"Ecstasy"-induced changes of cerebral glucose metabolism and their correlation to acute psychopathology

An 18-FDG PET Study

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Abstract. The aim of this study was to determine the acute effects of the "Ecstasy" analogue MDE (3,4-methylene dioxyethamphetamine) on cerebral glucose metabolism (rMRGlu) of healthy volunteers and to correlate neurometabolism with acute psychopathology. In a randomized double-blind trial, 15 healthy volunteers without a history of drug abuse were examined with fluorine-18-deoxyglucose (^{18}FDG) positron emission tomography (PET) 110–120 min after oral administration of 2 mg/kg MDE (n=7) or placebo (n=8). Two minutes prior to radiotracer injection, constant cognitive stimulation was started and maintained for 32 min using a word repetition paradigm to ensure constant and comparable mental conditions during cerebral glucose uptake. Individual brain anatomy was represented using T1-weighted 3D flash magnetic resonance imaging (MRI), followed by manual regionalization into 108 regions of interest and PET/MRI overlay. After absolute quantification of rMRGlu and normalization to global metabolism, normalized rMRGlu under MDE was compared to placebo using the Mann-Whitney U-test. Acute psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) and rMRGlu was correlated to PANSS scores according to Spearman. MDE subjects showed significantly decreased rMRGlu in the bilateral frontal cortex: left frontal posterior (–7.1%, P<0.05) and right prefrontal superior (–4.6%, P<0.05). On the other hand, rMRGlu was significantly increased in the bilateral cerebellum (right: +10.1%, P<0.05; left: +7.6%, P<0.05) and in the right putamen (+6.2%, P<0.05). There were positive correlations between rMRGlu in the middle right cingulate and grandiosity (r=0.87, P<0.05), both the right amygdala (r=0.90, P<0.01) and the left posterior cingulate (r=0.90, P<0.01) to difficulties in abstract thinking, and the right frontal inferior (r=0.85, P<0.05), right anterior cingulate (r=0.93, P<0.01), and left anterior cingulate (r=0.85, P<0.05) to attentional deficits. A negative correlation was found between the left frontal operculum (Broca's area) and attentional deficits (r=–0.85, P<0.05). The present study revealed acute neurometabolic changes under the "Ecstasy" analogue MDE, indicating a frontostriatocerebellar imbalance paralleling other psychotropic substances or various psychiatric disorders.

Key words: Ecstasy – Entactogens – PET – Fluorine-18-deoxyglucose

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Introduction

During the 1980s, the recreational drug "Ecstasy" (MDMA: 3,4-methylene dioxymethamphetamine) quickly spread in the USA and subsequently in Europe. MDMA, synthesized in 1912 as an appetite suppressant but never sold commercially, a derivative of phenylethylamine, shows a considerable chemical similarity to both stimulants of the amphetamine type and hallucinogens of the mescaline type. MDMA acts on the central nervous system through an indirect serotonergic and, to a lesser degree, also a dopaminergic mechanism via increased release of and decreased reuptake of 5-hydroxytryptamine (serotonin) and dopamine [1, 2]. There is also a less pronounced direct agonistic effect on the 5-HT2, 5-HT1 and D2 receptors [3].

In the meanwhile, the name "Ecstasy" has been used in the drug scene for both MDMA and MDMA-like drugs, including the ethyl analogue 3,4-methylene dioxyethamphetamine (MDE), which has essentially the same psychopharmacological effect as MDMA [4]. It is

currently being debated whether MDMA and MDE belong to a distinct class of psychotropic substances for which the term "entactogens" was coined [5, 6]. It is postulated that, along with their stimulating and mild hallucinogenic effect, these substances also show a so-called entactogenic effect, which is mainly characterized by emotional-affective effects. Aside from its popularity as a recreation drug, MDMA is also an important pharmacological tool in psycholytic therapy, a special kind of insight-oriented psychotherapy [4].

Despite the growing epidemiological and psychiatric relevance of the "ecstasy" analogues MDMA and MDE, to date there are no precise data on their acute effects on cerebral glucose metabolism, the main indicator for cortical and subcortical activity.

Therefore, the aim of this study was to assess (1) which changes in regional cerebral glucose metabolism (rMRGlu) appear in healthy subjects under the influence of a typical "Ecstasy" dose when compared to a placebo control group and (2) what correlations exist between cerebral metabolism and acute psychopathology.

Subjects and methods

This study was carried out in accordance with the Helsinki Declaration and was approved by the local ethics committee, the Federal Health Administration (BfArM) and the radiation protection authorities (BfS). It contains the nuclear medicine part of a more comprehensive interdisciplinary research project on experimentally induced psychoses, including MDE, methamphetamine and psilocybin [7, 8]. It was supported by grants from the Deutsche Forschungsgemeinschaft (DFG Go 717/1–1) and the Interdisciplinary Center for Clinical Research on Central Nervous System at the Medical Faculty of the Aachen University of Technology.

Subjects. Sixteen healthy volunteers (11 men, 5 women; range 27–45 years) were included in the study. The subjects had no current or previous history of relevant physical illness, no current or past axis I or II disorders (according to DSM-III-R), no family history of major psychiatric disorder in first-degree relatives, and they were not regularly taking medication. Before entering the study, subjects were screened with a standard psychiatric interview (SCID), a medical history, a clinical examination, electrocardiogram, and laboratory tests including blood cell counts, electrolytes, plasma creatinine and liver enzymes. None of the subjects received payment for participation, and all gave written informed consent.

Substances. MDE and placebo were obtained from the Pharmaceutical Institute of the University of Tübingen (Germany) and were prepared as capsules of identical appearance, the MDE capsules containing either 100 mg or 10 mg. The individual dose for each subject was calculated from the combination of capsules taken. If necessary, empty placebo capsules were added, so that each subject received five capsules. In a double-blind study design, each subject received orally either placebo or MDE capsules in a dose of 2 mg/kg, to a maximum of 140 mg MDE. One MDE subject had to be excluded from the final data analysis due to technical difficulties.

Protocol. Fasting subjects arrived between 8:00 and 9:00 a.m. They were given free access to water. An indwelling cannula was placed in the veins of both lower arms for subsequent blood taking. Drugs (MDE or placebo) were administered orally with some water between 10:00 and 11:00 a.m. and subjects were instructed to relax. Vital signs were taken throughout the entire experiment. Before and 90 min after oral drug ingestion, subjects were assessed psychopathologically using the Positive and Negative Syndrome Scale of Schizophrenia (PANSS). The PANSS has been well validated [9] and represents the continued development of two commonly used tests, the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Schedule. PANSS was evaluated by a formalized, semistructured interview. It has 33 items on a scale from 1 (normal) to 7 points (extremely abnormal) and comprises subscores for 7 positive (P1–P7), 7 negative (N1–N7), 16 general psychopathological (G1–G16) and 3 aggression risk symptoms. The subscore magnitude indicates the severity of illness. For the rMRGlu-PANSS correlations, we used the subscores P1–7, N1–7, G2 (anxiety), G4 (tension), G6 (depression) and G11 (attentional deficits).

At the height of the drug effect, 110–120 min after oral MDE administration, 157–267 MBq (mean dose: 232 MBq) fluorine-18-deoxyglucose was injected intravenously while the subject lay with closed eyes in the quiet and darkened PET scanner room. Two minutes before radiotracer injection, a constant auditory activation task was started for 32 min. For this activation task, stimulus words were presented via headphones. The words selected were some of commonest nouns of the German language [10]. A total of 640 words was recorded and delivered binaurally at a rate of 1 per 3 s over 32 min, with the subjects repeating each word aloud. The words produced by the subjects were taped for documentation. This activation task was performed to induce a constant and reproducible mental condition during the cerebral ^{18}-FDG uptake for 30 min because a "resting state" is a poorly defined mental condition that might (1) represent completely different mental activities from one subject to another and (2) may also vary considerably under the influence of psychoactive substances.

Imaging protocol (PET). A PET examination was performed using an ECAT 953/15 Scanner (Siemens/CTI, Knoxville, Tenn., USA). The emission scan started 30 min p.i. and continued for 30 min; it was performed in three successive bed positions (3×10 min) since the scanner had an axial field of view of 5.4 cm. In order to correct for photon attenuation, a 15-min transmission scan using eight germanium-68 ring sources was done for each bed position on another day. Input function was calculated by determining plasma activity of arterialized venous blood samples over time (20, 40, 60 s; 2, 4, 6, 8, 10, 20, 30, 40, 60 min p.i.). Reconstruction of 45 transversal attenuation-corrected slices, each 3.375 mm thick, in a 256×256 matrix was done with a Hanning filter (cutoff frequency 0.5). Spatial resolution was 6 mm full width at half maximum (FWHM). Absolute glucose consumption rate was calculated for each pixel (autoradiography method after Sokoloff et al. [11] and Phelps et al. [12]), using measured input function, tissue radioactivity concentration and blood glucose concentration. For quantification of grey matter glucose metabolism according to Phelps et al. (12), a set of rate constants K1–k4 (K1: 0.095, k2: 0.125, k3: 0.069, k4: 0.0055) and a lumped constant of 0.52 were used [13].

Imaging protocol (MRI). Magnetic resonance imaging (MRI) was performed on another day with a circular polarized Helmholtz headcoil in a Magnetom 1.5 Tesla (Siemens, Erlangen, Germany). Using a T1-weighted 3D flash sequence, a volume data set of the

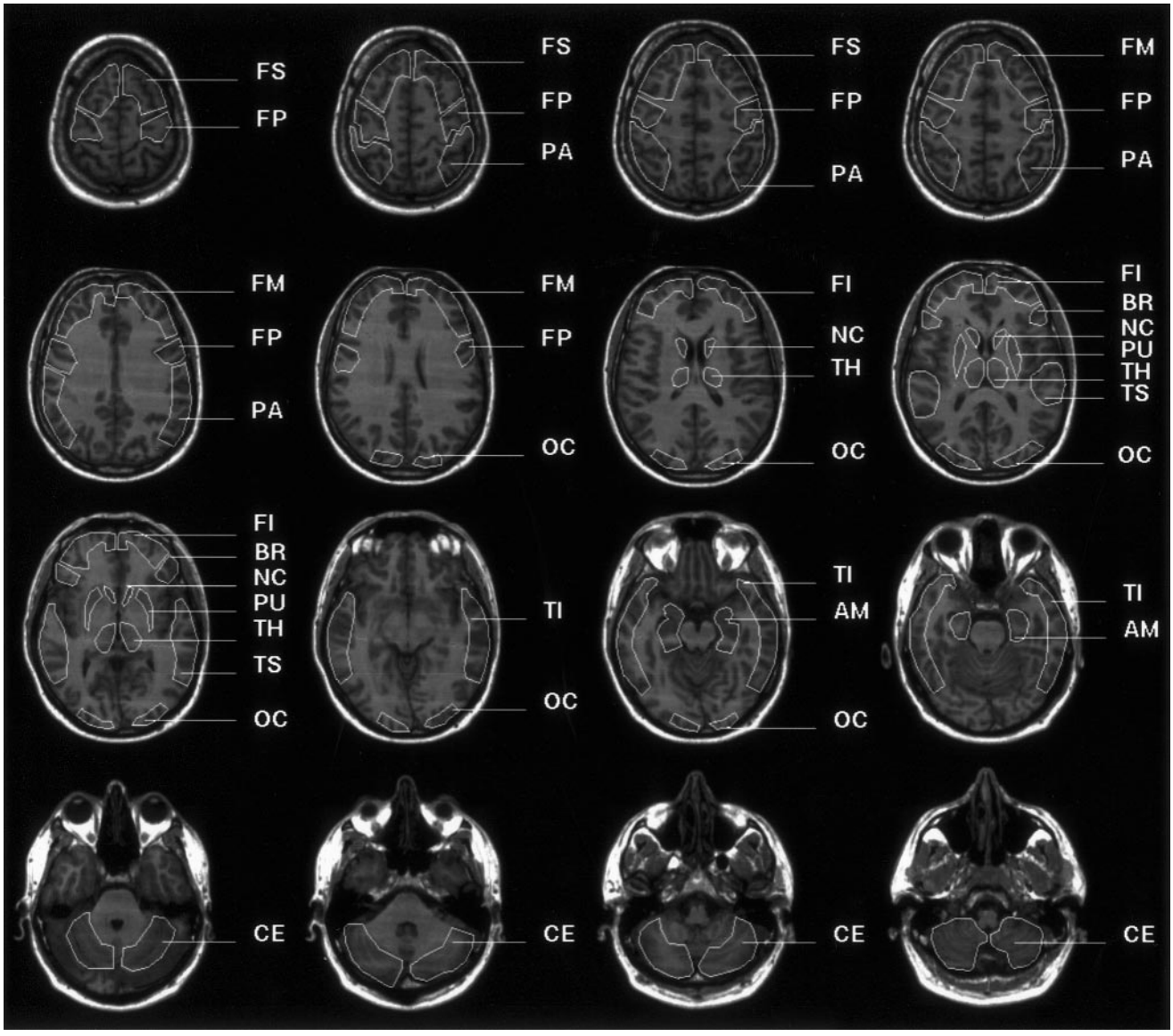

Fig. 1. Transaxial MRI slices of one subject with the manually defined regions of interest superimposed on individual PET slices after PET/MRI realignment (*FS* prefrontal superior, *FM* prefrontal middle, *FI* prefrontal inferior, *BR* frontal operculum, *FP* frontal posterior, *TS* temporal superior, *TI* temporal inferior, *PA* parietal, *OC* occipital, *CE* cerebellum, *NC* caudate nucleus, *PU* putamen, *TH* thalamus, *AM* amygdala, *CA* cingulum anterior, *CM* cingulum middle, *CP* cingulum posterior)

brain was obtained and reconstructed in coronal, transaxial and sagittal slices of 3 mm thickness (TE 5 ms, TR 40 ms, flip angle 40°).

Analysis of image data. A special head-holder system and a thermoplastic head mask enabled fixation of subject's head in exactly the same position in both examinations [14]. After conversion of data from MRI and PET to a uniform data file structure, data were transferred onto a computed system for image analysis (Unix system: SUN-SPARC 20). Exact realignment of MRI and PET data was checked using a special multipurpose imaging tool [15]. PET was adapted coronally, transaxially and sagittally to MRI, and layer thickness was transformed uniformly to 3.375 mm. Using the anatomical atlas by Talairach [16], cortical and subcortical structures were irregularly defined on each individual MRI with regions of interest (ROIs), which were superimposed on the respective PET data as an MRI/PET overlay. All regions were defined for both the right and left hemisphere. All together, 108 regions of interest were defined on each MRI (54 ROIs per hemisphere, Fig. 1). For minimizing the influence of the partial volume effect, each evaluated region exceeded the 2.5-fold volume of the full width at half maximum (FWHM) of the PET scanner. Because of the considerable intra- and interindividual variablity of cerebral glucose metabolism [17, 18], the absolute metabolic rate of glucose of each ROI (rMRGlu) was normalized to the global metabolic rate of glucose, calculated as the volume-weighted average of rMRGlu of all 108 evaluated regions.

For further statistical analysis, the 108 ROIs were summarized in the following (volume-weighted) 17 ROI groups per hemisphere: prefrontal superior, prefrontal middle, prefrontal inferior, frontal posterior, operculum frontale, temporal inferior, temporal superior, parietal, occipital, cerebellum, caudate nucleus, putamen,

thalamus, amygdala, anterior cingulate, middle cingulate and posterior cingulate.

Statistical analysis. For comparing the differences of cerebral glucose metabolism under MDE versus placebo, we performed the two-tailed U-test according to Mann and Whitney. No alpha adjustment for multiple testing was performed, because with a small number of subjects, no *P* value could pass the Bonferoni adjustment for multiple testing of independent sample tests, in particular. Therefore, the study results should be regarded as exploratory rather than confirmatory. For investigating the correlations between metabolic values and psychopathological scores (P1–P7, N1–N7, G2, G4, G6 and G11), correlation coefficients were calculated according to Spearman. Since multiple correlations were done, the statistical power of the coefficient obtained was additionally determined [19–21]. For correlations of small sample sizes, the statistical power should be greater than 80%. For a sample size of seven MDE subjects and a significance level of $P<0.05$, the statistical power is greater than 82% if the correlation coefficient is $r\geq0.85$. Therefore, we considered only correlations with $r\geq0.85$, whereas the total number of uncorrected correlations with $P<0.05$ was much higher. This method of defining a statistical power for analysis of small sample sizes is a standard procedure that is highly reliable for decreasing β-error and excluding chance from multiple correlation testing [20, 21], which could be also shown in other prospective studies [22, 23].

Results

The comparison of global cerebral glucose metabolism between placebo and MDE subjects revealed no significant differences (MDE: 41.8±11.1 µmol/min per 100 g; placebo: 50.1±18.1 µmol/min/100 g, $P=0.298$). The comparison of normalized rMRGlu MDE vs placebo is shown in Table 1. MDE subjects showed a significantly decreased normalized rMRGlu in the bilateral frontal cortex: left frontal posterior (–7.2%, $P<0.05$), right prefrontal superior (–4.6%, $P<0.05$). Increased normalized rMRGlu was found in the bilateral cerebellum (right: +10.1%, $P<0.01$; left: +7.6%, $P<0.05$) and in the right putamen (+6.3%, $P<0.05$), respectively. Figure 2 shows the characteristic normalized metabolic differences between the "Ecstasy" analogue and placebo.

The correlations between metabolic values and psychopathological scores are shown in Table 2. Since the placebo subjects showed no pathological psychometric values on PANSS, the correlations between regional glucose metabolism and psychopathology was performed only for the MDE group. There were positive correlations between middle right cingulate and grandiosity (P5; $r=0.87$, $P=0.011$), right amygdala and difficulties in abstract thinking (N5; $r=0.90$, $P=0.006$), left posterior cingulate and difficulties in abstract thinking (N5; $r=0.90$, $P=0.006$), right prefrontal inferior and attentional deficits (G11; $r=0.85$, $P=0.016$), right anterior cingulate and attentional deficits (G11; r=0.93, $P=0.003$), and left anterior cingulate and attentional deficits (G11; $r=0.85$, $P=0.016$). The only negative correlation was found between left frontal operculum (Broca's area) and attentional deficits (G11; $r=–0.85$, $P=0.016$).

Table 1. Comparison of normalized[a] regional glucose metabolism of MDE vs placebo subjects (mean ± SD)

Region	MDE rMRGlu (mean±SD)	Right hemisphere			MDE rMRGlu (mean±SD)	Left hemisphere		
		Placebo rMRGlu (mean±SD)	Changes (in %)	*P*		Placebo rMRGlu (mean±SD)	Changes (in %)	*P*
Prefrontal superior	1.068±0.050	1.119±0.039	–4.6	<0.05	1.084±0.038	1.105±0.053	–1.9	n. s.
Prefrontal middle	1.008±0.036	1.023±0.039	–1.5	n. s.	1.005±0.057	1.036±0.048	–3.0	n. s.
Prefrontal inferior	0.960±0.034	0.972±0.046	–1.3	n. s.	0.948±0.060	0.962±0.086	–1.5	n. s.
Frontal operculum	1.072±0.111	1.042±0.060	+2.9	n. s.	1.085±0.100	1.036±0.102	+4.7	n. s.
Frontal posterior	1.045±0.065	1.091±0.059	–4.2	n. s.	1.029±0.040	1.109±0.070	–7.2	<0.05
Temporal inferior	0.929±0.055	0.883±0.060	+5.2	n. s.	0.916±0.051	0.907±0.054	+1.0	n. s.
Temporal superior	1.062±0.052	1.047±0.052	+1.4	n. s.	1.018±0.075	1.046±0.064	–2.7	n. s.
Parietal	1.070±0.084	1.090±0.034	–1.8	n. s.	1.037±0.075	1.073±0.061	–3.4	n. s.
Occipital	1.123±0.036	1.105±0.080	+1.6	n. s.	1.113±0.072	1.097±0.068	+1.5	n. s.
Cerebellum	0.924±0.054	0.839±0.016	+10.1	<0.01	0.912±0.064	0.848±0.047	+7.6	<0.05
Caudate nucleus	1.030±0.096	1.047±0.076	–1.6	n. s.	1.078±0.096	1.071±0.084	+0.7	n. s.
Putamen	1.242±0.065	1.169±0.062	+6.3	<0.05	1.203±0.059	1.216±0.094	–1.1	n. s.
Thalamus	1.070±0.083	1.067±0.084	+0.3	n. s.	1.071±0.057	1.043±0.078	+2.7	n. s.
Amygdala	0.726±0.036	0.735±0.074	–1.2	n. s.	0.727±0.056	0.730±0.065	–0.4	n. s.
Cingulate anterior	0.987±0.068	0.920±0.074	+7.3	n. s.	0.894±0.125	0.898±0.086	–0.5	n. s.
Cingulate middle	0.927±0.103	0.944±0.083	–1.8	n. s.	0.913±0.079	0.909±0.084	+0.4	n. s.
Cingulate posterior	1.284±0.107	1.202±0.110	+6.8	n. s.	1.219±0.056	1.283±0.097	–5.0	n. s.

[a] rMRGlu values are normalized to the global cerebral glucose metabolism

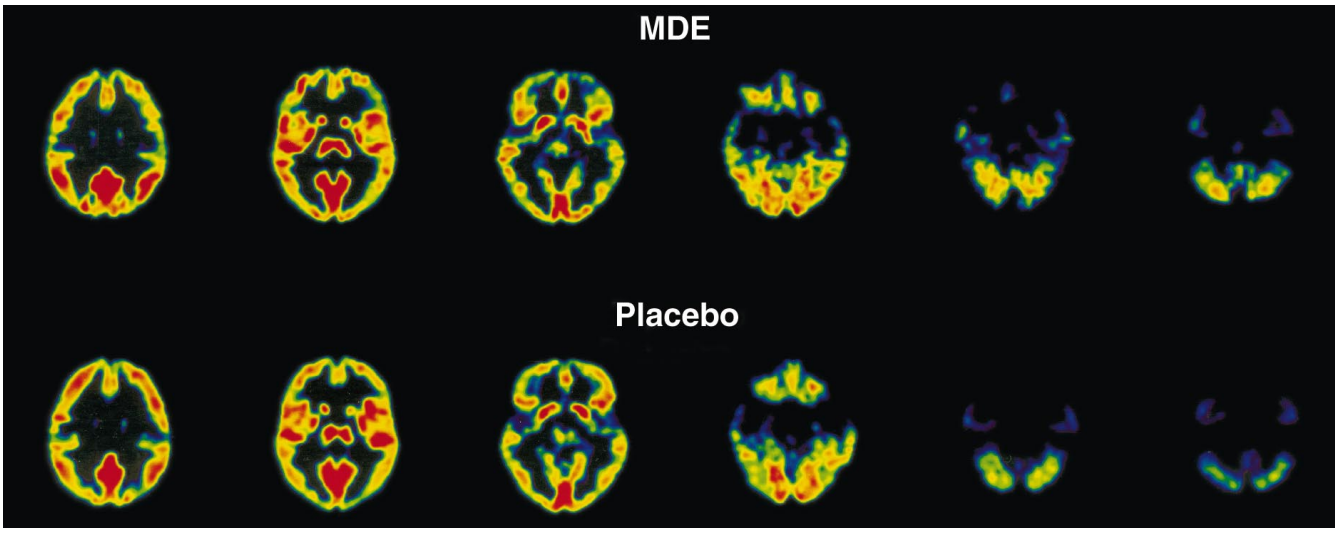

Fig. 2. *Top row* Transaxial ^{18}FDG PET slices (normalized to global glucose metabolism) under MDE; *bottom row* corresponding slices under placebo. There is decreased bifrontal and increased cerebellar glucose metabolism under MDE. The (statistically significant) metabolic increase of the right putamen is not clearly visible

Table 2. Interregional correlations of normalized glucose metabolism during word repetition and word association. Only significant correlations (statistical power >0.82: $r \geq 30.85$) are shown

	P 5 Grandiosity	N 5 Difficulties in abstract thinking	G 11 Attentional deficits
Prefrontal inferior,right			0.85*
Frontal operculum left			–0.85*
Cingulate anterior,			0.93**
Cingulate anterior,			0.85*
Cingulate middle, right	0.87*		
Cingulate posterior, left		0.90**	
Amygdala, right		0.90**	

*P<0,05; **P<0.01

Discussion

This study showed a characteristic pattern of cerebral metabolic alterations under MDE revealing changes of the frontostriato(thalamo)-cerebellar network [24], with rMRGlu reduced bifrontally and increased bilaterally in the cerebellum and in the right putamen. There were correlations between neuronal metabolism and acute psychopathology for important regions in cognition: different regions of the frontal cortex, various parts of the cingulate gyrus and the right amygdala.

Decreased frontal glucose metabolism or blood flow is characteristic in psychopathologically very different psychiatric conditions such as endogenous depression [25, 26], but has also been described in (mainly chronic) schizophrenics as hypofrontality [27, 28]. Acute patients show a clear correlation between cerebral blood flow and psychopathology [22, 23]. Major depressive disorder patients show a characteristic correlation between decreased frontal blood flow and severity of negative symptoms, but not decreased frontal blood flow and severity of depressive symptomatology [26]. We observed a significant correlation under MDE between right inferior frontal metabolism and attentional deficits, but no correlation with negative symptoms.

Pharmacologically induced hypofrontality such as that caused by MDE has also been observed under the acute influence of other psychotropic substances like amphetamines [29], cocaine [30] and morphine [31], whereas decreased whole-brain metabolism with the largest changes in the thalamus and occipital cortex has been described for benzodiazepines [32]. As a muscarinic acetylcholine receptor antagonist, scopolamine also induces a hypofrontal perfusion pattern, which is reversed by the CNS-active cholinesterase inhibitor physostigmin [33]. The common pattern of a decreased frontal metabolism or blood flow for very different psychotropic substances is all the more remarkable since disparate psychopathological conditions thus correlate with a similar neurometabolic finding. This again raises the question of whether and how much hypofrontality is an epiphenomenon that only represents a reduction of frontal neuronal activity as a result of various pathogenetically processes.

The only subcortical metabolic alteration under MDE is the finding of an increased metabolism in the right putamen. Pearlson et al. [30] reported significantly reduced blood flow in the left putamen and nucleus caudatus following i.v. administration of cocaine. Wolkin et al. [29] observed bilaterally reduced glucose metabolism in the striatum under amphetamine, whereas a medium oral methamphetamine dosage led to (non-significant) bilateral metabolism increases in the putamen [7]. This pat-

tern of opposite frontal cortex and striatum metabolisms under MDE could point to characteristic changes in the frontostriatocerebellar balance, which might play an important role in cognitive processing.

Aside from the changes in fronto striatal metabolism discussed so far, the most striking finding of this study is the evidence of a definite bilateral increase in cerebellar glucose metabolism under MDE. The most likely explanation, that this could be a neurometabolical correlate of heightened motor activity from a stimulating amphetamine-like action, is improbable since during the 30 min of cerebral glucose uptake and subsequent PET examination, the "Ecstasy" subjects showed no differences in motor activity from the control group. This is also confirmed by the fact that no bilateral rMRGlu increase in the precentral cortex could be observed.

The obvious increase in cerebellar metabolism under "Ecstasy" again brings up the question of participation of the cerebellum in cognitive and emotional processes, which has already been suggested by lesion studies [34], as well as various activation studies using PET and fMRI [35–38). An increase in cerebellar metabolism has also been described for the phenylethylamine stimulant methylphenidate (which revealed variable changes of global cerebral glucose metabolism [39]) and for tetrahydrocannabinol [40, 41], which is pharmacologically completely different from phenylethylamine derivatives like amphetamines or entactogens.

Alterations in the fronto(thalamo)-cerebellar balance, with decreased frontal and cerebellar blood flow, were also seen in unmedicated schizophrenic patients under cognitive activation [24], which again suggests a role of the cerebellum as a part of a functional network in cognitive processing.

As in this study, a typical methodological limitation of study designs on psychoactive drug is the frequent omission of a Bonferoni alpha adjustment because of the relatively small sample sizes [42]. The ethics committees are relatively rigorous in permitting the application of psychoactive substances on healthy volunteers and usually permit the examination of only a few test subjects. In this study, our volunteers were either physicians or psychologists, who were competent to assess the potential risks of MDE. Nevertheless, expansion of the sample size to increase the statistical validity was not approved. Strict application of the methodological criteria of conventional clinical studies to a large number of test subjects in effect makes studies on psychoactive drugs impossible, as is evident by the fact that despite their increasing medical and epidemiological importance, only a few PET studies have so far been done on this subject.

Looking at the correlations between acute symptomatology and the neurometabolic changes under MDE, most of these correlations were related to the cingulate gyrus: grandiosity to the middle right cingulate, difficulties in abstract thinking to the left posterior cingulate, and attentional deficits to the right and left anterior cingulate. The anterior cingulate is assumed to play an important role in the executive control of cognition associated with selective attention and motivation processes "selection for action": [43–47], response competition [48], and anticipation processes [49]. The finding of a positive correlation between attentional deficits and the anterior cingulate may be the expression of compensatory cingulate activation to counteract deficits of attention due to the emotional and perceptual changes caused by MDE.

The posterior cingulate cortex, which positively correlated with difficulties in abstract thinking under MDE, has been proposed to represent an evaluative region that is involved in assessing the environment and in memory [50]. Minoshima et al. [51] have suggested a role for the posterior cingulate in impairment of learning and memory and have found reduced glucose metabolism of this region as a predictive factor in the very early stages of Alzheimer's disease.

In addition to the correlations with different parts of the cingulate gyrus, there is a correlation between difficulties in abstract thinking and the right amygdala, which is thought to be associated with processing of affective information, fear conditioning [52], and startle reflex mediation as a marker for the aversiveness of an emotional state [53]. Remarkably, we found no significant correlation between the right amygdala and anxiety (G2) in the MDE subjects. The only negative correlation found under MDE was between attentional deficits and left frontal operculum (Broca's area), which is activated in different (verbal) association processes [47, 54–56], but we assume that it is not directly related to attentional functions.

In conclusion, this study describes the immediate action of the "Ecstasy" analogue MDE on the cerebral glucose metabolism of healthy non-users, who exhibited characteristic changes in frontal, striatal and cerebellar metabolism, which showed parallels both to other psychotropic substances as well as to various psychiatric disorders. The "Ecstasy" subjects showed correlations between acute psychopathology and neuronal metabolism, which point to the involvement of distributed functional centers in the brain which may form a cognitive network. Further research is necessary to determine how far these immediate changes in non-users are precursors of permanent metabolic alterations associated with long-term use.

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