response by a weak, non-startling stimulus (prepulse) which precedes the startle eliciting stimulus (pulse) by 30–500 ms. 5-HT (serotonin) depletion was shown to disrupt PPI both in rats (Prinssen et al. 2002) and in humans (Phillips et al. 2000). In contrast, acute administrations of the 5-$HT_{1A/2}$ agonist psilocybin or the 5-HT releaser MDMA increase PPI in humans (Gouzoulis-Mayfrank 1998; Vollenweider et al. 1999), although MDMA and other substances having similar pharmacological properties disrupt PPI in animals (Sipes and Geyer 1995; Martinez and Geyer 1997). Sensitization and habituation refer to an increase or decrease, respectively, in response after repeated stimulation (Thompson and Spencer 1966; Davis and File 1984). Early studies described a biphasic pattern of startle response in healthy humans consisting of an initial increase in amplitude over the first few trials followed by a gradual decrease (Davis and Heninger 1972; Ornitz and Guthrie 1989). According to the dual-process theory of response habituation (Groves and Thompson 1970), two independent, i.e. distinct, neuronal mechanisms subserving sensitization and habituation may interact to produce the net response to repeated stimulation. Early animal studies used different species and paradigms and yielded contradictory results on the role of 5-HT on sensitization and habituation (Davis and Sheard 1976; Geyer and Tapson 1988; Ehrlich et al. 1992; Hawkins et al. 1993; Burrell and Sahley 1999).

In the present study, we investigated the plasticity of the acoustic startle reflex in abstinent ecstasy (MDMA) users and controls. If MDMA users suffer neurotoxic brain damage and depletion of serotonin in their brain, we expected to find blunted PPI and/or alterations in habituation and sensitization depending on the extent of their previous use of ecstasy.

Materials and methods

Subjects

Twenty-three MDMA users (inclusion criterion: use of ecstasy on at least 20 occasions) were recruited directly in the dance scene by distribution of flyers near the entrance of dance clubs, via word-of-mouth and via the internet. Because most ecstasy users tend to experiment also with other typical club drugs, subjects who reported use of amphetamines, cocaine, cannabis or LSD were not excluded. However, subjects were excluded if they reported regular use of alcohol (defined as drunkenness occurring at a frequency of at least twice per month over 6 months or longer within the last 2 years), or regular use of other legal or illegal psychotropic drugs such as opiates and benzodiazepines (defined as use once per month or more frequently over 6 months or longer within the last 2 years). The control group consisted of 20 healthy persons (students and hospital employees) who were matched for age, sex and smoking status with the MDMA users and had no previous or current history of alcohol or drug use. Because nicotine and nicotine withdrawal are known to affect startle and PPI (Kumari et al. 1996; Duncan et al. 2001), all smokers were requested to smoke a cigarette within 20 min before the startle session started. Ecstasy users agreed to abstain from drug use for at least 7 days prior to the study with the exception of cannabis. Because daily moderate cannabis use was part of the lifestyle of many subjects, and because cannabis screens may remain positive for several weeks after the last use (thus making it impossible to verify reported abstinence), it was accepted that most subjects agreed to abstain from cannabis only on the study day. A structured interview was performed according to DSM-IV (SCID). Exclusion criteria for all participants were: (1) a positive drug screen on the study day except for cannabis; (2) any current or previous axis I psychiatric diagnosis except for drug abuse in the user group; and (3) any organic brain disorder, hearing impairment or relevant general medical condition requiring pharmacological treatment. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee at the Medical Faculty of the University of Technology (RWTH) Aachen.

Procedures

The eyeblink component of the acoustic startle reflex was measured. Two miniature electrodes were positioned below and lateral to the right eye over the orbicularis oculi muscle. The ground electrode was placed behind the right ear over the mastoid. Electromyographic (EMG) recordings of the orbicularis oculi muscle were processed and analyzed with a commercially available startle system (SR-Lab; San Diego Instruments, San Diego, Calif., USA). The prepulse and startle stimuli were presented binaurally through headphones (TDH-39-P; Maico, Minneapolis, Minn., USA), while subjects were seated comfortably in an armchair and were instructed to fixate on a blank space on the opposite wall.

The test session started with a 5-min acclimation period consisting of background broadband noise (70 dB white noise) which continued throughout the whole session. There were two different types of trials: a 115 dB burst of broadband noise with a duration of 20 ms presented alone (pulse alone trial) and this same burst preceded by a discrete 20 ms burst of 82 dB broadband noise with an interval of 100 ms between onset of prepulse and onset of pulse (prepulse trial). The session consisted of 42 trials separated into five blocks. Blocks 1, 3 and 5 contained only six pulse alone trials each. The two remaining blocks (2 and 4) contained both six prepulse trials and six pulse alone trials, which were presented in a pseudorandomized order. Ten different intertrial intervals (range 6–17 s) were used in an irregular order. The electromyographic activity was recorded in 250 1-ms epochs, starting with the onset of the startle-eliciting stimulus. The EMG signal was bandpass-filtered (100–1000 Hz) and the software parameters for analysis were identical to previous reports (Braff et al. 1992, 2001a).

Data analysis

Peak amplitude and peak latencies were measured automatically. In trials that showed no detectable blink response, the amplitude was scored as zero and latency data were discarded. Trials were discarded when the peak amplitude occurred after 80 ms following the onset of the startle-eliciting stimulus. Habituation, prepulse inhibition and sensitization were calculated for each subject.

Sensitization was calculated over the first four trials using the formula: [(mean amplitude trial 2–4/amplitude trial 1)×100]−100. Prepulse inhibition (PPI) was calculated as the reduction in startle amplitude in the prepulse trials compared to the amplitude of the pulse alone trials in the second and fourth block, using the formula: 100−[(amplitude prepulse/amplitude pulse alone trial)×100]. Two different habituation variables were calculated: 1) percent reduction in startle amplitude between the mean of the first and the fifth block ($HAB_{Block1-5}$), and 2) between the amplitude of the first trial and the mean amplitude of the fifth block ($HAB_{Trial1-Block5}$).

Group differences regarding startle magnitude (mean amplitude of the first block), PPI, sensitization and habituation variables were analyzed by means of unpaired two-tailed Student *t*-tests. In addition, and because we expected the possible alterations in startle parameters to be dose-dependent in ecstasy users, we divided them into two groups using the median-split procedure (life-time dose <90 ecstasy tablets, *n*=11, life-time dose ≥90 ecstasy tablets, *n*=12), and we analyzed the startle parameters of the two user groups and controls by means of analyses of variance (ANOVA). Finally, we analyzed the possible associations of startle parameters with the patterns of MDMA and other drug use using Pearson's correlation coefficient.

In addition, we analyzed the possible associations of startle parameters with personality traits such as sensation seeking and impulsivity using Pearson's correlation coefficient and the psychometric scores of the Sensation Seeking Scale (Zuckerman et al. 1978) and the Barratt Impulsiveness Scale (Barrat 1985). This last analysis was performed because previous electrophysiological studies indicated a relationship between sensation seeking or impulsivity and stimulus processing (intensity dependence of sensory evoked potentials (Zuckerman et al. 1988; Hegerl and Juckel 1993) or modulation of the startle reflex (Hutchison et al. 1999).

All analyses were performed using the SPSS software (version 11.0). Statistical significance was set at $P<0.05$, except for the correlation analyses between startle parameters and patterns of drug use where a more conservative level of significance was set in order to adjust for multiple testing (see Results).

Results

The groups of ecstasy users and controls were similar in terms of age and distribution of sex and smoking status (Table 1). Most ecstasy users reported regular concomitant use of cannabis and stimulant amphetamines, while very sporadic previous experiences with other drugs were reported by only a few subjects. The patterns of drug use are presented in Table 2. Using Pearson's correlation coefficient, we found a significant relationship between the cumulative dose of MDMA and the cumulative dose of amphetamine ($r=0.657$, $P=0.001$) as well as the age of onset of MDMA use ($r=-0.403$, $P=0.012$). Some control subjects

Table 1 Demographic data of ecstasy users and controls (means±SD)

Ecstasy users				Controls (*n*=20)
Lifetime dose MDMA	≥90 pills (*n*=12)	<90 pills (*n*=11)	All users (*n*=23)	
Mean age (years)	24.1±3.6	26.5±2.9	25.2±3.4	27.4±3.8
Men:women	9:3	9:2	18:5	16:4
Smoker:non-smoker	9:3	5:6	14:9	13:7

Table 2 Patterns of lifetime drug use in ecstasy users (means±SD; lifetime dose MDMA ≥90 pills, *n*=12; lifetime dose MDMA <90 pills, *n*=11). *X* subjects felt that they were unable to give a reliable estimate

Lifetime dose MDMA	Ecstasy		Cannabis		Amphetamine	
	≥90 pills	<90 pills	≥90 pills	<90 pills	≥90 pills	<90 pills
Subjects reporting regular use	12/12	11/11	6/12	6/11	8/12	3/11
Estimated lifetime dose	452.9±557.2 tablets*	48.3± 21.9 tablets*	X	X	164.9±206.0 g*	23.2±44.1 g*
Average frequency of use in days per month	3.2±4.6	0.4±0.7	14.9±13.8	11.1±12.7	1.3±1.6*	0.2±0.6*
Average daily or 1 night dose	1.3±0.9 tablets	1.0±0.9 tablets	555.0±912.4 mg	281.8±182.0 mg	433.3±830.8 mg	245.5±512.6 mg
Age at onset of use	18.2±2.7 years*	21.1±3.0 years*	15.2±3.1 years	16.5±2.1 years	17.3±3.0 years*	20.0±2.4 years*
Time since last dose in days	138.6±184.6 days	563.6±737.8 days	6.1±6.8 days	3.1±2.6 days	68.6±74.0 days	15.3± 5.1 days
Total time of use in months	33.5±23.5	23.8±13.8	70.5±38.9	70.0±54.2	29.1±16.5	20.9±28.4
THC-screen in urine sample on study day	–	–	6 positive/ 6 negative	6 positive/ 5 negative	–	–

* Significant difference between the two user groups (one-tailed, unpaired *t*-test, $P<0.05$)

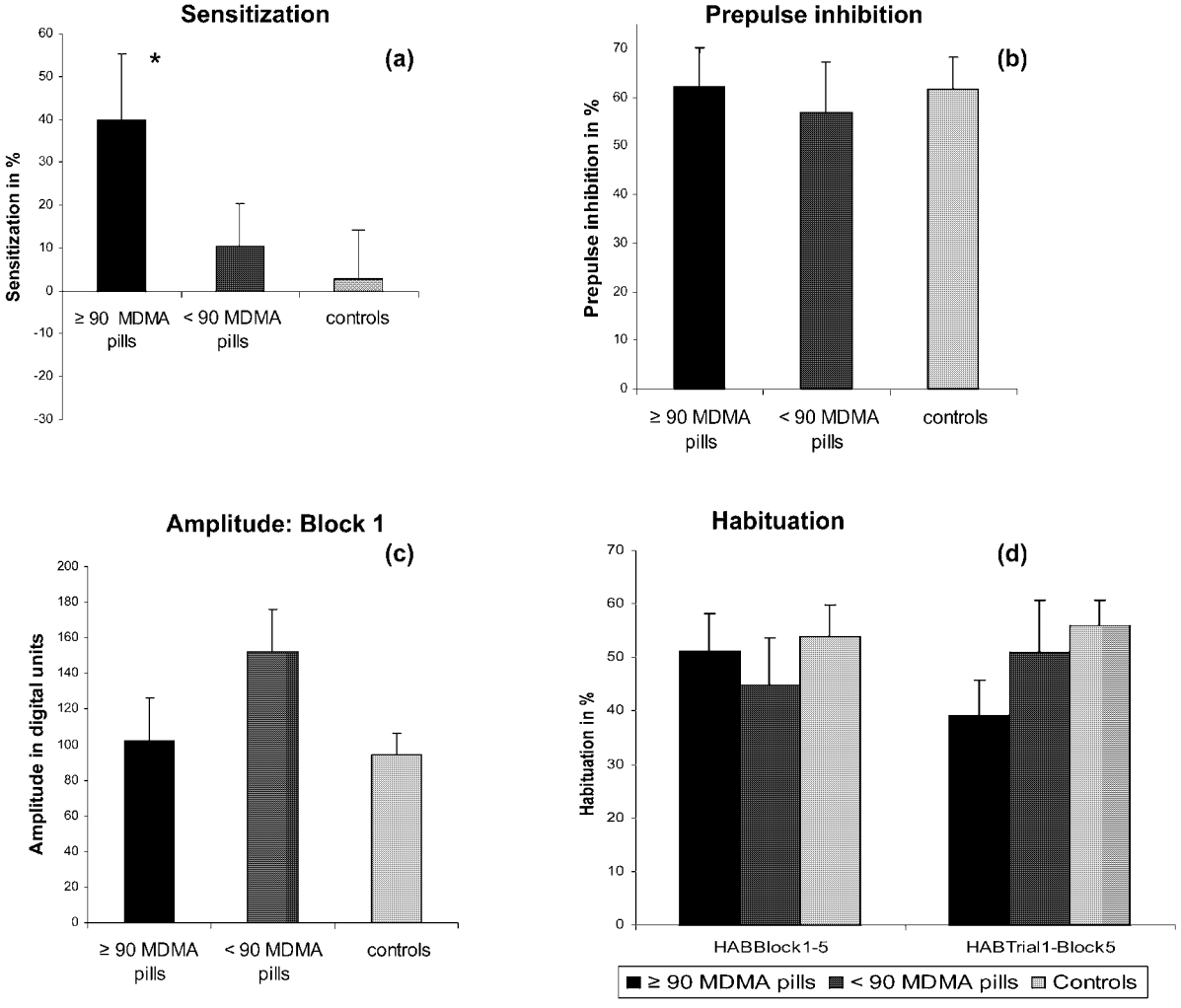

Fig. 1 Startle parameters in ecstasy users and controls (means±SE). **c** in digital units, **a**, **b** and **d** in percent (* significant difference between the ≥90 and the <90 MDMA pills groups and between the ≥90 pills group and controls; ANOVA, post-hoc LSD test, $P<0.05$)

reported very sporadic previous experiences with cannabis, but no regular use of any drugs at present or in the past.

The descriptive statistics of the startle parameters are presented in Fig. 1. There were no significant differences between the entire group of ecstasy users and the control group (magnitude: $t=-1.48$, $df=41$, $P=0.147$; PPI: $t=0.24$, $df=40$, $P=0.814$; sensitization: $t=-1.01$, $df=39$, $P=0.312$; $HAB_{Block1-5}$:$t=0.72$, $df=41$, $P=0.479$ and $HAB_{Trial1-Block5}$: $t=1.36$, $df=39$, $P=0.181$). The analysis of startle parameters for both user groups (<90 and ≥90 pills) and controls (ANOVA) just failed to reach the significance level ($F=2.98$, $df=2,38$, $P=0.063$). However, post-hoc tests (LSD) revealed differences between the ≥90 MDMA pills and the <90 MDMA pills group ($P=0.035$) and between the ≥90 MDMA pills group and controls ($P=0.044$) suggesting a trend towards sensitization in heavy users, but not in the <90 pills group and controls. Indeed, inspection of the individual data revealed that all but one heavy user, but only six out of 20 non-users and four out of the 11 users of the <90 pills group displayed sensitization of the startle reflex (data not shown). The descriptive statistics also suggest a lower degree of reflex habituation in the heavy users when habituation was calculated on the basis of the first trial ($HAB_{Trial1-Block5}$); however, these differences were not significant ($P>0.2$). Finally, there were no significant group effects on startle magnitude or PPI.

Correlations between startle parameters and patterns of drug use with $P<0.05$ are presented in Table 3. These data suggest higher sensitization and lower habituation of the startle reflex in subjects with early onset of ecstasy (and other drug) use. However, it should be noted that no single correlation passed the level of significance after adjustment of the P-value for multiple comparisons (Bonferonni correction for 90 correlations: $P<0.00056$; correlations of age of onset, estimated lifetime dose, average frequency of use, average daily or 1 night dose, time since last dose and total years of use for ecstasy, amphetamines and cannabis with sensitization, $HAB_{Block1-5}$, $HAB_{Trial1-Block5}$, amplitude block 1 and PPI).

Table 3 Correlations between patterns of drug use and startle parameters (n=23; P<0.05). r Pearson correlation coefficient

	Sensitization	Habituation ($HAB_{Trial1\text{-}Block5}$)
MDMA use		
Age of onset	r=–0.607, P=0.002	r=0.483, P=0.02
Amphetamine use		
Age of onset	r=–0.620, P=0.005	r=0.500, P=0.029
Cannabis use		
Age of onset	r=–0.485, P=0.035	–

A higher sensitization was associated with a lower amplitude of the startle reflex in the first trial [Pearson r=–0.481 P=0.001, n=43 (all study participants)]. Since descriptive statistics suggested lower amplitude in trial 1 in heavy users (94.8±96.4 digital units) compared to the <90 MDMA pills and the control group (184.9±105.6 and 116.4±71.8 digital units, respectively), we ran an additional ANOVA for the amplitude of the first trial for both user groups and controls, Again, this analysis just failed to reach significance (F=3.23, df=2,38, P=0.051). In the post-hoc tests (LSD) only the difference between the two user groups was significant (P=0.02), whereas the difference between the <90 MDMA pills and the control group failed significance (P=0.052), and the difference between the control group and the heavy users was far away from significance (P=0.52). Nevertheless, we ran an additional analysis of variance for sensitization for the two user groups with the amplitude of the first trial as the covariate (ANCOVA). In this analysis, the group difference in sensitization did not reach statistical significance after elimination of the effect of the covariate (F=3.59, df=1,21, P=0.073).

Finally, there was no significant correlation between the psychometric scores on the Sensation Seeking Scale and the Barratt Impulsiveness Scale with any of the startle parameters.

Discussion

The aim of the present study was to investigate the plasticity of startle reflex in currently abstinent ecstasy (MDMA) users. Because MDMA has a well recognised neurotoxic potential upon central serotonergic neurons (Ricaurte et al. 1992, 2000; McCann et al. 1998, 2000; Reneman et al. 2001) and because serotonin is involved in prepulse inhibition (PPI), habituation and sensitization phenomena (review in Geyer et al. 2001), we expected to find blunted PPI and other abnormalities in the plasticity of startle reflex depending on the extent of previous ecstasy use. We examined 23 currently abstinent MDMA users and 20 matched controls and found no group differences on any startle parameter. After splitting the MDMA users into two groups depending on their estimated lifetime dose (<90 and ≥90 MDMA pills), we still found no differences in PPI, but we found a trend toward increased sensitization in heavy users compared to both the <90 MDMA pills group and controls. At first glance, these findings might appear to be in line with our hypothesis of a dose-dependent effect of MDMA on startle plasticity. However, the results of the correlation analyses do not support this hypothesis. If any, high sensitization (and low habituation) of the startle reflex seemed to be related to a younger age at the onset of MDMA and other drug use, and not to a heavier pattern of use.

Consequently, our results demonstrate high sensitization of the startle reflex in heavy ecstasy users, but the significance of this finding is uncertain. The correlations between sensitization and age at onset of ecstasy, amphetamine and cannabis use, as well as between habituation and age of onset of ecstasy and amphetamine use suggest that this finding is nonspecific to a particular substance. Hence, it would be premature to conclude that the higher sensitization in heavy ecstasy users is a consequence of ecstasy use, and, more specifically, a consequence of ecstasy-related neurotoxicity. Needless to say, a neurotoxicity-related threshold effect without further alteration with doses higher than the hypothetical threshold dose may still be involved in our findings. This threshold model would be in line with our findings of higher sensitization in heavy users without positive correlation between sensitization and cumulative dose. However, it is also possible that the high sensitization is in fact unrelated to the use of the specific drug MDMA.

First, the sensitization process may be influenced by the magnitude of initial reflex response, although, on the basis of our data, the stronger sensitization in heavy users cannot be explained by a lower level of initial startle amplitude alone. Second, we cannot rule out the possibility that environmental factors, such as repeated exposure to the stress of loud, high frequency music and drugs during raves may influence the plasticity of the startle reflex in heavy users, who are known to attend such events more frequently than non-users or occasional users. Finally, the phenomenon of sensitization of the startle reflex might be functionally related to another phenomenon of sensory information processing, the intensity dependence of sensory evoked potentials. This term refers to the usual increase of amplitude of evoked potentials with increasing intensity of the sensory stimulus (review in Carrillo-de-la-Penna 1992). It is known that high-intensity dependence is associated with both low functioning of serotonergic neurotransmission (Hegerl and Juckel 1993) and serotonin-dependent personality traits such as high novelty or sensation seeking (Zuckerman 1990; Hegerl et al. 1995). Moreover, an association of high intensity dependence of sensory evoked potentials with drug use disorders was reported in early studies (Zuckerman 1972). Two previous studies demonstrated high intensity-dependence of auditory evoked potentials in ecstasy users, one of them with (Croft et al. 2001) and one without indication for an association of this finding with the extent of previous drug use (Tuchtenhagen et al.

2000). In our study, there were no significant correlations between serotonin-dependent personality traits and startle sensitization or any other startle parameter in ecstasy users. Nevertheless, an association of the relatively high sensitization (and low habituation) of the startle reflex in our sample of heavy ecstasy users with primary psychophysiological features that are related to proneness for drug use cannot be ruled out with certainty.

Needless to say, the concomitant amphetamine and cannabis use is an important confound in our study and most other open-field studies with populations of ecstasy users, which adds to the difficulties regarding the interpretation of our results. There is evidence that acute administration of amphetamines and cannabis affects startle modification, e.g. the indirect dopamine agonist amphetamine modulates acoustic startle reaction in animals and humans (overview by Swerdlow et al. 2003), and the non-selective cannabinoid receptor agonist CP 55940 has a blunting effect on PPI of the startle reflex in rats (Mansbach et al. 1996; Martin et al. 2003). Nevertheless, studies on the long-term effects of chronic administration of amphetamines or cannabis on startle behavior in humans have not been reported. Therefore, the long-term effects of the use of these drugs on startle plasticity remain to be elucidated.

In conclusion, heavy ecstasy users present with high sensitization of the acoustically elicited startle reflex. However, this finding appears to be unrelated to the extent of previous ecstasy use, and it may reflect preexisting psychophysiological features of this sample of ecstasy users, who were mostly poly-drug users. Hence, modulation of the startle reflex does not appear to be a reliable parameter for investigations into the functional consequences of ecstasy-related neurotoxicity in humans. In the future, more certainty about the relations between ecstasy use and startle modification may be obtained from longitudinal investigations.

Acknowledgements This work was supported by a grant of the German Research Foundation (Deutsche Forschungsgemeinschaft; DFG) to E. Gouzoulis-Mayfrank (DFG GO 717/4-1). The authors thank Bianca Till, Gernot Hensen and Bastian Thimm for their support in recruiting the participants of this study. M.A. Geyer has an equity interest in San Diego Instruments, Inc.

References

Barrat ES (1985) Impulsiveness subtraits: arousal and information processing. In: Spence JT, Izard CE (eds) Motivation, emotion, and personality. Elsevier, North Holland, pp 137–146

Bhattachary S, Powell JH (2001) Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or "ecstasy": evidence for cognitive impairment. Psychol Med 31:647–658

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

Braff DL, Grillon C, Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry 49:206–215

Braff DL, Geyer MA, Light GA, Sprock J, Perry W, Cadenhead KS, Swerdlow NR (2001a) Impact of prepulse characteristics on the detection of sensorimotor gating deficits in schizophrenia. Schizophr Res 49:171–178

Braff DL, Geyer MA, Swerdlow NR (2001b) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234–258

Burrell BD, Sahley CL (1999) Serotonin depletion does not prevent intrinsic sensitization in the leech. Learn Mem 6:509–520

Carrillo-de-la-Pena MT (1992) ERP augmenting/reducing and sensation seeking: a critical review. Int J Psychophysiol 12:211–220

Croft RJ, Klugman A, Baldeweg T, Gruzelier JH (2001) Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. Am J Psychiatry 158:1687–1692

Daumann J, Fimm B, Willmes K, Thron A, Gouzoulis-Mayfrank E (2003) Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study. Cognit Brain Res16:479–487

Davis M, File SE (1984) Intrinsic and extrinsic mechanisms of habituation and sensitization: Implications for the design and analysis of experiments. In: Peeke HVS, Petrinovich LF (eds) Habituation, sensitization and behavior. Academic Press, New York, pp 287–323

Davis M, Heninger GR (1972) Comparison of response plasticity between the eyeblink and vertex potential in humans. Electroencephalogr Clin Neurophysiol 33:283–293

Davis M, Sheard MH (1976) *p*-Chloroamphetamine (PCA): acute and chronic effects on habituation and sensitization of the acoustic startle response in rats. Eur J Pharmacol 35:261–273

Duncan E, Madonick S, Chakravorty S, Parwani A, Szilagyi S, Efferen T, Gonzenbach S, Angrist B, Rotrosen J (2001) Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology 156:266–272

Ehrlich JS, Boulis NM, Karrer T, Sahley CL (1992) Differential effects of serotonin depletion on sensitization and dishabituation in the leech, *Hirudo medicinalis*. J Neurobiol 23:270–279

Filion DL, Dawson ME, Schell AM (1998) The psychological significance of human startle eyeblink modification: a review. Biol Psychol 47:1-43

Fischer C, Hatzidimitriou G, Wlos J, Katz J, Ricaurte G (1995) Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (±)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). J Neurosci 15:5476–5485

Geyer MA, Tapson GS (1988) Habituation of tactile startle is altered by drugs acting on serotonin-2 receptors. Neuropsychopharmacology 1:135–147

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156:117–154

Gouzoulis-Mayfrank E, Heekeren K, Thelen B, Lindenblatt H, Kovar KA, Sass H, Geyer MA (1998) Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behav Pharmacol 9:561–566

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H (2000) Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry 68:719–725

Gouzoulis-Mayfrank E, Daumann J, Sass H (2002) [Chronic neurotoxic damage in ecstasy (MDMA) users. Review of the current state of research]. [German]. Nervenarzt 73:405–421

Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J (2003) Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. Prog Neuropsychopharmacol Biol Psychiatry (in press)

Groves PM, Thompson RF (1970) Habituation: a dual-process theory. Psychol Rev 77:419–450

Hatzidimitriou G, McCann UD, Ricaurte GA (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven

years previously: factors influencing abnormal recovery. J Neurosci 19:5096–5107
Hawkins RD, Kandel ER, Siegelbaum SA (1993) Learning to modulate transmitter release: themes and variations in synaptic plasticity. Annu Rev Neurosci 16:625–665
Hegerl U, Juckel G (1993) Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatry 33:173–187
Hegerl U, Gallinat J, Mrowinski D (1995) Sensory cortical processing and the biological basis of personality. Biol Psychiatry 37:467–472
Hutchison KE, Wood MD, Swift R (1999) Personality factors moderate subjective and psychophysiological responses to *d*-amphetamine in humans. Exp Clin Psychopharmacol 7:493–501
Kehne JH, Padich RA, McCloskey TC, Taylor VL, Schmidt CJ (1996) 5-HT modulation of auditory and visual sensorimotor gating: I. Effects of 5-HT releasers on sound and light prepulse inhibition in Wistar rats. Psychopharmacology 124:95–106
Koch M (1999) The neurobiology of startle. Prog Neurobiol 59:107–128
Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR (1992) Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? Am J Drug Alcohol Abuse 18:331–341
Kumari V, Checkley SA, Gray JA (1996) Effect of cigarette smoking on prepulse inhibition of the acoustic startle reflex in healthy male smokers. Psychopharmacology 128:54–60
Mansbach RS, Rovetti CC, Winston EN, Lowe JA, III (1996) Effects of the cannabinoid CB1 receptor antagonist SR141716A on the behavior of pigeons and rats. Psychopharmacology 124:315–322
Martin RS, Secchi RL, Sung E, Lemaire M, Bonhaus DW, Hedley LR, Lowe DA (2003) Effects of cannabinoid receptor ligands on psychosis-relevant behavior models in the rat. Psychopharmacology 165:128–135
Martinez DL, Geyer MA (1997) Characterization of the disruptions of prepulse inhibition and habituation of startle induced by alpha-ethyltryptamine. Neuropsychopharmacology 16:246–255
McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA (1998) Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. Lancet 352:1433–1437
McCann UD, Eligulashvili V, Ricaurte GA (2000) (±)3,4-Methylenedioxymethamphetamine ("ecstasy")-induced serotonin neurotoxicity: clinical studies. Neuropsychobiology 42:11–16
Morgan MJ (1999) Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 141:30–36
Ornitz EM, Guthrie D (1989) Long-term habituation and sensitization of the acoustic startle response in the normal adult human. Psychophysiology 26:166–173
Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268
Phillips MA, Oxtoby EK, Langley RW, Bradshaw CM, Szabadi E (2000) Effects of acute tryptophan depletion on prepulse inhibition of the acoustic startle (eyeblink) response and the N1/P2 auditory evoked response in man. J Psychopharmacol 14:258–265
Prinssen EP, Assie MB, Koek W, Kleven MS (2002) Depletion of 5-HT disrupts prepulse inhibition in rats: dependence on the magnitude of depletion, and reversal by a 5-HT precursor. Neuropsychopharmacology 26:340–347
Reneman L, Lavalaye J, Schmand B, de Wolff FA, van Den BW, den Heeten GJ, Booij J (2001) Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. Arch Gen Psychiatry 58:901–906
Ricaurte GA, Martello AL, Katz JL, Martello MB (1992) Lasting effects of (±)-3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. J Pharmacol Exp Ther 261:616–622
Ricaurte GA, Yuan J, McCann UD (2000) (+/-)3,4-Methylenedioxymethamphetamine ("ecstasy")-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology 42:5–10
Rodgers J (2000) Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology 151:19–24
Sipes TA, Geyer MA (1994) Multiple serotonin receptor subtypes modulate prepulse inhibition of the startle response in rats. Neuropharmacology 33:441–448
Sipes TA, Geyer MA (1995) 8-OH-DPAT disruption of prepulse inhibition in rats: reversal with (+)WAY 100,135 and localization of site of action. Psychopharmacology 117:41–48
Sipes TE, Geyer MA (1996) Functional behavioral homology between rat 5-HT_{1B} and guinea pig 5-HT_{1D} receptors in the modulation of prepulse inhibition of startle. Psychopharmacology 125:231–237
Swerdlow NR, Stephany N, Wasserman LC, Talledo J, Shoemaker J, Auerbach PP (2003) Amphetamine effects on prepulse inhibition across-species: replication and parametric extension. Neuropsychopharmacology 28:640–650
Thompson RF, Spencer WA (1966) Habituation: a model phenomenon for the study of neuronal substrates of behavior. Psychol Rev 73:16–43
Tuchtenhagen F, Daumann J, Norra C, Gobbele R, Becker S, Pelz S, Sass H, Buchner H, Gouzoulis-Mayfrank E (2000) High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 22:608–617
Vollenweider FX, Remensberger S, Hell D, Geyer MA (1999) Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. Psychopharmacology 143:365–372
Zakzanis KK, Young DA (2001) Memory impairment in abstinent MDMA ("ecstasy") users: a longitudinal investigation. Neurology 56:966–969
Zuckerman M (1972) Drug usage as one manifestation of a "sensation-seeking" trait. In: Keup W (ed) Drug abuse: current concepts and research. Charles C. Thomas, Springfield, Ill., pp 154–163
Zuckerman M (1990) The psychophysiology of sensation seeking. J Person 8:313–345
Zuckerman M, Eysenck S, Eysenck HJ (1978) Sensation seeking in England and America: cross-cultural, age, and sex comparisons. J Consult Clin Psychol 46:139–149
Zuckerman M, Simons RF, Como PG (1988) Sensation seeking and stimulus intensity as modulators of cortical, cardiovascular, and electrodermal response: a cross-modality study. Person Indiv Diff 9:361–372