Nuclear Medicine Communications, 2001, **22,** 889–897

Nuclear Medicine Communications

Long-term effects of 'ecstasy' abuse on the human brain studied by FDG PET

R. BUCHERT,[1,*] J. OBROCKI,[2] R. THOMASIUS,[2] O. VÄTERLEIN,[1] K. PETERSEN,[2] L. JENICKE,[1] K.H. BOHUSLAVIZKI[1] and M. CLAUSEN[1]

Departments of [1]Nuclear Medicine and [2]Psychiatry and Psychotherapy, University Hospital Eppendorf, Hamburg, Germany

Received 14 February 2001, and accepted 26 March 2001

Summary

The popular recreational drug, 'ecstasy', mainly contains 3,4-methylenedioxymethamphetamine (MDMA) as the psychotropic agent. MDMA is suspected of causing neurotoxic lesions to the serotonergic system as demonstrated by animal studies, examinations of human cerebrospinal fluid, and the first positron emission tomography (PET) studies using the serotonin transporter ligand [^{11}C]-McN5652. Damage of serotonergic afferents might mediate long-lasting alterations of cerebral glucose metabolism as a secondary effect. To study a relationship between ecstasy use and long-lasting alterations, PET using 2-[^{18}F]-fluoro-2-deoxy-d-glucose (FDG) was performed in 93 ecstasy users and 27 subjects without any known history of illicit-drug abuse. As an index of glucose metabolism, mean normalized FDG uptake was determined in both groups using a computerized brain atlas, and was compared for a selected number of brain regions. FDG uptake was normalized in each individual by dividing local FDG uptake by the maximum FDG uptake in the individual's brain. Within the group of ecstasy users we examined the relationship between FDG uptake and cumulative ecstasy dose, time since last ecstasy ingestion at the time of PET scanning, and age at first ecstasy use, respectively. Normalized FDG uptake was reduced within the striatum and amygdala of ecstasy users when compared to controls. No statistically significant correlation of the FDG uptake and the cumulative dose of ecstasy was detected. A positive correlation was found in the cingulate between FDG uptake and the time since last ecstasy ingestion. As compared to the control group, normalized FDG uptake in the cingulate was reduced in ecstasy users who took ecstasy during the last 6 months, while it was elevated in former ecstasy users who did not consume ecstasy for more than 1 year. FDG uptake was significantly more affected in ecstasy users who started to consume ecstasy before the age of 18 years. In conclusion, ecstasy abuse causes long-lasting effects on glucose metabolism in the human brain. These effects are more severe in the case of very early abuse. However, several questions still remain to be answered, i.e. the correlation of the neuronal alterations and the history of ecstasy use (cumulative dose, and time since the last dose) and its reversibility. (© 2001 Lippincott Williams & Wilkins)

Keywords: Ecstasy, cerebral glucose metabolism, positron emission tomography, 2-[^{18}F]-fluoro-2-deoxy-d-glucose.

Introduction

The designer drug 'ecstasy', with its major constituent 3,4-methylenedioxymethamphetamine (MDMA), has become increasingly popular among adolescents and young adults in western industrial nations [1]. In Germany abuse of ecstasy dramatically increased from 1990 to 1995, and since then remained constant at a rather high level: 4.0% of males and 2.3% of females aged between 14 and 21 years have practical experience of ecstasy [2].

Ecstasy is appreciated for its acute psychotropic effects, such as euphoria, increase of psychomotor drive and subjective intensification of sensory perception [3]. In addition to these positively experienced effects, acute adverse symptoms have also been described. States of anxiety and depression are the most commonly reported phenomena [4]. However, it remains unclear to what

*Address all correspondence to Dr Ralph Buchert, Department of Nuclear Medicine, University Hospital Eppendorf, Martinistr. 52, D20246 Hamburg, Germany. e-mail: buchert@uke.uni-hamburg.de

extent ecstasy abuse causes delayed or even chronic alterations of the human central nervous system [5]. Animal experiments indicate that MDMA and related compounds cause long-lasting effects on serotonergic neurons in the brain of both rats [6–11] and non-human primates [12–16] at doses that approach those used by humans. A few examinations of the brain serotonergic system in human ecstasy users gave evidence that ecstasy is neurotoxic in humans in a similar way. Measurement of serum prolactin concentration revealed blunted responses to intravenous L-tryptophan in recreational users of MDMA as evidence for altered serotonergic function [17]. In a controlled inpatient setting for measurement of biological and behavioural indexes of central serotonin concentration, significantly lowered levels of 5-hydroxyindoleacetic acid, the major metabolite of serotonin, were found in the cerebrospinal fluid of ecstasy users [18]. Subtle, but significant deficits in cognitive processes such as verbal and visual memory, attention and learning, as well as psychobehavioural changes caused by past exposure to MDMA, have been reported by a number of different groups [19–21]. For a more direct assessment and visualization of the long-term effects of ecstasy, single photon emission computed tomography (SPECT) and positron emission tomography (PET) with potent serotonin transporter ligands have been applied. SPECT using [^{123}I]-(1*R*)-2-*β*-carboxymethoxy-3-*β*-(4-iodophenyl)-tropane ([^{123}I]*β*-CIT) [22] showed a cortical reduction of binding to the serotonin transporter in long-term MDMA users as compared to MDMA naive but drug-using controls [23]. PET using [^{11}C]-McN5652 [24] applied in humans revealed decreased global and regional serotonin transporter binding in former ecstasy users [25].

Functional alterations of central serotonergic neurons are expected to affect local energy metabolism of cortical and subcortical brain structures. Using quantitative [^{14}C]-deoxyglucose autoradiography in rats, statistically significant effects were observed in 20 out of 60 brain areas sampled 5 min after the administration of MDMA [26]. Some of the effects resembled those previously reported with cocaine, amphetamine, and phencyclidine. Again, in rats, a significant increase in glucose utilization was found in sub-regions of the hippocampus, 2 weeks after injection of MDMA [27]. In humans, PET using the glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) might be used to detect long-term alterations of glucose utilization. So far, FDG PET has only been applied for the determination of acute ecstasy effects on the cerebral glucose metabolism of healthy volunteers, without a history of drug abuse [28]. Therefore, the aim of this prospective study was to detect long-lasting alterations of central nervous glucose metabolism after repeated ecstasy abuse.

This study was part of a larger one concerning neurological and psychiatric complications and long-term alterations induced by ecstasy abuse [29].

Subjects, materials and methods

Ecstasy users

Ecstasy users were recruited from discotheques. They were tested for psychopathology with a semi-structured interview based on the *Composite International Diagnostic Interview* (CIDI) [30]. Their drug-histories were ascertained by using a standardized questionnaire. The plausibility of the ecstasy users' self-assessment with respect to cumulative ecstasy dose and time since last dose was evaluated by testing hair samples [31]. Alcohol abuse was excluded according to the methods given in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [32]. Since ecstasy users are known to consume several drugs in varying doses, the urine of all subjects was screened for the presence of amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, and opiates on the days of PET scanning. Ecstasy users who tested positive for any of these substance groups, except 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 between 1 and 11 years (3.2 ± 2.1 years). Estimated cumulative ecstasy doses ranged from between 1 and 3000 tablets. PET scans were performed between 3 days and 96 months after the last ecstasy ingestion.

The study was approved by the local ethics committee and by the German federal board for radiation protection. All participants gave their written informed consent.

Table 1. Demographics and ecstasy history.

Variable	*Ecstasy users*	*Controls*
n	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)	NA
LI (month)	6.4 ± 14.3 (0.09–96)	NA
FI (years)	19.5 ± 3.5 (14–29)	NA

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

Control group

The control group consisted of 27 oncology patients (14 females and 13 males), who were examined by using whole-body FDG PET, including the 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.

PET imaging

PET imaging was performed on a full-ring, whole-body system ECAT EXACT 921/47 (Siemens/CTI, Knoxville, TN, USA) [33] in 2-dimensional mode. This system covers an axial field-of-view of 16.2 cm by collecting 47 transversal slices with 3.375 mm slice thickness.

Ecstasy users fasted for at least 6 h prior to PET scanning. Forty-five min after intravenous injection of 180–250 MBq FDG, emission scans of the brain were acquired for 20 min. Ecstasy users were asked to keep their eyes open.

Controls fasted for at least 6 h prior to PET. As part of our standard protocol for whole-body scanning of oncology patients an 8 min emission scan of the brain was acquired 40–60 min after intravenous injection of 300–400 MBq FDG.

Acquired sinograms were corrected for random coincidences, radioactive decay, dead time, and varying detector efficiency. Calculated attenuation correction for the brain was applied as provided by the scanner software (ECAT 6.5B, Siemens/CTI, Knoxville, TN, USA). No scatter correction was performed. Transverse images with 128×128 pixels were reconstructed by filtered back-projection using a Hanning filter with cut-off 1.0 of the Nyquist frequency resulting in pixels of 2×2 mm and an in-plane reconstructed resolution of 9 mm (full width at half maximum (FWHM)).

Volume of interest analysis

In order to ensure statistical robustness (multiple comparison) a limited number of brain regions were selected a priori for quantitative evaluation of glucose uptake. The following brain structures were selected according to the present literature [14, 34, 35] and a pilot study published previously [36]: cingulate, Brodman's area 10 and 11, caudate, putamen, amygdala and hippocampus.

Selected structures were analysed by the volumes of interest (VOIs) technique using the commercial software package Karolinska Computerized Brain Atlas (CBA) [37, 38]. First, individual data were automatically transformed to the stereotactic space of the atlas. Inelastic inter-subject registration was performed by adapting parameters for size (three parameters), position (six parameters), and shape (seven parameters). As the cost function, a measure of voxel similarity between the individual brain and the FDG PET brain template of the atlas was used. After transformation, FDG uptake was normalized to the subject's average brain uptake in the 15% of voxels with highest uptake. The mean value of these voxels was set to 100%. VOIs predefined in the atlas for right and left brain hemispheres were placed within the normalized images. Maximum normalized FDG uptake within each VOI was measured in all individuals ('hottest pixel analysis'). In the following, 'maximum normalized FDG uptake' will be denoted 'FDG uptake' for simplicity.

Statistical evaluation

The two-tailed Student's t test for unpaired data was used to evaluate statistical differences between the FDG uptake of ecstasy users and controls. The t test was performed for equal (homoscedastic) or unequal (heteroscedastic) variances according to the result of Levene's test. No Bonferroni adjustment was applied.

To analyse the extent to which FDG uptake in ecstasy users was affected by the history of ecstasy abuse two-way analysis of variance was performed. First, cumulative dose and time since last ecstasy ingestion were chosen as independent variables. Second, cumulative dose and age at first ecstasy ingestion were taken as independent variables. The following subgroups of ecstasy users were considered in order to achieve equally sized subgroups: (1) cumulative dose (CD) <300 tablets ($n=44$), $\geqslant 300$ tablets ($n=46$); (2) time since last ecstasy ingestion (LI) <1 month ($n=42$), 1–6 months ($n=20$), 6–12 months ($n=11$), >12 months ($n=17$); and (3) age at first ecstasy ingestion (FI) $\leqslant 18$ years ($n=46$), >18 years ($n=45$).

In order to measure the extent to which a linear relationship between FDG uptake and cumulative dose, time since last ecstasy ingestion and age at first ingestion, respectively, may hold, product–moment correlation coefficients were computed. Statistical significance of non-vanishing correlation coefficients was evaluated by using the two-tailed t test. $P<0.05$ was considered to be statistical significant for all tests.

Results

FDG uptake was reduced in cingulate, Brodman's area 11, putamen, caudate, amygdala and hippocampus bilaterally within the ecstasy user group as compared to 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 means of both groups was detected in the left caudate (Fig. 1), in which the 95% confidence interval did not include zero. The non-parametric Mann–Whitney *U* test yielded the same levels of statistical significance. However, there was no single region in which all ecstasy users had either smaller or higher glucose uptake 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. There was no interaction between cumulative dose and time since last ecstasy ingestion.

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 Brodman's area 10, and in the left hippocampus. A tendency was observed in the amygdala bilaterally. When compared to the control group, FDG uptake was more severely reduced in ecstasy users who started to use ecstasy before the age of 18 years. No interaction between cumulative dose and age at first ecstasy ingestion could be detected.

There was no indication for a linear relationship between FDG uptake and cumulative ecstasy dose (Table 3). In the caudate, in which the reduction of FDG uptake in ecstasy users as compared to controls was most prominent, there was a slight positive correlation of the

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

		FDG uptake		*t test*	
ROI		*Ecstasy users*	*Controls*	*df*	*P*
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.
Values in bold type indicate statistical significance ($P<0.05$).
ROI, region of interest; FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose; BA, Brodman's area; df, degrees of freedom.

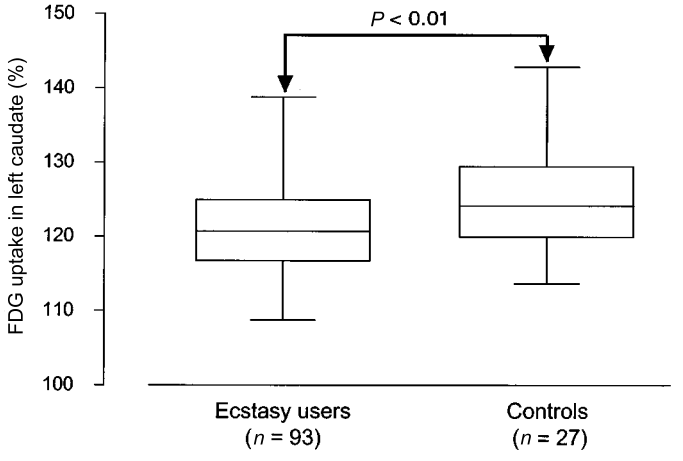

Fig. 1. Box-and-whisker plot of FDG uptake in the left caudate in ecstasy users and controls.

Table 3. Product moment correlation coefficients for the correlation between FDG uptake and cumulative dose (CD), time since last ecstasy ingestion (LI) and age at first ingestion (FI).

ROI		*CD*	*LI*	*FI*
BA 10	right	0.16	−0.15	0.13
	left	**0.24***	0.01	0.18
BA 11	right	0.18	−0.19	0.03
	left	0.09	−0.16	0.08
Putamen	right	0.07	0.05	**0.21***
	left	0.07	0.06	**0.24***
Caudate	right	−0.13	0.07	**0.25***
	left	−0.14	0.19	0.14
Cingulate	right	−0.12	**0.48*****	0.12
	left	−0.07	**0.43****	0.18
Amygdala	right	0.07	0.03	0.24
	left	−0.06	0.03	0.11
Hippocampus	right	−0.11	0.09	0.14
	left	−0.11	−0.04	**0.21***

Abbreviations as in the footnote to Table 2.
*$P<0.05$; **$P<0.01$; ***$P<0.001$. The number of subjects was: CD = 71, LI = 54, FI = 91.
Values in bold type indicate statistical significance ($P<0.05$).

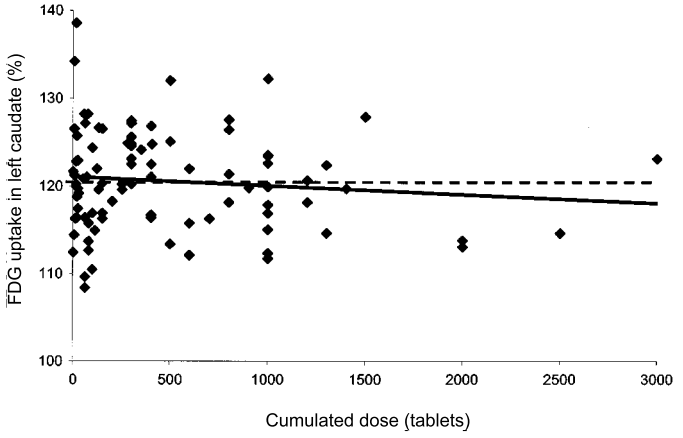

Fig. 2. FDG uptake in the left caudate versus cumulated dose in ecstasy users (◆). Linear regression (continuous line) yielded $y = -0.001x+121.1$, $R^2 = 0.011$. The correlation coefficient was not significantly different from zero. The dotted line marks the mean FDG uptake in the controls.

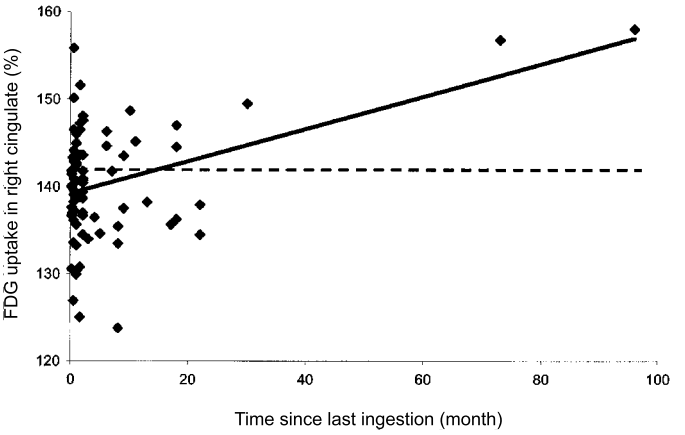

Fig. 3. FDG uptake in the right cingulate versus time since last ecstasy ingestion in ecstasy users (◆). Linear regression (continuous line) yielded $y = 0.185x+139.3$, $R^2 = 0.166$. The correlation coefficient was significantly different from zero (0.48, $P < 0.001$). The dotted line marks the mean FDG uptake in the controls.

reduction of FDG uptake and the cumulative ecstasy dose, which, however, was not statistically significant (Fig. 2). 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 (Table 3, Fig. 3). A statistically significant slight positive correlation between FDG uptake and age at start of ecstasy use was found in the putamen in both hemispheres, in the right caudate, and in the left hippocampus (Fig. 4).

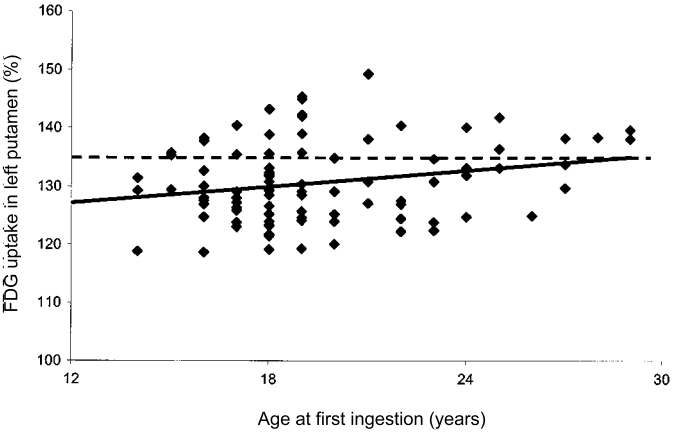

Fig. 4. FDG uptake in the left putamen versus age at first ecstasy ingestion in ecstasy users (◆). Linear regression (continuous line) yielded $y = 0.464x+121.6$, $R^2 = 0.057$. The correlation coefficient was significantly different from zero (0.24, $P < 0.05$). The dotted line marks the mean FDG uptake in the controls.

Discussion

Limitations of the study

A kind of limitation of the present study arises from different patterns of drug abuse within the ecstasy user group itself. Ecstasy users also consume additional drugs, such as cocaine or cannabis, and ecstasy itself comprises a heterogeneous composition of psychoactive drugs. Besides methylenedioxymethamphetamine (MDMA) ecstasy contains other entactogenes such as methylenedioxy-N-ethylamphetamine (MDEA), methylenedioxyamphetamine (MDA) and methylbenzodioxolylebutamine (MBDB) in varying doses [39, 40]. These drugs differ in their specifity for the serotonin transporter (MDA < MDMA < MDEA < MBDB). In addition, ecstasy contains amphetamines in varying doses [41]. Finally, there are falsifications of ecstasy tablets containing caffeine or atropine, and even placebo. For these reasons the detected effects may not strictly be ascribed to ecstasy or MDMA abuse, although MDMA is, and was, the main psychoactive component of ecstasy [42, 43].

Data on cumulative ecstasy dose and time since last dose were obtained by self-assessment of the ecstasy users. Plausibility of these data was evaluated by testing of hair samples. Although there was an obvious discrepancy between self-assessment and hair analysis in only a few ecstasy users, these data are subject to some uncertainties. The shortness of most of the user's hairs

restricted objective information about drug abuse by toxicological analysis of hair samples to at most the last few months. Both uncertainties due to self-assessment and uncertainties about the composition of ecstasy tablets rendered the detection of a correlation between cumulative dose and/or time since last dose ingestion and FDG uptake difficult.

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 psychical condition during PET scanning was rather different from the condition of ecstasy users, who were quite relaxed. This may introduce confounding effects [44]. 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.

The PET imaging protocol differed for ecstasy users and controls. In ecstasy users a 20 min emission scan was performed at precisely 45 min after injection of about 230 MBq FDG, while in controls an 8 min emission scan was acquired about 60 min after injection of about 370 MBq FDG. While the effect of scan duration and FDG dose on statistical image quality cancel to a large extent, there might be a systematic effect due to the different time intervals between injection and PET scanning. It is known that FDG uptake in the brain is still increasing at 45 min post-injection [45]. Therefore, the absolute FDG uptake, as measured by the standardized uptake value (SUV), for example, is expected to be higher in controls than in ecstasy users. However, assuming the same kinetic in all gray matter areas [46] this effect is cancelled by the image normalization applied, and, therefore, should not affect the results.

A further difference in the imaging protocol concerns the position of the individuals from the time of injection until the acquisition. While ecstasy users lay on a couch in the waiting room until they went to the scanner room, controls sat on a chair in the waiting room. However, due to radiation safety reasons controls were not allowed to walk around. Therefore, there is very little difference in movement activity during the uptake period, which is not expected to cause the observed difference in FDG uptake in the basal ganglia between ecstasy users and controls.

For the purpose of attenuation correction a post-injection transmission scan was performed with three rotating ^{68}Ge rod sources in ecstasy users, but not in controls. Thus, attenuation correction for both ecstasy users and controls was performed by calculations based on a simplified model consisting of a uniform brain surrounded by uniform skull of predefined, constant thickness. These simplifications led to an increased variance of the FDG uptake within the group of ecstasy users and in the control group, particularly at brain levels at which the true skull thickness in a transversal slice deviates from the predefined value, e.g. limbic structures (cingulate, amygdala, hippocampus). In these areas calculated attenuation correction renders detection of differences with sufficient statistical significance more difficult.

The VOIs of the Karolinska Computerized Brain Atlas (CBA) were defined by manual segmentation of the atlas brain. Since segmentation was performed for both brain hemispheres independently, VOIs corresponding to the same structure in left and right hemisphere are not symmetric. In particular, they differ in size for some extent, e.g. putamen and caudate are slightly larger in the left hemisphere than in the right hemisphere, 8.60 vs 7.76, and 7.22 vs 6.68 ml, respectively. This may cause evaluation of the left structure to be less sensitive to remnant mismatch between the transformed individual brain and the atlas brain. This in turn may reduce the variance of 'left' FDG uptake, and thus, explain that statistical significance of our findings is slightly higher in the left than in the right hemisphere.

Prior to VOI evaluation each brain image was individually normalized to the average FDG uptake in the 15% brain voxels with highest uptake. This normalization implies that voxels with highest FDG uptake are not affected by ecstasy induced effects. According to our findings this assumption seems to be not fulfilled completely since putamen and caudate, which show the most significant difference between ecstasy users and controls, belong to the 15% brain voxels with highest uptake. However, since the total volume of putamen and caudate ($\sim$30 ml) is only about 20% of the normalization volume, the effect of a slightly reduced FDG uptake in these structures on the normalization might be neglected.

In the present work 'hottest voxel analysis', i.e. sampling the voxel with the highest uptake, has been used to characterize glucose uptake within a given structure. This approach is known to be susceptible to statistical fluctuations [47]. However, if applied to sufficiently smoothed data it has been demonstrated to be the best method of discriminating between groups of subjects supposed to differ with respect to glucose utilization within small brain structures [48].

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, putamen and caudate, were affected in both hemispheres. This would not be expected if the P values were small due to type I errors.

Glucose metabolism

Findings in animal studies, examinations of human cerebrospinal fluid, and first PET studies using a ligand with high affinity and selectivity for the serotonin transporter suggest that the popular recreational drug ecstasy might produce long-lasting damage to serotonergic neurons in the brain [5–18, 22, 23, 25]. In the present paper, FDG PET was used to study corresponding alterations of regional cerebral glucose metabolism. Ninety-three users of ecstasy and 27 subjects without any known history of illicit drug abuse were compared for a limited number of brain regions.

When compared to controls, FDG uptake in ecstasy users was significantly reduced in the striatum of both hemispheres. 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 ecstasy ingestion. Reduction of FDG uptake was more severe in those ecstasy users who started their consumption before the age of 18 years. These results support the hypothesis that ecstasy affects a structural component of human brain serotonergic neurons, since decrease of FDG uptake was most significant in regions with strong serotonergic innervation [49]. Our results are in good agreement with the PET findings of McCann and co-workers who found a significantly reduced binding of the selective serotonin transporter ligand [^{11}C]-McN5652 in the striatum of 14 previous ecstasy users when compared to 15 controls [25].

When focusing on the reversibility of ecstasy induced alterations of brain glucose metabolism, in the present study a correlation 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, which was followed by overcompensation after this period (Fig. 3). Although this result is driven mainly by the two high data points (time since last ingestion 76 and 93 months, respectively), 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. However, it should be noted that similar observations were reported by Scheffel and co-workers using [^{11}C]-McN5652 PET in baboons [16]. Their study showed that serotonin transporter binding was reduced in all brain regions 40 days after MDMA ingestion. Follow-up PET studies 9 and 13 months later showed regional differences in the recovery of serotonin transporters, with increased binding beyond control levels in several brain regions and persistent decrease in others. This is in good agreement with the results of Semple *et al*. [23] and Reneman *et al*. [50], who, using [^{123}I]β-CIT SPECT reported evidence for recovery from alterations of brain serotonergic neurons after withdrawing MDMA. Semple *et al*. [23] described a positive partial correlation of tracer uptake in many brain regions and the interval since the last tablet intake in a group of 10 male ecstasy users. In accordance with our results, the strongest correlation was found in the cingulate [23]. Reneman *et al*. observed no difference in the 5-HT transporter density in individuals who stopped using MDMA more than 2 years ago when compared to controls [50]. However, in MDMA treated squirrel monkeys an abnormal 5-HT innervation pattern was found by Hatzidimitriou *et al*. as long as 7 years after MDMA treatment, although the deficits were less severe than at 18 months after the treatment [51].

There is a close correlation between local FDG uptake and local energy metabolism. However, 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. Thus, FDG PET can, in principle, not be used as a diagnostic tool for ecstasy induced neurological alterations in individuals. However, FDG PET is complementary to PET with specific ligands, e.g. [^{11}C]-McN5652. Together, these two approaches might form the basis to fully understand the alterations of neuronal activity underlying the long-term psychopathological and neurological sequelae of ecstasy abuse.

Conclusion

Ecstasy abuse may cause lasting effects on central nervous activity in humans, with teenagers being at higher risk than adults. These effects may account for delayed psychopathological and neuropsychological phenomena following ecstasy abuse. However, correlation of neuronal alterations and ecstasy intake and reversibility of neuronal alterations still remain unclear.

Acknowledgement

This study was supported by the Bundesministerium für Gesundheit (GZ: 326-172/33), Germany.

References

1. Elk C. MDMA (Ecstasy): useful information for health professionals involved in drug education programs. *J Drug Educ* 1996; **26:** 349–356.

2. Schuster P, Wittchen H-U. Ecstasy- und Halluzinogengebrauch bei Jugendlichen. Gibt es eine Zunahme? *Verhaltenstherapie* 1996; **6:** 222–232.
3. Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 1986; **18:** 319.
4. McGuire PK, Cope HT, Fahy A. Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'). *Br J Psychiatry* 1994; **165:** 391–395.
5. McCann UD, Ricaurte GA. Strategies for detecting subclinical monoamine depletions in humans. *NIDA Res Monogr* 1993; **136:** 53–62.
6. Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS. Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 1986; **241:** 338–345.
7. Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar MJ, De Souza EB. 3,4-Methylenedioxymethamphetamine and 3,4-methylendioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [^{3}H] paroxetine-labeled serotonin uptake sites. *J Pharmacol Exp Ther* 1987; **242:** 911–916.
8. Battaglia G, Yeh SY, De Souza EB. MDMA-induced neurotoxicity: parameter of degeneration and recovery of brain serotonin neurons. *Pharmacol Biochem Behav* 1988; **29:** 269–274.
9. Slikker W, Ali SF, Scallet AC, Frith CH, Newport GD, Baily JR. Neurochemical and neurohistological alterations in the rat and monkey produced by orally administered methylenedioxymethamphetamine (MDMA). *Toxicol Appl Pharmacol* 1988; **94:** 448–457.
10. Lew R, Sabol KE, Chou C *et al*. Methylenedioxymethamphetamine induced serotonin deficits are followed by partial recovery over 52 week period. Part I: Synaptosomal uptake and tissue concentrations. Part II: radioligand binding and autoradiography studies. *J Pharmacol Exp Ther* 1996; **276:** 846–854 (part I); and 885–865 (part II).
11. Seiden LS, Sabol KE. Methamphetamine and methylenedioxymethamphetamine neurotoxicity: possible mechanisms of cell destruction. *NIDA Res Monogr* 1996; **163:** 251–276.
12. Ricaurte GA, DeLanney DE, Irwin I, Langston JW. Toxic effects of MDMA on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. *Brain Res* 1988; **446:** 165–168.
13. Ricaurte GA, Forno LS, Wilson MA, DeLanny LE. (±)3,4-Methylenedioxymethamphetamine (MDMA) selectively damages central serotonergic neurons in non-human primates. *JAMA* 1988; **260:** 51–55.
14. Ricaurte GA, Martello AL, Katz JL, Martello MB. Lasting effects of (±)-3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. *J Pharmacol Exp Therap* 1992; **261:** 616–622.
15. Kleven MS, Woolverton WL, Seiden LS. Evidence that both intragastric and subcutaneous administration of methylenedioxymethamphetamine produce serotonin neurotoxity in rhesus monkeys. *Brain Res* 1989; **488:** 121–125.
16. Scheffel U, Szabo Z, Mathews WB *et al*. *In vivo* detection of short- and long-term MDMA neurotoxicity – a positron emission tomography study in the living baboon brain. *Synapse* 1998; **29:** 183–192.
17. Price LH, Ricaurte GA, Krystal JH, Heninger GR. Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users. Preliminary observations. *Arch Gen Psychiatry* 1989; **46:** 20–22.
18. McCann UD, Ridenour A, Shaham Y, Ricaurte GA. Serotonin neurotoxicity after (±)3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'): a controlled study in humans. *Neuropsychopharmacology* 1994; **10:** 129–138.
19. Gerra G, Zaimovic A, Giucastro G *et al*. Serotonergic function after (±)3,4-methylene-dioxymethamphetamine ('Ecstasy') in humans. *Int Clin Psychopharmacol* 1998; **13:** 1–9.
20. Morgan MJ. Memory deficits associated with recreational use of 'ecstasy' (MDMA). *Psychopharmacology (Berlin)* 1999; **141:** 30–36.
21. McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. Cognitive performance in (±) 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users: a controlled study. *Psychopharmacology (Berlin)* 1999; **143:** 417–425.
22. Fujita M, Takatoku M, Matoba Y *et al*. Differential kinetics of [^{123}I]beta-CIT binding to dopamine and serotonin transporters. *Eur J Nucl Med* 1996; **23:** 431–436.
23. Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* 1999; **175:** 63–69.
24. Suehiro M, Scheffel U, Ravert HT, Dannals RF, Wagner HN. [^{11}C](+)McN5652 as a radiotracer for imaging serotonin uptake sites with PET. *Life Sci* 1993; **53:** 883–892.
25. McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ('ecstasy') on brain serotonin neurons in human beings. *Lancet* 1998; **352:** 1433–1437.
26. Wilkerson G, London ED. Effects of methylenedioxymethamphetamine on local cerebral glucose utilization in the rat. *Neuropharmacology* 1989; **28:** 1129–1138.
27. Sharkey J, McBean DE, Kelly PA. Alterations in hippocampal function following repeated exposure to the amphetamine derivative methylenedioxymethamphetamine ('Ecstasy'). *Psychopharmacology (Berlin)* 1991; **105:** 113–118.
28. Schreckenberger M, Gouzoulis-Mayfrank E, Sabri O *et al*. Investigations on the effects of 'ecstasy' on cerebral glucose metabolism: an ^{18}F-FDG PET study. *Nuklearmedizin* 1998; **37:** 262–267.
29. Thomasius R. User groups and risk levels. An empirical study based on psychiatric–psychodynamic-, EEG-, EP, PET- and other medical diagnostics of 100 Ecstasy users. *Wiener Zeitschrift für Suchtforschung* 1998; **21:** 9–13.
30. Wittchen HU, Semler G. Composite international diagnostic interview – CIDI-interviewheft. Weinheim: Beltz, 1991.
31. Skopp G, Aderjan R, Koster J. Hair analysis in the diagnosis of toxic hepatitis after Ecstasy abuse. *Dtsch Med Wochenschr* 1995; **120:** 1165–1168.

32. Diagnostic and statistical manual of mental disorders. 4th. edn. Washington: American Psychiatric Association, 1994.
33. Wienhard K, Eriksson L, Grootoonk S, Casey M, Pietrzyk U, Heiss W-D. Performance evaluation of the positron scanner ECAT EXACT. *J Comput Assist Tomogr* 1992; **16:** 804–813.
34. Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or 'Ecstasy'). *Psychopharmacology* 1995; **119:** 247–260.
35. Sabol KE, Lew R, Richards RE, Vosmer GL, Seiden LS. Methylenedioxymethamphetamine induced serotonin deficits are followed by partial recovery over a 52 week period. Part I: Synaptosomal uptake and tissue concentrations. *J Pharmacol Exp Ther* 1996; **276:** 846–854.
36. Obrocki J, Buchert R, Väterlein O, Thomasius R, Beyer W, Schiemann T. Ecstasy – Long term effects on the human central nervous system revealed by positron emission tomography. *Br J Psychiatry* 1999; **175:** 186–188.
37. Thurfjell L, Bohm C, Bengtsson E. CBA – an atlas-based software tool used to facilitate the interpretation of neuroimaging data. *Computer Methods and Programs in Biomedicine* 1995; **47:** 51–71.
38. Andersson JLR, Thurfjell L. Implementation and validation of a fully automatic system for intra- and inter-individual registration of PET brain scans. *J Comput Assist Tomogr* 1997; **21:** 136–144.
39. Nichols DE. Differences between the mechanism of action of MDMA, MBDB and the classic hallucinogenes. Identification of a new therapeutic class: Entactogens. *J Psychoactive Drugs* 1986; **18:** 305–313.
40. Schmoldt A. Pharmakologische und toxikologische Aspekte. In: Thomasius R, ed. Ecstasy – Wirkungen, Risisken, Interventionen. Stuttgart: Ferdinand Enke Verlag, 1999: 23–38.
41. Wolff K, Hay AWM, Sherlock K, Conner M. Contents of 'Ecstasy'. *Lancet* 1995; **346:** 100–1101.
42. Rauschgift-Jahresbericht Bundesrepublik Deutschland 1997. Wiesbaden: Bundeskriminalamt (BKA), 1998.
43. Rauschgift-Jahresbericht Bundesrepublik Deutschland 1998. Wiesbaden: Bundeskriminalamt (BKA), 1999.
44. Malison RT, Price LH, Berman R *et al*. Reduced brain serotonin transporter availability in major depression as measured by [I-123]-2β-carbomethoxy-3β-(4-iodophenyl)-tropane and single photon emission tomography. *Biological Psychiatry* 1998; **44:** 1090–1098.
45. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979; **6:** 371–388.
46. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE. Noninvasive determination of local cerebral metabolic rate of glucose in man. *Am J Physiol* 1980; **238:** E69–E82.
47. Duarte P, Smith RJ, Hustinx R, Couturier O, Alavi A. Hottest pixel analysis: useful value or statistical artifact? *J Nucl Med 1999;* **40(Suppl.):** 292P.
48. Kuwert T, Ganslandt T, Jansen P *et al*. Influence of size of regions of interest on PET evaluation of caudate glucose consumption. *J Comput Assist Tomogr* 1992; **16:** 789–794.
49. Nieuwenhuys R. Chemoarchitecture of the brain. Heidelberg: Springer, 1985.
50. Reneman L, Lavalaye J, de Bruin K *et al*. No difference in 5-HT transporter densities in individuals who stopped using MDMA ('Ecstasy') as compared to controls. *J Nucl Med* 2000; **41(Suppl):** 106P.
51. Hatzidimitriou G, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with ($\pm$)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 1999; **19:** 5096–5107.