

Specific neurotoxicity of chronic use of ecstasy

J. Obrocki ^{a,*}, A. Schmoldt ^b, R. Buchert ^c, B. Andresen ^a, K. Petersen ^a,
R. Thomasius ^a

^a Department of Psychiatry and Psychotherapy, University Hospital Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

^b Department of Legal Medicine, University Hospital Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

^c Department of Nuclear Medicine, University Hospital Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Abstract

The use of the illicit drug ecstasy (mainly containing methylenedioxymethamphetamine, MDMA) is widespread among young people in western Nations. Animal experiments indicate that MDMA is a potent neurotoxin specifically affecting the serotonergic system. A few functional neuroimaging studies revealed central nervous alterations after the repeated use of ecstasy. We examined 94 ecstasy users in comparison to 27 control subjects by means of positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG). The FDG uptake rates were globally reduced in ecstasy users, most pronounced in the striatum. The uptake rates tended to be negatively correlated with the cumulative ecstasy doses. The results indicate that younger ecstasy users may be more vulnerable with regard to neurotoxicity. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Ecstasy is widely appreciated probably due to subjective effects like euphoria, empathy, peacefulness and intensification of sensory perception. Yet acute states of anxiety, depression, mistrust and deteriorated perception were reported as well (Gouzoulis-Mayfrank, 1999; Mørland, 2000). With regard to lasting effects most users seem to ignore the neurotoxic potential of the drug (Boot et al., 2000). The use of ecstasy may lead to transient (Series et al., 1994) and lasting (McGuire

and Fahy, 1991; Schifano, 1991) delusional disorder, depression (Benazzi and Mazzoli, 1991; McCann and Ricaurte, 1991), panic disorder (Pallanti and Mazzi, 1992; McCann and Ricaurte, 1992) and depersonalization disorder (Wodarz and Böning, 1993; McGuire et al., 1994). Apart from mediating personality traits (Schifano, 2000) these psychiatric disorders could be an expression of underlying neurotoxic lesions.

2. Neurotoxicity of amphetamine analogues

Since more than 30 years it is known that amphetamine and related substances are neurotoxic. Guinea pigs and rats treated with 4-chloro-

* Corresponding author. Tel.: +49-4121-7980; fax: +49-4121-798-785.

E-mail address: obrocki@uke.uni-hamburg.de (J. Obrocki).

N-methylamphetamine (PCMA) revealed reductions in serotonin and 5-hydroxyindole acetic acid (5-HIAA) (Pletscher et al., 1964). Sanders-Bush et al. (1972) found reduced levels of tryptophan hydroxylase (TPH), 5-HIAA and serotonin in rat brains after treatment with *p*-chloroamphetamine (PCA). Striatal concentrations of dopamin and tyrosine hydroxylase (TH) were decreased in rats after treatment with methamphetamine (Kogan et al., 1976). The TH activity was also reduced in the striatum after experimental administration of amphetamine (Ellison et al., 1978). Methylenedioxyamphetamine was shown to induce a loss of cerebral serotonin and 5-HIAA (Ricaurte et al., 1985). The depletions of these neuronal markers indicate neurotoxic lesions of serotonergic and dopaminergic systems. Early reports sparked a series of studies which led to the discovery that methylenedioxyamphetamine analogues were particularly toxic to brain serotonergic neurons (Ricaurte and McCann, 1992). Some of these analogues are recreationally abused [e.g. 3,4-methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDEA), *N*-methyl-3,4-methylenedioxyethylamphetamine (MBDB)] and may to a varying extent constitute the drug ecstasy (Gouzoulis-Mayfrank, 1999). MDMA, however, is widely regarded as its main or even sole ingredient.

3. Selective neurotoxicity of MDMA

Various animal studies have demonstrated that MDMA selectively affects the serotonergic system. Brain concentrations of TPH, 5-HIAA and serotonin were decreased in rats treated with MDMA whereas the concentrations of the dopaminergic markers TH and dopamine were not affected (Stone et al., 1986). Commins et al. (1987) found dose-dependent decreases of serotonin in hippocampus, hypothalamus, striatum and neocortex in rats treated with different doses MDMA (2×10 –40 mg/kg per 24 h on 4 days). Further studies led to similar results

(Mokler et al., 1987; Colado et al., 1992). After a single dose of MDMA the concentrations of serotonin and 5-HIAA were reduced by 30% in hippocampus and neocortex (Colado et al., 1992). The treatment with MDMA (2×20 mg/kg per 24 h for 4 days) led to a decrease of 5-HIAA by 30–60% in rat hippocampus, neocortex, striatum, hypothalamus and mid-brain. Additionally the paroxetine-labelled uptake sites were reduced by 50–75%. In contrast the concentrations of the catecholaminergic markers norepinephrine, dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid were not altered (Battaglia et al., 1987). Immunocytochemical studies revealed a lasting loss of serotonergic axons in the forebrain after MDMA treatment (40 mg/kg per 24 h for 4 days). Axons within the hippocampus, lateral hypothalamus and basal forebrain were only partially affected (O'Hearn et al., 1988).

4. Long-term studies

After treatment with 40 mg/kg per 24 h MDMA for 4 days rat brains revealed characteristic alterations 52 weeks later. Despite a partial normalization, serotonin concentrations were significantly reduced in frontoparietal and occipitotemporal cortex and hippocampus. Serotonin transporter binding was also reduced 52 weeks after MDMA administration as demonstrated by autoradiography (Sabol et al., 1996; Lew et al., 1996). In non-human primates concentrations of serotonin and 5-HIAA decreased in brain, spinal cord and cerebrospinal fluid after MDMA treatment (2×5 mg/kg per 24 h for 4 days) (Ricaurte et al., 1988a). Furthermore the density of immunoreactive serotonergic axons was reduced throughout the cortex. Serotonergic cell bodies within the dorsal raphe nucleus also revealed pathological alterations (Ricaurte et al., 1988b). The concentrations of serotonin, 5-HIAA and the serotonin transporter were decreased 18 months after MDMA treatment (Ricaurte et al., 1992). Following a partial recovery after 10 weeks the concentrations were markedly reduced in hippocampus, caudate and frontal cortex.

Within thalamus and hypothalamus, however, serotonin concentrations were elevated in comparison to control levels, possibly as an expression of pathological hyperinnervation in these structures. Even 7 years after MDMA treatment the density of immunoreactive serotonergic axons was reduced in monkey cerebral cortices (Hatzidimitriou et al., 1999).

5. Studies on humans

In an early investigation on the neurotoxicity of ecstasy in humans, there was no difference in cerebrospinal fluid concentrations of 5-HIAA between ecstasy users and control subjects (Peroutka et al., 1987). Price et al. (1989) investigated the prolactin concentration after intravenous administration of L-tryptophan, as a measure for the function of the serotonergic system. In comparison to the control group prolactin secretion was tendentially decreased in the ecstasy user group but the results statistically were not significant. In another study 5-HIAA concentrations in the cerebrospinal fluid from ecstasy users were found to be reduced by 26%. The authors pointed out that the reduction of 5-HIAA might be a consequence of the lesion of central serotonergic neurons, but that the effect was not necessarily specific since ecstasy users tend to use other illegal drugs as well (Ricaurte et al., 1990). In a further study 30 ecstasy users were compared with 28 control subjects (McCann et al., 1994). The control group included subjects with a history of substance abuse (except for ecstasy). In the ecstasy user group 5-HIAA levels were significantly reduced in cerebrospinal fluid. Prolactin concentrations after administration of L-tryptophan were similar in both groups. The stimulation of the serotonergic system with fenfluramine resulted in a significantly reduced release of cortisol and prolactin in ecstasy users after 3 weeks of abstinence. Twelve months later cortisol concentrations had normalized whereas the prolactin concentrations remained decreased (Gerra et al., 2000). This result might reflect a partial regeneration after 1 year of abstinence. In a

post mortem study of a single ecstasy user striatal levels of serotonin and 5-HIAA were reduced by 50–80% while dopamine concentrations were not affected (Kish et al., 2000). Chang et al. (1999) investigated a group of 21 ecstasy users in comparison to 37 control subjects by means of magnet resonance spectroscopy. They found elevated concentrations of myoinositol and interpreted the result as an expression of a reactive gliosis after neurotoxic lesion.

6. Functional neuroimaging

In a first study applying positron emission tomography (PET) with the specific serotonergic ligand McN-5256 in the living baboon brain serotonin transporter binding was decreased 40 days after MDMA exposure in all brain regions examined. After 9 and 13 months specific binding in the hypothalamus had increased above initial rates whereas it remained decreased in the neocortex (Scheffel et al., 1998). The same group (McCann et al., 1998) examined 14 ecstasy users and found a global and local reduction of serotonin transporter binding in comparison to a control group. The decrease was positively correlated with the lifetime ecstasy doses. In an own pilot study we examined seven ecstasy users by means of FDG PET (Obrocki et al., 1999). Compared with a control group glucose metabolic rates were reduced in hippocampus and striatum and increased in Brodmann's area 10 and 11. Semple et al. (1999) examined ten ecstasy users and ten control subjects who had taken other drugs than ecstasy, with single photon emission computed tomography (SPECT). Binding rate of the specific ligand [123I]β-CIT to the serotonin transporter was reduced in cortical regions of ecstasy users. Reneman et al. (2000) conducted a SPECT study with the postsynaptic 5-HT_{2A} receptor ligand [123I]-5-I-R91150. The binding rate was elevated as a possible expression of a serotonin receptor up-regulation following the lesion of serotonergic afferents. In a further SPECT study the regional cerebral blood flow

(rCBF) was reduced in a group of 21 ecstasy users but the results did not reach statistical significance (Chang et al., 2000). About 3 weeks after experimental administration of MDMA (2.25–4.75 mg/kg) rCBF was reduced in visual cortex, caudate, parietal and dorsolateral frontal cortex. After 2–3 months rCBF rose above initial values in the caudate and globus pallidus.

7. Neurotoxicology

MDMA exerts its effects in a time-dependent manner. Initially the serotonin release is increased via a competitive uptake mechanism, followed by a decrease of serotonin, 5-HIAA and TPH activity. The TPH activity remains decreased whereas the concentrations of serotonin and 5-HIAA normalize within 24 h followed by a long-term decrease subsequently. This decrease is associated with the loss of serotonergic terminals (McKenna and Peroutka, 1990). The neurotoxic effect can possibly be blocked by serotonin reuptake inhibitors, indicating the involvement of the serotonin transporter (Schmidt, 1987). As this effect only starts 6 h after MDMA exposure the neurotoxicity might be mediated by metabolites or endogenous substances. This hypothesis is supported by the finding that MDMA, directly injected into the brain did not seem to cause neurotoxic lesions (Paris and Cunningham, 1992). It is assumed that neurotoxicity is mediated by the formation of free radicals followed by a destruction of neuronal cell membranes (Colado and Green, 1995). The increased extracellular serotonin concentration may also contribute to a subsequent receptor mediated activation of glycogen phosphorylase from astrocytes, resulting in a pathological local, 'energy metabolism' in the vicinity of serotonergic synapses (Poblete and Azmitia, 1995). MDMA also affects non-serotonergic neurotransmitter systems (Battaglia et al., 1988; Burgess et al., 2000). Despite the dopaminergic system does not seem to be affected by MDMA-induced long-term neurotoxicity, extracellular dopamine concentrations may increase transiently (White et al., 1994). This effect possibly is mediated by the activation of 5-HT₂ het-

eroreceptors (Gudelsky et al., 1994) and, after high doses of MDMA, by an inhibition of dopamine reuptake. The surplus dopamine may be taken up into serotonergic nerve endings where it is deaminated by the monoamine oxidase B resulting in an increased formation of hydrogen peroxide and subsequently the destruction of neuronal membranes (Sprague and Nichols, 1995; Andresen and Schmoldt, 2000). Neurotoxic effects of MDMA were reduced after experimental inhibition of the dopaminergic system (Stone et al., 1988; Schmidt et al., 1990), whereas vegetative reactions remained unaffected (Liechti and Vollenweider, 2000). Within the hippocampus, however, the neurotoxic mechanism seems to be dopamine-independent (Shankaran and Gudelsky, 1998).

The activation of the GABAergic system might inhibit the release of dopamine leading to a reduction of dopamine-mediated neurotoxicity (reviewed in, Green et al., 1995). The administration of clomethiazole before and after MDMA exposure revealed a neuroprotective effect in neocortex and hippocampus (Colado et al., 1992). It is assumed that the increase of the GABAergic transmission might inhibit glutaminergic neurons followed by an inhibition of calcium-dependent cytotoxic proteases, which are activated, via *N*-methyl-D-aspartate (NMDA) receptors. Kramer et al. (1995) have shown that the protein kinase C is activated by MDMA. In isolated striatal tissue Schatz et al. (2000) demonstrated that MDMA is able to activate NMDA and dopamine D₂ receptors directly. As MDMA is probably demethylated through CYP 2D6 it was considered that different phenotypes, fast and slow metabolizers, might react differently to MDMA exposure (Tucker et al., 1994). Slow metabolizers, therefore, might be less prone to neurotoxic lesions due to the reduced formation of toxic metabolites but on the other hand might bear a higher risk in developing acute symptoms as a result of reduced MDMA metabolism. In seven cases of acute ecstasy intoxication, however, no correlation with slow CYP 2D6 metabolism was detected (O'Donohoe et al., 1998). It has to be assumed that several CYP 450 isoenzymes are involved in the metabolism of MDMA (Kreth et al., 2000)

and that mainly CYP-independent mechanisms may contribute to its degradation (Maurer et al., 2000). In summary the pathogenesis after MDMA exposure is not fully understood. Most probably it has to be regarded as a concerted action, with multiple transmitter systems involved (Fischer et al., 2000).

8. Neuropsychology

First studies on animal behavior did not lead to convincing results with regard to MDMA-induced neurotoxicity (Robinson et al., 1993). This might be the reason for the relative delay of neuropsychological studies on humans. A first attempt was made by Krystal et al. (1992) who hinted at possible memory deficits as a consequence of ecstasy use. Despite a marked increase in ecstasy consumption (Thomasius et al., 1997) it took another 5 years until neuropsychological testing was widely applied. From 1998 on several studies emanated (Bolla et al., 1998; Morgan, 1998, 1999; Parrott and Lasky, 1998; Parrott et al., 1998; Dafters et al., 1999; Semple et al., 1999; McCann et al., 1999; Andresen et al., 2000; Wareing et al., 2000) reporting statistically significant neurocognitive decrements of ecstasy users in comparison to ecstasy-naïve control subjects. Several studies attempted to control for the concomitant use of other drugs since ecstasy users tend to use other drugs than ecstasy (McGuire, 2000). Intelligence levels were also reduced in heavy ecstasy users (Gouzoulis-Mayfrank et al., 2000). The premorbid intelligence might have a moderating effect on neurocognitive performance after ecstasy abuse (Bolla et al., 1998). Yet, no convincing causal relations between neurochemical alterations and neuropsychological parameters have been established so far (McCann et al., 1999). The strongest neurotoxic impact may be assumed for memory decline and, clinically, drug-induced amnesic syndromes (Spatt et al., 1997; Thomasius, 2000). It seems plausible that the reported neurotoxic lesions may lead to cognitive impairments but it remains unresolved to what extent predisposing psychological factors might determine the extent of neurocognitive deficits (Curran, 2000).

9. FDG PET study

For our study we assumed that ecstasy-induced functional alterations of the serotonergic system might affect local energy metabolism of cortical and subcortical brain structures. We, therefore, applied PET using the glucose analogue FDG in order to detect long-term alterations of glucose utilization. The aim of this prospective study was to investigate the effect of repeated ecstasy abuse on central nervous glucose metabolism. We were further interested in possible correlation between glucose metabolic rates and cumulated ecstasy doses, time since last ecstasy ingestion and age at first ecstasy ingestion, respectively. This study was part of an extended investigation on neurological and psychiatric complications induced by ecstasy (Thomasius, 1998).

9.1. Subjects

Ecstasy users were recruited from discotheques. They were tested for psychopathology with a semi structured interview based on the Composite International Diagnostic Interview (CIDI) (Wittchen and Semler, 1991). Drug histories were ascertained by using a standardized questionnaire. The plausibility of the ecstasy user's self-assessment with respect to cumulative ecstasy dose and time since last dose was evaluated by analyzing hair samples. Alcohol abuse was excluded according to the criteria given in the Diagnostic and Statistical Manual of mental disorders, 1994. Since ecstasy users tend to consume other drugs as well, the urine of all subjects was screened for the presence amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites and opiates on the days of the PET scanning. Ecstasy users who tested positive for any of these substances (except for traces of cannabinoids) were excluded from the study. PET scans were obtained from 94 ecstasy users. The scan of one ecstasy user could not be evaluated due to repeated head movement during the acquisition. Demographic data and ecstasy abuse of the remaining 93 ecstasy users are given in Table 1. These 43 females and 50 males, aged between 18 and 37 years, had taken ecstasy for 1–11 years

Table 1
Demographics and ecstasy-history

	Ecstasy users	Controls
<i>n</i>	93	27
Age (years)	23.1 ± 3.9 (18–37)	24.1 ± 4.2 (15–30)
Gender: male/female	50/43	13/14
CD (tablets)	483 ± 578 (1–3000)	Ø
LI (month)	6.4 ± 14.3 (0.09–96)	Ø
FI (years)	19.5 ± 3.5 (14–29)	Ø

Data are given as mean ± 1 standard deviation (range). NA, data not available; Ø, not applicable; CD, cumulative dose; LI, time since last ecstasy ingestion; FI, age at first ecstasy ingestion.

(3.2 ± 2.1 years). Estimated cumulative ecstasy doses ranged between 1 and 3000 tablets. PET scans were performed between 3 days and 96 months after last ecstasy ingestion. The control group consisted of 27 oncology patients (14 females and 13 males), who were examined by means of whole-body FDG PET, including brain, in chronological order in clinical routine (Table 1). Exclusion criteria were age above 30 years, obvious psychiatric and neurological disorders, or reported PET findings in the brain. Details on the

PET imaging procedure, on volume of interest analysis and on the statistical evaluation are given elsewhere (Buchert et al., 2001). The study was approved by the local ethical committee and by the German federal board for radiation protection. All participants gave their informed written consent.

9.2. Results

FDG uptake was reduced in cingulate, Brodmann's area 11, putamen, caudate, amygdala and hippocampus bilaterally within the ecstasy user group as compared with the control group (Table 2). Elevated values were found in Brodmann's area 10 only. Statistical significance ($P < 0.05$) was reached in putamen and caudate bilaterally, and in the left amygdala. A tendency ($P < 0.1$) was observed in the right amygdala and in the left hippocampus. The most prominent difference in the mean values between both groups was detected in the left caudate, in which the 95% confidence interval did not include zero. The non-parametric Mann–Whitney *U*-test yielded in the same levels of statistical significance. However, there was no single region in which all ecstasy users had either lower or higher uptake

Table 2
Comparison of normalized FDG-uptake in 93 ecstasy users and 27 controls

ROI		FDG-uptake		<i>t</i> -test	
		Ecstasy users	Controls	df	<i>P</i>
BA 10	Right	140.1 ± 8.9	138.7 ± 9.5	118.0	0.477
	Left	141.2 ± 7.8	138.5 ± 8.8	118.0	0.122
BA 11	Right	121.3 ± 8.5	123.8 ± 8.6	118.0	0.172
	Left	117.8 ± 9.2	118.1 ± 9.7	118.0	0.886
Putamen	Right	131.6 ± 7.0	135.9 ± 9.6	34.5	0.038
	Left	130.7 ± 6.8	134.4 ± 8.0	118.0	0.016
Caudate	Right	118.7 ± 6.5	122.6 ± 8.2	35.9	0.029
	Left	120.6 ± 5.6	124.8 ± 7.2	35.6	0.008
Cingulate	Right	140.6 ± 6.6	142.0 ± 8.4	35.8	0.413
	Left	139.6 ± 8.1	141.2 ± 7.9	118.0	0.383
Amygdala	Right	78.5 ± 6.1	81.1 ± 6.4	40.6	0.076
	Left	80.8 ± 6.2	84.2 ± 6.8	39.3	0.026
Hippocampus	Right	90.5 ± 5.8	91.6 ± 4.7	51.4	0.319
	Left	91.1 ± 6.2	93.5 ± 5.9	118.0	0.074

Data are presented as mean ± 1 standard deviation BA, Brodmann's area; df, degrees of freedom; *P*, *P*-value.

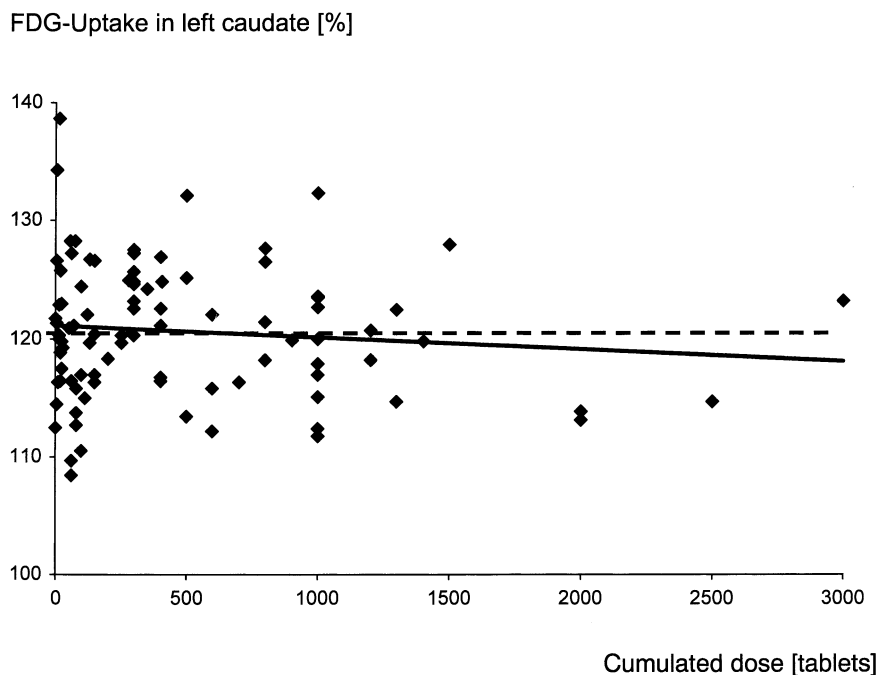


Fig. 1. FDG uptake in the left caudate versus cumulated dose in ecstasy users. Linear regression (continuous line) yielded $y = -0.001x + 121.1$, $R^2 = 0.011$. The correlation coefficient was not significantly different from zero. The dotted line marks the mean FDG uptake in the controls.

rates than all of the controls. Two-tailed analysis of variance of FDG uptake with respect to cumulative ecstasy dose and time since last ecstasy ingestion revealed a statistically significant relationship between FDG uptake and time since last ecstasy ingestion in the left cingulate and in the right amygdala. However, no relationship between FDG uptake and cumulative ecstasy dose could be detected. Two-tailed analysis of variance of FDG uptake with respect to cumulative ecstasy dose and age at first ecstasy ingestion revealed a statistically significant relationship between FDG uptake and age at first ecstasy ingestion bilaterally in the putamen and in the caudate, in the left Brodmann's area 10 and in the left hippocampus. A tendency was observed in the amygdala bilaterally. When compared with the control group, FDG uptake was more severely reduced in ecstasy users who started to use the drug before the age of 18. No interaction between cumulative dose and age at first ingestion could be detected. There was no indication for a linear relationship be-

tween FDG uptake and cumulative ecstasy dose. In the caudate, where the reduction of FDG uptake in ecstasy users as compared with controls was most prominent, there was a slight positive correlation of the reduction of FDG uptake and the cumulative ecstasy dose, which, however, was statistically not significant (Fig. 1). Concerning FDG uptake and time since last ecstasy ingestion, there was a statistically significant correlation of about 0.5 in the cingulate in both hemispheres (Fig. 2). A statistically significant slight positive correlation between FDG uptake and age at start of ecstasy use was found in the putamen bilaterally, in the right caudate, and in the left hippocampus (Fig. 3).

9.3. Discussion

9.3.1. Limitations

Some limitation of the present study arises from different patterns of drug abuse within the ecstasy user group. Ecstasy users also consume additional

drugs like cocaine or cannabis. Furthermore ecstasy itself may comprise a variety of psychactive substances like amphetamines or even caffeine or atropine in varying doses (Wolff et al., 1995). Yet, MDMA is widely regarded as its main or even sole ingredient. Drug histories were objectivated by means of toxicological analyses of hair samples. Still, data on cumulative ecstasy doses may bear uncertainties since these were obtained by self-assessment. The age-matched control group consisted of oncology patients from clinical routine. In general, these were not exposed to the same environmental factors as ecstasy users (raves etc.). In addition, their physical condition during PET scanning was rather different from the condition of ecstasy users, who were relatively relaxed. However, it should be noted that the results of the analysis of the relationship of brain glucose metabolism and drug history in the group of ecstasy users are not affected by limitations of the control group. In the statistical evaluation no Bonferroni adjustment (alpha adjustment) was applied to take into account multiple testing

(number of regions of interest (ROIs), number of correlations). However, the regions showing the statistically most significant difference in the group means, caudate and putamen, were affected in both hemispheres. This would not be expected if the P values were small due to type I errors.

9.3.2. Glucose metabolism

While there was no clear evidence for a relationship of FDG uptake with the cumulative ecstasy dose or the time since last ecstasy ingestion at the time of PET scanning, there was a statistically significant correlation with the age at first ingestion. Reduction of FDG uptake was more severe in those ecstasy users who started their consumption before the age of 18. These results support the hypothesis that ecstasy affects a structural component of human brain serotonergic neurons, since decrease of FDG uptake was most pronounced in regions with dense serotonergic innervation. When focussing on the reversibility of ecstasy induced alterations of brain glucose metabolism, in the present study a correlation

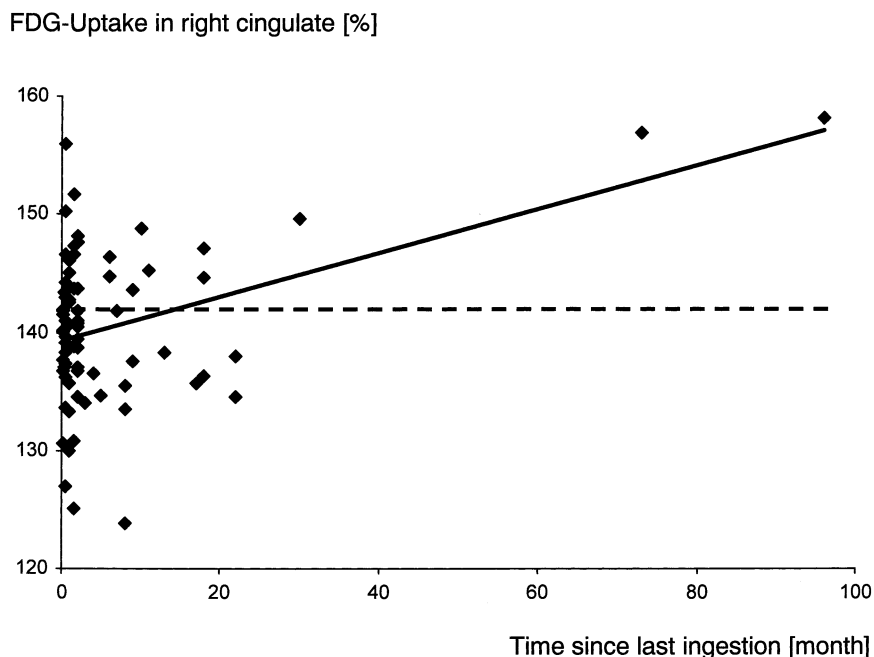


Fig. 2. FDG uptake in the right cingulate versus time since last ecstasy ingestion in ecstasy users. Linear regression (continuous line) yielded $y = 0.185x + 139.3$, $R^2 = 0.166$. The correlation coefficient was significantly different from zero (0.48, $P < 0.001$). The dotted line marks the mean FDG uptake in the controls.

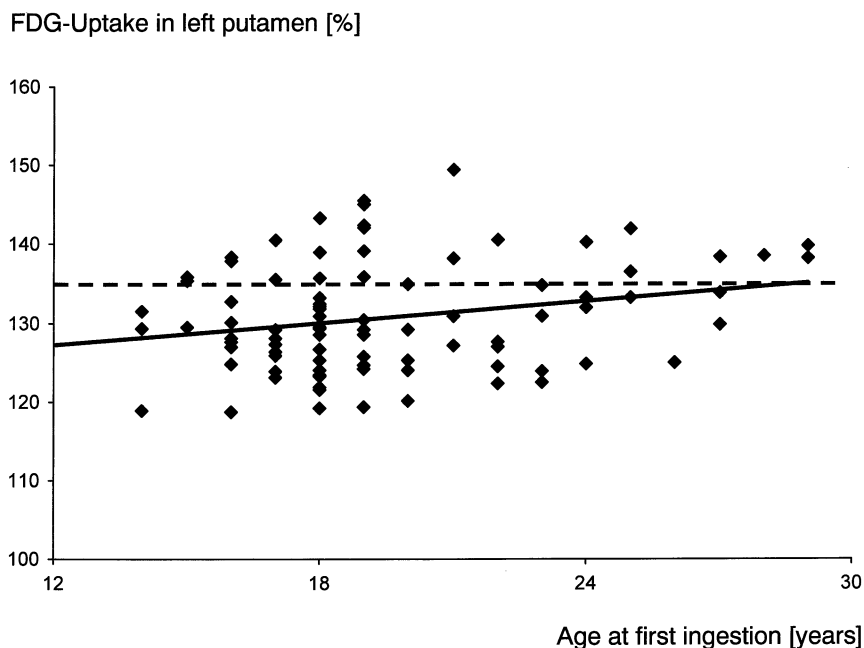


Fig. 3. FDG uptake in the left putamen versus age at first ecstasy ingestion in ecstasy users. Linear regression (continuous line) yielded $y = 0.464x + 121.6$, $R^2 = 0.057$. The correlation coefficient was significantly different from zero (0.24, $P < 0.05$). The dotted line marks the mean FDG uptake in the controls.

between FDG uptake and time since last ecstasy ingestion was detected in the cingulate only. In the first 12 months after the last ecstasy ingestion FDG uptake was reduced, followed by an overcompensation after this period. Although this result is mainly driven by two high data points, the coefficient for the correlation between FDG uptake and time since last ecstasy ingestion remains positive (but no more statistically significant different from zero) when removing these data points. Scheffel et al. (1998) found increased serotonin transporter binding beyond control levels in several brain regions and a persistent decrease in others 9 and 13 months after MDMA exposure. It has to be pointed out that FDG PET does not selectively display the activity of the serotonergic system, but rather reflects total neuronal activity. Consequently, in the present study, the differences of regional glucose metabolism between ecstasy users and controls were both, rather small and statistically significant in restricted brain regions only. However, FDG PET can be regarded as complementary to PET with specific ligands in

that it reflects transneuronal effects after assumed lesions of the serotonergic system.

10. Conclusion

There is strong evidence that MDMA is a potent serotonergic neurotoxin. As the main constituent of the drug ecstasy it may induce long-term alterations of human central nervous function and neuropsychiatric deficits consequently. Teenagers seem to be more susceptible to neurotoxicity than adult ecstasy users. It is not clear yet to what extent the long-term effects of ecstasy use are reversible or dose-dependent.

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