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Intensity dependence of auditory evoked dipole source activity in polydrug ecstasy users: evidence from an 18 months longitudinal study

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Abstract

Numerous animal studies have been able to demonstrate neurotoxic damage to central serotonergic systems after exposure to 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). It has been suggested that a high loudness dependence of auditory evoked potentials (LDAEP) and, particularly, of the tangential N1/P2 source activity is associated with a low functioning of serotonergic activity. Therefore, the LDAEP may be used as a non-invasive indicator for a possible neurotoxic damage caused by the long-term use of ecstasy in recreational users. We recorded auditory evoked potentials (AEP) with a passive listening paradigm in 18 polydrug ecstasy users at baseline (t_1) and after 18 months (t_2). Several aspects of ecstasy use, such as frequency of use, cumulative lifetime dose or period of abstinence were associated with the LDAEP for several tangential dipoles at both measuring times. However, we failed to demonstrate any significant relationship between drug use reported at follow-up and AEP changes from baseline to follow-up. Despite some incertitude these data suggest, yet do not unambiguously confirm, the hypothesis that abstinent ecstasy users present with diminished central serotonergic activity. This feature of information processing is potentially related to the neurotoxic potential of ecstasy. However, alternative interpretations of these data refer to possible pre-existing traits and the potential impact of other illicit drugs, particularly amphetamine, since ecstasy users typically exhibit polydrug use patterns. Thus, further research with larger sample sizes and prospective study designs are needed to definitively establish a causative link between ecstasy use and neurotoxicity-related dysfunctions in sensory processing.

Keywords
auditory evoked potentials, ecstasy, MDMA, neurotoxicity, serotonin

Introduction

The popular recreational drug (±)3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is a serotonergic neurotoxin in animals. High and/or repeated doses of MDMA lead to widespread reductions of serotonin (5-HT), its metabolite 5-Hydroxyindoleacetic acid (5-HIAA) and 5-HT transporter binding in brain tissue of rats and non-human primates (Battaglia *et al.*, 1987; Schmidt, 1987; Ricaurte *et al.*, 1992, 2000). 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, 2005; Reneman *et al.*, 2001). 5-HT 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 (Green *et al.*, 2003). So far, the most consistent findings have been dose-related impairments of learning and memory performance (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). However, at this stage, the linkage between ecstasy use and memory decline cannot be considered fully proven, since cross-sectional open trial studies with user populations and controls suffer from inherent methodological problems and confounding variables such as polydrug use patterns, uncertain dosage, purity and chemical composi-

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tion of the illegally purchased drugs, and different motivational levels, life styles, cognitive strategies and premorbid performance levels (review in Curran, 2000).

Recent studies suggest that electrophysiological measures of sensory processing may be used to obtain an indirect indication of central serotonergic neurotransmitter malfunctions. One method relates to the loudness dependence of early cortical components of auditory evoked potentials with a strong dependence in terms of more robust increase of the amplitude with louder stimuli indicating a low serotonergic innervation tonus and vice versa (Hegerl and Juckel, 2000). This association is supported by converging arguments from preclinical and clinical studies. For example, early studies showed that 5-HT serum levels in depressive patients correlated negatively with the intensity dependence of the auditory evoked N1/P2 component (Hegerl *et al.*, 1991). In addition, a high intensity dependence of the auditory evoked N1/P2 component predicted good clinical response to serotonin agonists in clinical populations (Hegerl *et al.*, 2001). Furthermore, the auditory evoked N1/P2 component and, particularly, its tangential dipole source activity increased strongly with higher stimulus intensities in persons with personality traits thought to be associated with diminished serotonergic activity such as high novelty or sensation seeking (Zuckerman, 1990; Juckel *et al.*, 1995; Hegerl *et al.*, 1995a, b). Finally, in a more recent study the loudness dependence of auditory evoked potentials correlated with the serotonin transporter availability in patients with obsessive-compulsive disorder (Pogarell *et al.*, 2004).

To date two cross-sectional studies have established an increased intensity dependence of auditory evoked potentials in ecstasy users compared to control groups (Tuchtenhagen *et al.*, 2000; Croft *et al.*, 2001). However, an association of the intensity dependence with the extent of previous ecstasy use was shown only in one of these two studies (Croft *et al.*, 2001). Given the cross-sectional designs of both prior auditory evoked potentials (AEP) investigations in ecstasy users these findings should be considered preliminary since, it might be hypothesized that differences between ecstasy users and controls occurred only due to an accidental pre-existing low serotonergic innervation in ecstasy users. Hence, it remains unclear whether the electrophysiological abnormalities are actually attributable to ecstasy use. Furthermore, if in fact ecstasy use has caused the higher intensity dependence of AEP it is uncertain how this serotonergic marker changes during longer periods of prolonged use or abstinence from ecstasy. A suitable strategy to disentangle long-term sequelae of ecstasy use from pre-existing abnormalities and to investigate possible changes over time is the use of longitudinal study designs with user populations. Hence, the purpose of the present longitudinal study with a follow-up period of 18 months was to determine to what extent the intensity dependence of auditory evoked dipole source activity in polydrug ecstasy users persists, reverses or intensifies after prolonged use or abstinence. To our knowledge, this is the first longitudinal study on sensory evoked potentials in ecstasy users.

Methods

Participants

At baseline (t_1) 60 ecstasy users were initially recruited directly in the dance scene by students who were involved in the study, via word-of-mouth and via the Internet. This sample was fully independent from the sample of a previous investigation of our group (Tuchtenhagen *et al.*, 2000). Concomitant use of other typical club drugs (amphetamines, cocaine, cannabis and LSD) was accepted. However, subjects were excluded if they reported substantial use of alcohol (defined as drunkenness occurring at a frequency of at least twice per month over 6 months or longer within the last 2 years), or regular use of other legal or illegal psychotropic drugs such as opiates and benzodiazepines (defined as use once per month or more frequently over 6 months or longer within the last 2 years). To initially construct a dipole source model for the auditory evoked potentials we recruited a control group consisting of 30 healthy persons who were matched for age, sex and level of education with the MDMA users. Controls had no previous or current history of alcohol or drug use other than moderate use of cannabis. Due to technical problems with the electroencephalographic (EEG) equipment and rejections because of artefacts we were unable to process the baseline data of 14 ecstasy users. Therefore, these users were not re-examined at t_2. Another 15 subjects moved without giving notice of their new address, four participants simply lost interest in the study, one subject served a sentence as a consequence of drug dealing and two subjects developed a manifest psychiatric disorder and were, therefore, excluded from the follow-up. From the remaining 24 subjects six data sets had to be rejected because of artefacts or deficient AEP recording. Finally, 18 data sets (15 male and three female subjects) were available for longitudinal analyses. At baseline the average age of these 18 subjects was 24.72 ± 3.75 years.

Procedure

For both baseline and follow-up all ecstasy users agreed to abstain from drug use for at least 7 days prior to the study with the exception of cannabis. Because daily moderate cannabis use was part of the life style of many subjects and because cannabis screens may remain positive for several weeks after the last use (thus making it impossible to verify reported abstinence) we accepted that most subjects would only abstain from cannabis on the study day. Drug screens were performed on the study day with urine samples for stimulant amphetamines, methylenedioxyamphetamines (ecstasy), cocaine and its metabolite, marijuana, benzodiazepines, barbiturates and opiates. All subjects underwent a structured interview according to the DSM-IV (SCID). In addition, we took a medical history and detailed history of drug use. Exclusion criteria for all participants were: (1) a positive drug screen on the study day except for cannabis; (2) any current or previous axis I psychiatric diagnosis except for drug abuse in the user group; and (3) any organic brain disorder or relevant general medical condition requiring pharmacological treatment.

Auditory evoked potentials with a passive listening paradigm

were recorded using a Neuroscan EEG recording system with a 32-channel preamplifier. The 33 Ag^+/Cl^- scalp electrodes were applied using a modified 10/20 scheme with Fz as reference. Transition resistance was less than 10 kΩ. Recordings were performed in a sound-attenuated and darkened room. Subjects were seated in a comfortable chair and were instructed to relax, but keep their eyes open and listen passively to the acoustic stimuli without paying special attention to them. After detailed description of the study to the subjects, written informed consent was obtained and subjects were paid for their participation. Stimuli consisted of sinus tones of 1 kHz frequency and 30 ms duration with a rise and fall time of 10 ms. Tones were presented binaurally with a closed headphone (Phillips SBC 484). Interstimulus intervals were randomized between 1.5 and 2.5 s. Stimuli of 60, 70, 80 and 90 db were presented continuously in randomized order. Recordings were performed continuously. The study was in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee at the RWTH Aachen.

Data processing and statistical analyses

Changes in drug use patterns during the follow-up period were analysed by means of paired t-tests. Raw AEP data were imported into BESA 2000 software (MEGIS, Munich, Germany). Continuous data were separated into epochs of a 600 ms time interval per stimulus with a 200-ms pre-stimulus interval. A low cut-off filter (0.2 Hz, 6 db/oct slope) was used to reduce slow activities. After excluding all epochs containing eye blink artefacts, data for each channel were averaged. For source deconvolution, a three shell spherical head model assuming a scalp thickness of 6 mm (0.33 [1/(Ωm)]), a skull thickness of 7 mm (0.0042 [1/(Ωm)]) and a conductivity of the brain of 0.33 [1/(Ωm)] was applied. On the basis of the grand average data of the control subjects, a source model was constructed consisting of two pairs of tangential and radial dipoles placed symmetrically in the region of the auditory cortex (see Fig. 1). Dipole source analysis is considered a methodological advance in this context, because the two N1/P2-subcomponents, generated by the primary and secondary auditory cortex, can be separated. According to studies of dipole source analysis (Scherg *et al.*, 1989; Scherg, 1991), the tangentially oriented dipole of the N1/P2 component of AEP represents mainly the activity of the primary auditory cortex; whereas, the radially oriented dipole represents the activity of the secondary auditory cortex in the more lateral part of the temporal lobe (Hegerl *et al.*, 1994). Although serotonergic fibres from the raphe nuclei project to virtually every brain area, relatively high rates of serotonergic innervation have been found in the primary sensory cortex; whereas, serotonergic innervation in the secondary sensory areas is clearly lower (Takeuchi and Sano, 1983; Azmitia and Gannon, 1986; Morrison and Foote, 1986; Campbell *et al.*, 1987; Lewis *et al.*, 1987). Based on these considerations, it has been suggested that the intensity dependence of the tangential auditory evoked N1/P2 source activity is a more sensitive electrophysiological measure of the serotonergic innervation of the cerebral cortex than the amplitude of the entire N1/P2 component (Hegerl *et al.*, 2001).

The amplitudes of the major deflections of the tangential source activities were determined and entered into a repeated measures analysis of variance. In order to obtain information about the impact of ecstasy use patterns during the follow-up period parameters of drug use (cumulative dose, average number of sessions per month, average single dose and days passed since last use) were used as within-subject covariates. For exemplification we, additionally, calculated the ascending slope median (ASM, sum of all possible amplitude differences/6) for each tangential dipole at both measuring times. The ASM and the Δ ASM (ASM (t_1) − ASM (t_2)) for each tangential dipole were, then, correlated with drug use patterns reported at t_1 and during the 18 months follow-up period. All procedures were performed using SPSS Version 11.0 (SPSS Inc., Chicago, Ill).

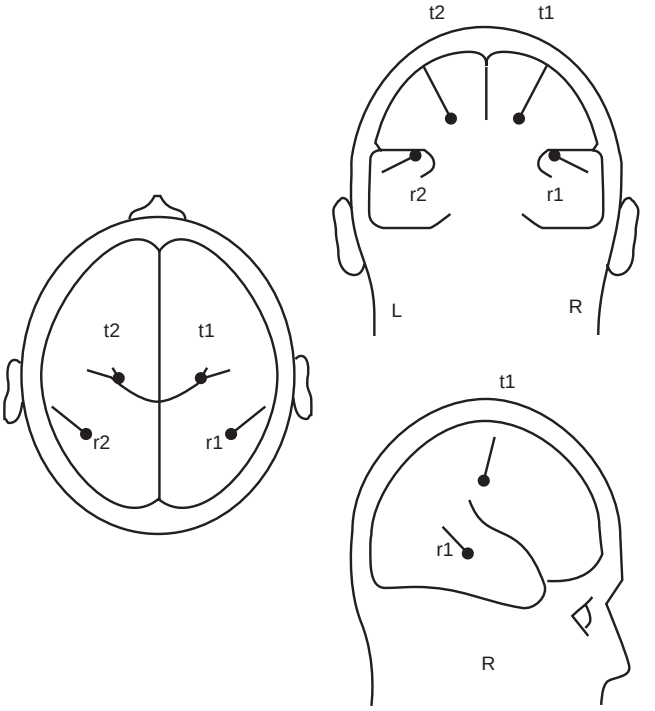

Figure 1 Source model, consisting of two pairs of tangential (t) and radial dipoles (r) placed symmetrically in the region of the auditory cortex

Results

Drug histories

The patterns of drug use at baseline (t_1) and during the follow-up period (t_2) are presented in Table 1. During the follow-up period ecstasy users had reduced their single ecstasy dose ($p = 0.015$, $t = 2.697$) and reported a longer period of abstinence from ecstasy ($p = 0.010$, $t = -2.880$). Four subjects reported complete abstinence from ecstasy over the follow-up period, five users took ecstasy only occasionally (one to ten pills) and nine subjects con-

Table 1 Patterns of ecstasy, cannabis and amphetamine use in polydrug ecstasy users ($n = 18$) at baseline (t_1) and during the 18 months follow-up period (t_2) (mean $\pm$ standard deviation)

	Reported use at baseline (t1)			Reported use during follow-up period (from t_1 to t_2)		
	Ecstasy	Amphetamine	Cannabis	Ecstasy	Amphetamine	Cannabis
Regular/sporadic/no use	18/0/0	10/3/5	14/4/0	9/3/6	2/7/9	9/6/3
Lifetime/Interim dose	271.39 $\pm$ 494.83 tablets	56.75 $\pm$ 124.24 g	X	23.78 $\pm$ 35.42 tablets	9.18 $\pm$ 24.00 g	X
Duration of regular use (months)	32.33 $\pm$ 30.69	18.33 $\pm$ 19.38	58.33 $\pm$ 39.03	7.44 $\pm$ 8.68	5.89 $\pm$ 22.25	12.78 $\pm$ 8.20
Average frequency of use (days per month)	2.11 $\pm$ 1.62	5.33 $\pm$ 7.12*	15.83 $\pm$ 12.88	1.38 $\pm$ 3.38	0.77 $\pm$ 1.38*	12.11 $\pm$ 12.43
Average daily or one night dose	2.17 $\pm$ 1.90 tablets*	325.01 $\pm$ 297.64 mg	592.05 $\pm$ 139.54 mg	0.97 $\pm$ 0.80 tablets*	175.00 $\pm$ 267.47 mg	502.94 $\pm$ 688.62 mg
Age at onset of use	19.83 $\pm$ 2.99	19.13 $\pm$ 3.42	15.29 $\pm$ 1.98	–	–	–
Time since last dose (days)	218.33 $\pm$ 419.46*	198.31 $\pm$ 329.867	1.86 $\pm$ 2.18	386.39 $\pm$ 614.27*	36.11 $\pm$ 55.71	20.80 $\pm$ 63.57

Abbreviations: X – subjects felt that they were unable to give a reliable estimate, * – significant differences between reported use at baseline (t_1) and follow-up (t_2) (paired t-test, 2-tailed)

tinued using ecstasy regularly (>20 pills). Moreover, subjects had lowered their frequency of amphetamine use ($p = 0.015$, $t = 2.697$). Cannabis use patterns did not change significantly. Regular use of any other psychotropic drug was not reported.

Loudness dependence of auditory evoked potentials (LDAEP)

Amplitudes of the left and right tangential dipole for baseline and follow-up are given in Fig. 2. We found a significant main effect for stimulus intensity for all four tangential dipole amplitudes (baseline tangential left: $p < 0.0001$, $F = 18.44$; baseline tangential right: $p < 0.0001$, $F = 17.28$; follow-up tangential left $p = 0.010$, $F = 5.37$; follow-up tangential right: $p = 0.017$, $F = 4.65$), but no main effect for measuring time (t_1 vs. t_2) (tangential left: $p = 0.496$, $F = 0.52$; tangential right: $p = 0.953$, $F = 0.01$).

While in former longitudinal studies (e.g. Daumann *et al.*, 2004) we were able to unambiguously assign subjects to distinct subgroups of abstinent and continuing users, this was implausible in the present study. Nevertheless, we tried to follow the established statistical evaluation and initially applied t-statistics to our data. For this purpose, the group of ecstasy users was divided into nine subjects reporting complete abstinence or occasional ecstasy use (one to ten pills) over the follow-up period of 18 months and nine subjects who reported continued ecstasy use of at least 20 tablets. However, this analysis produced no significant results (data not shown). Subsequently, we conducted a repeated measures analysis of variance for the entire sample with parameters of drug use as within-subject covariates. For the left tangential dipole we found significant influences of the reported ecstasy use on the effect of stimulus intensity (lifetime cumulative dose at baseline: $p = 0.012$, $F = 4.85$; duration of regular use at baseline: $p = 0.021$, $F = 4.13$; frequency of use at baseline: $p = 0.009$, $F = 5.19$; average single dose at baseline: $p = 0.034$, $F = 3.58$; interim cumulative dose during follow-up period: $p = 0.049$, $F = 3.18$; frequency of use during follow-up period: $p = 0.011$, $F = 5.00$; duration of regular use during follow-up period: $p = 0.008$. $F = 5.45$). We found no significant interaction between ecstasy use

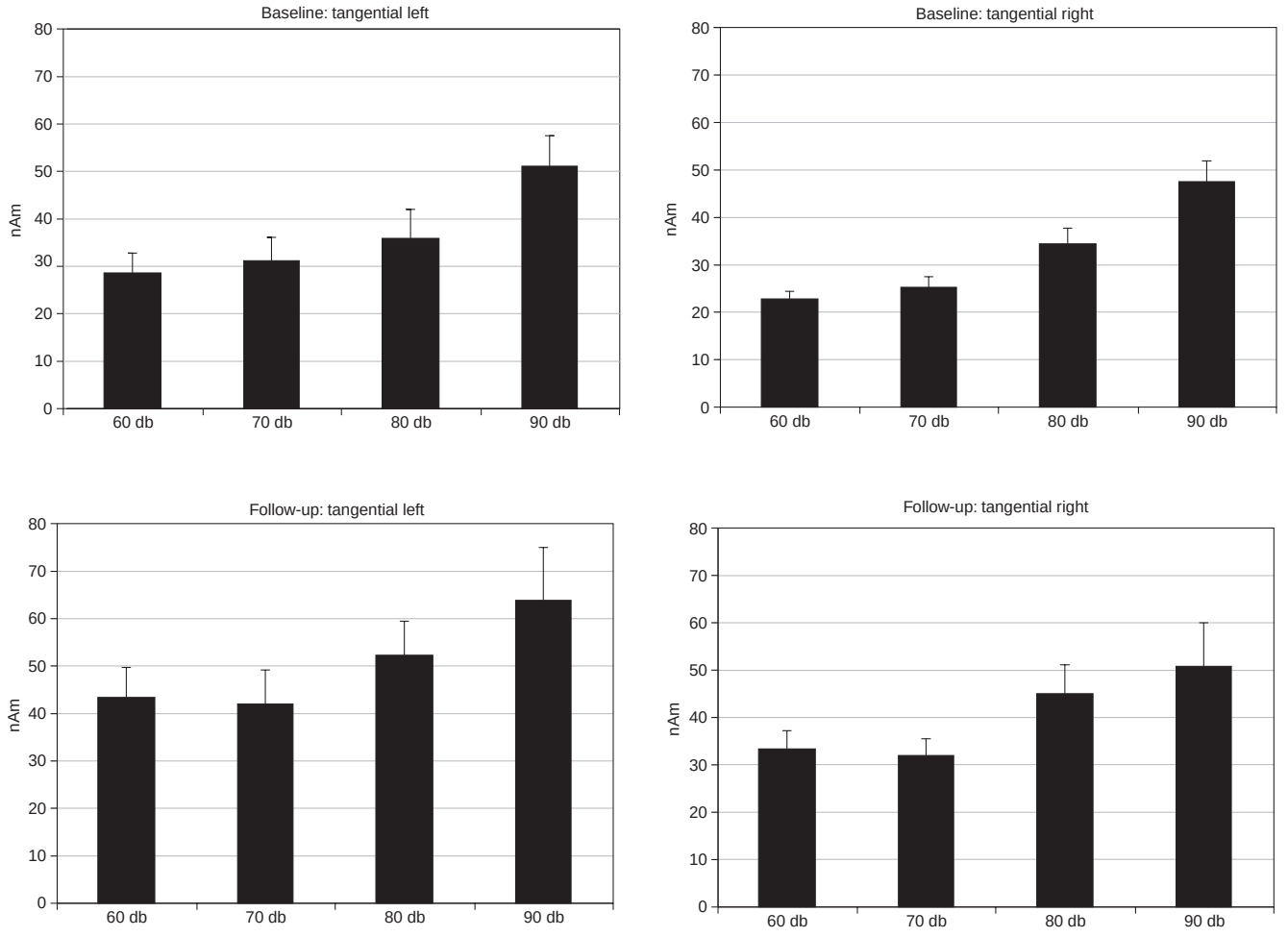

Figure 2 Mean amplitudes and standard error of means of the tangential dipole source activities of the auditory evoked N1/P2 component (nAm) in ecstasy users ($n = 18$) at baseline (t_1) and follow-up (t_2)

parameters and the amplitude of the right tangential dipole. Finally, regarding ecstasy we found no effects in terms of stimulus intensity × measuring time × drug use interactions. With regard to amphetamine use we observed a significant influence of the reported baseline cumulative dose on the effect of stimulus intensity for the right dipole ($p = 0.013$, $F = 4.46$). For the left dipole we found a significant interaction in terms of stimulus intensity × measuring time × average follow-up single dose ($p = 0.021$, $F = 3.91$). Cannabis use parameters had no influence at the chosen statistical threshold.

Correlation analyses between ecstasy use patterns and the ascending slope median (ASM) of the tangential dipoles revealed a significant association of frequency of use (t_1) and the left ASM (t_1) ($r = 0.569$, $p = 0.014$). Furthermore, for the right tangential dipole we found several significant correlations with the pattern of ecstasy use (age at onset of use (t_1): $r = -0.484$, $p = 0.42$; lifetime dose (t_1): $r = 0.652$, $p = 0.003$; average one-night dose (t_2): $r = 0.592$, $p = 0.010$; time since last dose (t_2): $r = -0.498$, $p = 0.036$; frequency of use (t_2): $r = 0.594$, $p = 0.009$). In addition, the ASM for the latter dipole was correlated with lifetime amphetamine use (t_1) ($r = 0.599$, $p = 0.009$). Again, we found no significant influence of cannabis use patterns. Finally, Δ ASM scores showed no significant correlations with drug use patterns.

Discussion

The aim of the present investigation was to explore the impact of the use of the serotonergic neurotoxin MDMA (ecstasy) on the loudness dependence of auditory evoked potentials (LDAEP), which is considered as an index of serotonergic neurotransmission in the brain. We examined and followed-up 18 recreational polydrug ecstasy users over a period of 18 months. In order to separate the tangential dipole of the N1/P2 component from the radial dipole, a dipole source analysis was performed. The tangential dipole represents the highly serotonergically innervated primary sensory cortex, whereas the less densely serotonergically innervated secondary sensory cortex is represented by the radial dipole (Hegerl *et al.*, 1994). According to our hypothesis, we expected the LDAEP of the tangential dipoles to be higher with heavy and more frequent ecstasy use. Moreover, we hypothesized that the LDAEP may change during the follow-up period depending on altered drug use patterns.

Over the follow-up period one half of our sample reported complete abstinence from or only occasional use of ecstasy (<10 pills); the other half continued using ecstasy regularly (>20 pills). For the entire sample we found a significant effect for stimulus intensity for all tangential dipoles, but without any significant changes over the follow-up period. Abstinent/occasional users did not differ from continuing users in terms of LDAEP or its change over time. This might be explicable by the fact that on the basis of the reported ecstasy use during the follow-up period subjects were not unambiguously assignable to distinct subgroups of abstinent and continuing users. Hence, we decided to conduct a repeated measures analysis of variance for the entire sample with parameters of drug use as within-subject covariates. According to this analysis, several aspects of ecstasy use, such as frequency of use, cumulative lifetime dose or period of abstinence were found to be associated with the LDAEP for several tangential dipoles. This feature of information processing may be related to the well-recognized neurotoxic potential of ecstasy. This interpretation is in line with both prior AEP studies. Croft and co-workers (2001) found higher stimulus intensity dependence in 22 long term ecstasy users compared to 19 cannabis users and 20 drug-naive controls. This dysfunction was related to the cumulative dose, but not to the frequency of use. Croft and co-workers (2001) interpreted these results as strong evidence for a causative link between MDMA use and 5-HT dysfunction, since regular self-medication should not be sufficient to explain this pattern of correlations. In a previous study by our own research group 28 abstinent MDMA users showed a higher LDAEP in the tangential dipole source activity of the auditory evoked N1/P2 component compared to two matched control groups consisting of drug-naive persons and regular users of cannabis (Tuchtenhagen *et al.*, 2000). However, in this former study we found no correlation between the intensity dependence of the evoked potentials and the amount of ecstasy use. While in this former study we were limited to present the acoustic stimuli in blocks of ascending intensity, we were now able to use a randomized presentation of stimuli of different intensities. According to a study by Carillo-de-la-Pena (1998) randomized stimulus presentations produce higher amplitudes in the high intensity levels than ascending or descending block presentations. This effect may be due to a lower degree of habituation with randomized presentation of stimuli (Juckel *et al.*, 1995). Hence, the randomized stimulus presentation might have caused a higher degree of variance in the present data making it possible to detect significant associations with independent variables such as drug use. Thus, in terms of significant associations between the LDAEP and drug use patterns with the present study we were able to provide the first replication of the study by Croft *et al.* (2001) likely due to an improved stimulus presentation compared to our previous study (Tuchtenhagen *et al.*, 2000). Interestingly, Croft and co-workers (2001) were able to distinguish the influence of frequency of use and the cumulative lifetime dose of ecstasy, since both parameters were unrelated. However, in our study both usage indices were correlated (t_1: $r = 0.564$, $p = 0.015$; t_2: $r = 0.423$, $p = 0.080$) and therefore, it was implausible to disentangle them.

Despite the finding of general associations between the extent of ecstasy use and LDAEP we failed to demonstrate any significant relationship between drug use reported at follow-up and changes of the LDAEP from baseline to follow-up. If the LDAEP in ecstasy users was neurotoxicity-related then we would expect the neurotoxic effect and its functional consequences to increase with continued use or decrease with abstinence. Hence, the present data may be interpreted as evidence *against* MDMA-related neurotoxicity in ecstasy users. For example, it might be hypothesized that the observed association between ecstasy use and information processing reflects a pre-existing characteristic feature of information processing in ecstasy users. Evidence from both older and more recent work suggests a relationship between LDAEP and distinct personality traits such as high sensation seeking, novelty seeking, extraversion, impulsivity and psychopathy (Lukas, 1987; Barratt *et al.*, 1987; Zuckerman *et al.*, 1988; Stenberg *et al.*, 1988;

Raine, 1989; Zuckerman, 1990; Carillo-de-la-Pena, 1992; Hegerl and Juckel, 1993; Hegerl *et al.*, 1994, 1995a, b; Juckel *et al.*, 1995). Within the *augmenting/reducing* concept first proposed by Buchsbaum and Silverman (1968) a high intensity dependence (*augmenting*) of sensory evoked activity is viewed as reflecting a central mechanism regulating neuronal sensitivity and providing the organism with an optimal level of sensory stimulation. Moreover, a relationship between high intensity dependence of sensory evoked potentials and the development of drug or alcohol abuse has been discussed in the older literature (Zuckerman, 1972). Hence, the associations between LDAEP and extent of MDMA use in our sample of ecstasy users might reflect a predisposing factor for the development of drug use in general, rather than a consequence of the use of ecstasy. However, we found no significant influence of cannabis use and, compared to ecstasy use, only a minor influence of amphetamine use providing strong evidence against the concept of a high LDAEP solely reflecting a pre-existing trait factor for the onset of drug use per se. Furthermore, it might be hypothesized that in our sample the amount of ecstasy used by our sample during the 18 months follow-up period was not sufficient to worsen the already existing MDMA-induced serotonergic deficit. Moreover, altered stimulus processing in ecstasy users may emerge relatively early after the onset of regular MDMA use and persist even after 18 months of abstinence. This interpretation would be in line with primate studies which showed that regeneration of serotonergic axons may take very long and may remain incomplete (Hatzidimitriou *et al.*, 1999). Interestingly, recent positron emission tomography (PET) studies using 5-HT transporter ligands provided some evidence for recovery of ecstasy-induced alterations of the serotonergic system in former users (Reneman *et al.*, 2001; Buchert *et al.*, 2004; McCann *et al.*, 2005). However, given the cross-sectional design of these studies, the question of recovery of the serotonergic system after prolonged periods of abstinence from ecstasy use is still unanswered.

Although the longitudinal design of this investigation might help to overcome some methodological shortcomings of open-trial studies there are still limitations that should be acknowledged. While a few years ago we were able to recruit a reasonable number of ecstasy users with concomitant use of cannabis only (e.g. Gouzoulis-Mayfrank *et al.*, 2000), this was impossible in the present study. Both at baseline and follow-up several subjects reported regular concomitant use of cannabis and stimulant amphetamines. Although analyses mainly revealed associations between evoked potentials and ecstasy use, the use of amphetamine may also play a role. (Meth-)amphetamine has been shown to induce neurotoxicity with depletion of dopamine and serotonin as well as damage of dopaminergic and serotonergic nerve terminals (Kita *et al.*, 2003). Thus, we cannot rule out the possibility that concomitant use of amphetamine might have influenced our data. Another fundamental problem of virtually every open-field study with user populations derives from the fact that the drug history was assessed by self-reports and, therefore, may contain inaccuracies. At least, subjects were interviewed about their drug histories without knowledge of the precise inclusion and exclusion criteria, and they had no motivation to falsify their data consciously. Furthermore, previous studies with similar designs suggested that self-reports of illicit drug use are fairly reliable (Brown *et al.*, 1992; Harrison *et al.*, 1993). Finally, data rejection because of artefacts, deficient AEP recording and the high drop-out rate during the follow-up period result in a relatively small sample size. Through this, alpha levels were not Bonferroni-adjusted. Thus, the statistical power of the present study is limited.

Taken together and despite some incertitude our data along with previous studies (Tuchtenhagen *et al.*, 2000; Croft *et al.*, 2001) suggest that ecstasy use appears to be associated with alterations in information processing. This alteration is possibly related to the well-recognized neurotoxic potential of MDMA, which is restricted to the serotonergic system. However, crucial limitations and alternative interpretations of our data refer to potential pre-existing traits and to the possible impact of other illicit drugs, particularly amphetamine, since ecstasy users typically exhibit polydrug use patterns. Further research with larger sample sizes and longitudinal as well as prospective designs is needed to definitively establish a causative link between ecstasy use and neurotoxicity-related dysfunctions in sensory processing.

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