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# Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study

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**Abstract**

3,4-Methylenedioxymethamphetamine (MDMA), an illicit recreational drug, damages serotonergic nerve endings. Since the cerebrovasculature is regulated partly by the serotonergic system, MDMA may affect cerebral blood flow (CBF) in humans. We evaluated 21 abstinent recreational MDMA users and 21 age- and gender-matched healthy subjects with brain SPECT and MRI. Ten of the MDMA subjects also had repeat SPECT and MRI after receiving two doses of MDMA. Abstinent MDMA users showed no significantly different global or regional CBF (rCBF) compared to the control subjects. However, within 3 weeks after MDMA administration, rCBF remained decreased in the visual cortex, the caudate, the superior parietal and dorsolateral frontal regions compared to baseline rCBF. The decreased rCBF tended to be more pronounced in subjects who received the higher dosage of MDMA. Two subjects who were scanned at 2–3 months after MDMA administration showed increased rather than decreased rCBF. Low-dose recreational MDMA use does not cause detectable persistent rCBF changes in humans. The lack of long-term rCBF changes may be due to a non-significant effect of serotonergic deficits on rCBF, or regeneration of

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serotonergic nerve terminals. The subacute decrease in rCBF after MDMA administration may be due to the direct effect of MDMA on the serotonergic system or the indirect effects of its metabolites on the dopaminergic system; the preliminary data suggest these effects may be transient. 

*Keywords:* Substance abuse; Single photon emission computed tomography; Magnetic resonance imaging; Serotonin

## 1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy' or 'Adam', has been used illicitly by millions of individuals; however, little is known about its neurobiologic effects. MDMA is a methamphetamine derivative first synthesized in 1914 in Germany; it was experimented with as an adjunct to psychotherapy two decades ago (Shulgin and Nichols, 1978). In the past decade, MDMA has become a recreational drug of increasing popularity, particularly among young people in the rapidly growing 'rave' scene as the preferred 'dance drug' of choice, and by gay party patrons (Lewis and Rose, 1995). Given the dramatically escalating use of MDMA, there exists a pressing need to evaluate how the drug might affect brain function in MDMA users.

In rodents, MDMA has been shown to damage serotonergic (5-HT) neurons after single or multiple doses (Battaglia et al., 1988; Ricaurte et al., 1988; Lew et al., 1996; Sabol et al., 1996); the neurotoxicity appears to be limited to axon terminals (Molliver, 1987; Baumgarten and Zimmerman, 1992). Studies in monkeys showed persistent reductions of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and 5-HT uptake sites at 2 weeks and at 18 months after MDMA administration (Ricaurte et al., 1988), but complete recovery appears to occur in some regions such as the thalamus and the hypothalamus (Ali et al., 1993). Since it is believed that humans are generally more sensitive than monkeys to the toxic effects of drugs, humans who use MDMA might be at risk from its neurotoxic effects. Biological data gathered on the effects of MDMA in humans are limited (Grob et al., 1996) but are beginning to emerge. Several studies evaluated the cerebrospinal fluid 5-HIAA concentrations in MDMA users and found either normal (Peroutka, 1987) or decreased levels (Ricaurte et al., 1993; McCann et al., 1994). Recent neuroimaging studies have shown decreased 5-HT transporter on positron emission tomography, and increased myoinositol, a glial marker, on proton spectroscopy of abstinent MDMA users (McCann et al., 1998; Chang et al., 1999). Abnormal neuropsychiatric and neuropsychological function in MDMA users has also been reported (Green et al., 1995; Bolla et al., 1998).

Since MDMA is a serotonergic (5-HT) specific neurotoxin, a dysfunction of 5-HT mechanisms may play a role in the rCBF changes. Serotonergic regulation of cerebrovasculature has long been implicated and documented in cerebrovascular diseases such as migraine (Fozard, 1989), and cerebral blood vessels at all levels in the cerebrovascular tree are innervated by 5-HT neurons (Cohen et al., 1996). This study evaluates the possible chronic and subacute effects of MDMA on brain function as measured by regional cerebral blood flow (rCBF).

## 2. Methods

### 2.1. Subjects

Twenty-one subjects with a history of recreational MDMA use (17 males and 4 females, ages $43.4 \pm 12.5$ years, education $15.9 \pm 2.2$ years) and 21 age-, gender- and socioeconomically-matched drug-naïve healthy subjects (17 males and 4 females, ages $43.7 \pm 11.7$ years, education: $16.2 \pm 2.3$ years) were consecutively recruited and studied with magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT). MDMA subjects were recruited from local advertisements and screened using a standardized questionnaire. They were included in the study if they had used low doses of MDMA

(< 3 mg/kg per use) recreationally (≥ 6 times/year) for at least 1 year, and had been abstinent for at least 2 weeks prior to the study. Each subject underwent a semi-structured psychiatric interview (by a psychiatrist, C.G.), physical and neurological examination, to ensure the subject was free of any personal or family history of mental or medical illnesses. Each subject had a urine toxicology screen prior to the study. MDMA usage and history of other drug use were also recorded. Subjects were excluded if they: (1) had a positive urine screen [for amphetamines (which would be positive if MDMA were used within 24–48 h), cocaine, marijuana, barbiturates or benzodiazepines]; (2) were on medications for any chronic psychiatric or medical illnesses; (3) had a history of alcohol abuse or substance dependence (except for MDMA and nicotine) according to the DSM-IV diagnostic criteria; (4) had a history of head trauma with loss of consciousness for more than 30 min; (5) were pregnant; (6) had metallic objects in their body. After complete description of the study to the subjects, written informed consent approved by our institution was obtained.

The MDMA users had a median education level of 15.8 years (range: 12–20 years); all of the subjects were employed or in school. None of the subjects had cognitive complaints or a criminal record. The MDMA subjects had used the drug only recreationally and last used MDMA $6.6 \pm 7.7$ months (median = 4.0 months, range = 0.5–26 months) previously. Duration of use was $8.6 \pm 4.9$ years (median: 10 years, range: 1–17 years), and the estimated total number of times of MDMA use was $211 \pm 340$ times (median: 75 times, range: 6–1500 times). The average cumulative lifetime exposure to MDMA, based on the total number of times used and the average dose per use (125–225 mg), was 13.1 g (range: 0.5–263 g). Some of the subjects had experimented with other substances in the past, more than 6 months ago, usually at low recreational doses and were never dependent on them. These substances included lysergic acid diethylamide-25 (71% of the subjects), marijuana (83%), mushrooms (46%) and other amphetamines (29%). Only three subjects admitted to having used cocaine up to three times in their lifetimes but were never dependent on cocaine. MDMA was reportedly the primary drug of choice for all the subjects.

Ten of the MDMA users (6 males, 4 females; ages $38.4 \pm 12.5$ years) participated in repeat imaging studies after receiving MDMA as inpatients at our Clinical Study Center as part of a Phase I study of MDMA (Grob et al., 1996). These 10 subjects had last used MDMA $7.43 \pm 8.1$ months earlier (range: 0.5–24 months) and had used MDMA $171 \pm 226$ times (range: 6–750 times) within $7.47 \pm 4.0$ years (range: 1.5–12 years). Each subject received two doses of MDMA orally, on two sessions within 1 week (except for two of the subjects who received the second dose 21 days later), for a total dose of $3.5 \pm 0.8$ mg/kg (range: 2.25–4.75 mg/kg) or a total of $253 \pm 63$ mg (range: 156.8–348.5 mg) (Table 3). To minimize the acute effects of MDMA, each subject had repeat MRI and SPECT scans $25.3 \pm 21.3$ days (10–80 days) after the second dose of MDMA. Eight of the 10 subjects were scanned within 3 weeks after they received MDMA. Subjects were again asked to refrain from MDMA or any other drug use, and urine toxicology screen was repeated to ensure absence of amphetamines prior to the second imaging study.

### 2.2. MRI

MRI was performed on a 1.5-T scanner (General Electric, Signa 5.4, Milwaukee, WI). The examination began with a sagittal T1 weighted localizer (TE/TR 11/500 ms, 4-mm slice thickness, 1-mm gap, 24-cm FOV), followed by a coronal fast double spin echo sequence (TE1/TE2/TR 17/102/4000 ms, 5-mm slice thickness, no gap, 24-cm FOV) and an axial fast inversion recovery (IR) scan (TE/TI/TR 32/120/4000 ms, 3.5-mm slice thickness, no gap, 24-cm FOV). The IR sequence yields excellent contrast between white matter, gray matter, and CSF, and is optimal for co-registration with SPECT and delineation of anatomical regions.

### 2.3. SPECT

Each subject was evaluated with both 133-xenon ($^{133}$Xe, Dupont, Billerica, MA) and technetium-

99m hexamethylpropyleneamine oxime ($^{99m}$Tc-HMPAO, Ceretec, Amersham, Arlington Heights, IL) using a brain-dedicated SPECT scanner (Headtome II, Shimadzu). The subjects were scanned in the supine position, with eyes closed but awake. Three axial slices ($64 \times 64$-pixel matrices, spatial resolution 20 mm) at 2, 6, and 10 cm above the orbitomeatal line were obtained over 6 min. After 1 min of baseline acquisition, the subjects inhaled 1100 MBq of $^{133}$Xe gas and oxygen mixture for 1 min, and were scanned for 4 min during washout. Absolute rCBF was calculated from six sequential images using a monoexponential model, and the $^{133}$Xe end-tidal concentration air curve as the input function.

Next, 1100 MBq of $^{99m}$Tc HMPAO was administered to obtain higher-resolution perfusion maps. The scanning was started 1 h after HMPAO injection. Twelve axial contiguous slices were acquired (16-mm slice thickness, 30-min scan time, 8-mm resolution). All images were evaluated for technical assurance by a nuclear physician (F.S.M.). Final rCBF measurements were obtained by calibrating the higher resolution $^{99m}$Tc-HMPAO scans with absolute rCBF from the $^{133}$Xe images, using a non-linear regression model (Payne et al., 1996).

### *2.4. Quantification of $^{133}$Xe-calibrated HMPAO SPECT using co-registered MRI*

$^{133}$Xe -calibrated $^{99m}$Tc-HMPAO images were co-registered with MRI and corrected for partial volume effects of cerebrospinal fluid, using a surface-based co-registration program (Itti et al., 1997a,b). The SPECT images were re-sliced according to each subject's MRI. Global CBF, global volume of cerebrospinal fluid (CSF), %CSF, and global brain volume were automatically determined. The rCBF in selected brain regions was quantified by drawing regions of interest (ROIs) on the co-registered MRI (Fig. 1) by one investigator (L.C.) blinded to the drug use status of the subjects. The intra-subject rCBF measurements, drawn by the same observer 2 weeks apart, showed high reproducibility ($r = 0.98$).

### *2.5. Statistical analysis*

Statistical analyses were performed using STATISTICA, 4.5 (StatSoft, Inc.). Comparisons of rCBF between the MDMA users and the control subjects were performed using a three-way mixed-model analysis of variance (ANOVA), with the drug use status as a between-variable, and the brain hemisphere and brain region as within-variables. In the MDMA users, multiple linear regression analyses of global and rCBF, global brain volume and global %CSF on cumulative lifetime MDMA exposure and time since last MDMA use were performed. In eight of the 10 MDMA users who received MDMA and were scanned between 1.5 and 3 weeks later, rCBF post-MDMA administration was compared to that at baseline and to that of the eight matched comparison subjects using a three-way repeated measures ANOVA, with the within-variables group/drug status, brain hemisphere, and brain region. The effects of time since MDMA administration, and the dosage of MDMA received on the rCBF changes were evaluated using linear regression analyses. Overall *P*-values from the ANOVAs were corrected for multiple comparisons using the Huynh–Feldt test. Statistically significant effects and interactions in the ANOVAs were further evaluated using post-hoc analyses with Fisher's PLSD tests; *P*-values $\leq 0.001$ ($0.05/50$, after Bonferroni correction) for multiple comparisons were considered statistically significant.

## 3. Results

### *3.1. Global and regional CBF, and global brain volume in MDMA users*

All MDMA users and normal control subjects had normal MRI with no focal brain lesions. After co-registration of each SPECT and the corresponding intra-subject MRI, and partial volume correction, the global CBF in the abstinent MDMA users was only 2.3% lower compared to the matched control subjects (Table 1). In the

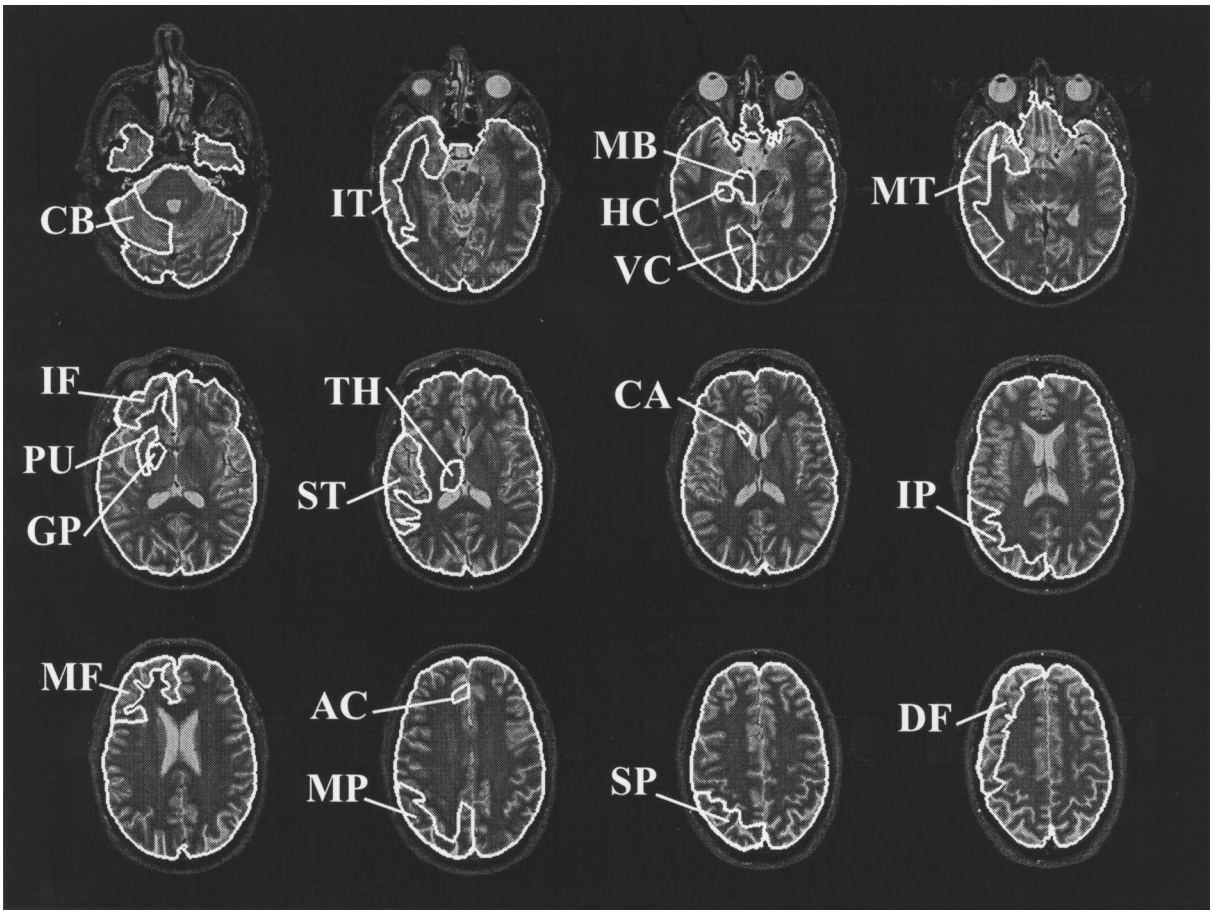


Fig. 1. Axial MR images showing representative regions of interest (ROIs) in which rCBF was determined from co-registered SPECT. Cerebellum (CB), temporal cortex (inferior temporal, IT; middle temporal, MT; superior temporal, ST), midbrain (MB), hippocampus (HC), visual cortex (VC), frontal cortex (inferior frontal, IF; mid-frontal, MF; dorsolateral frontal, DF), putamen (PU), globus pallidus (GP), thalamus (TH), caudate (CA), parietal cortex (inferior parietal, IP; mid-parietal, MP; superior parietal, SP), anterior cingulum (AC).

individual regions, MDMA users showed mild, but not significant, reductions in rCBF compared to the control subjects ($F_{1,40} = 0.23$; $P < 0.64$; Table 1, Fig. 2). Regional CBF showed no interaction between drug status and brain region ($F_{13,520} = 1.10$; $P < 0.36$) or drug status and hemisphere ($F_{1,40} = 1.44$; $P < 0.24$), despite significant differences of rCBF in the brain regions ($F_{13,520} = 82.7$; $P < 0.000001$) and interaction between brain region and hemisphere ($F_{13,520} = 3.0$; $P = 0.0003$). In addition, 3-way ANOVA among drug status, region and hemisphere showed no interaction effect ($F_{13,520} = 0.84$; $P < 0.62$). Likewise, global brain volume, global CSF, and %CSF were not different between the MDMA users and comparison subjects (Table 1).

Additionally, global and regional CBF did not correlate significantly with the duration, frequency, or recency of MDMA use. Global brain volume, however, correlated negatively with the duration of MDMA use even when co-varied for age ($r = -0.57$, $P = 0.02$).

### 3.2. Effects of MDMA administration

In the eight subjects who received MDMA and were scanned between 2 and 3 weeks later, global CBF and rCBF on post-MDMA SPECT scans

Table 1
Global and regional CBF, brain volume and global %CSF (mean ± S.D.)

| Region of interest | MDMA users ($n = 21$) | | Comparison subjects ($n = 21$) | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Brain volume ($cm^3$) | 1337.9 ± 155.1 (+0.20%) | | 1335.2 ± 138.3 | |
| Global CSF volume ($cm^3$) | 169.7 ± 56.4 (+22.4%) | | 138.6 ± 47.4 | |
| Global CSF (%) | 11.2 ± 3.5 (+20.4%) | | 9.3 ± 3.0 | |
| Global CBF (ml/100 g per min) | 42.8 ± 8.4 (−2.3%) | | 43.8 ± 6.7 | |
| Cerebellum | 48.8 ± 9.7 (−1.2%) | 49.6 ± 9.8 (−0.4%) | 49.4 ± 7.0 | 49.8 ± 6.9 |
| Visual cortex | 55.8 ± 9.9 (+1.5%) | 55.9 ± 10.8 (+1.1%) | 55.0 ± 7.8 | 55.3 ± 7.4 |
| Inf temporal cortex | 41.6 ± 7.9 (−5.9%) | 41.2 ± 8.2 (−4.0%) | 44.2 ± 6.7 | 42.9 ± 6.4 |
| Mid temporal cortex | 45.0 ± 8.6 (−4.7%) | 44.7 ± 8.4 (−2.2%) | 47.2 ± 7.1 | 45.7 ± 6.0 |
| Sup temporal cortex | 47.2 ± 8.6 (−2.9%) | 47.0 ± 9.2 (−1.9%) | 48.6 ± 7.6 | 47.9 ± 7.8 |
| Globus pallidus | 46.3 ± 8.9 (−3.3%) | 46.5 ± 7.8 (−1.9%) | 47.9 ± 7.5 | 47.4 ± 7.1 |
| Putamen | 51.4 ± 9.5 (−2.5%) | 51.3 ± 9.7 (−2.5%) | 52.7 ± 8.9 | 52.6 ± 8.6 |
| Thalamus | 52.6 ± 8.9 (−3.1%) | 53.1 ± 9.7 (−4.5%) | 54.3 ± 8.7 | 55.6 ± 9.5 |
| Inf parietal cortex | 45.3 ± 8.0 (−4.4%) | 45.2 ± 8.1 (−3.8%) | 47.4 ± 7.8 | 47.0 ± 8.1 |
| Sup parietal cortex | 45.2 ± 8.6 (−4.8%) | 44.6 ± 8.5 (−6.3%) | 47.5 ± 8.7 | 47.6 ± 8.4 |
| Dorsal/lat frontal | 47.0 ± 9.5 (−3.3%) | 47.3 ± 9.4 (−1.5%) | 48.6 ± 8.3 | 48.0 ± 8.4 |
| Ant cingulum | 50.2 ± 10.7 (−2.0%) | 51.3 ± 12.6 (−3.0%) | 51.2 ± 9.7 | 52.9 ± 9.9 |
| Inf frontal | 39.0 ± 9.5 (−3.0%) | 39.0 ± 8.9 (−2.0%) | 40.2 ± 7.4 | 39.8 ± 7.9 |
| Mid frontal | 46.5 ± 9 (+0.9%) | 45.5 ± 10.9 (+0.4%) | 46.1 ± 8.5 | 45.3 ± 9.1 |

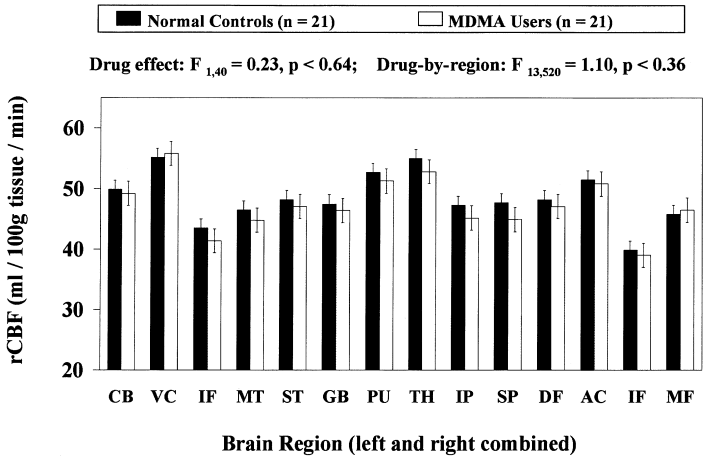


Fig. 2. Bar graphs depicting rCBF (averaged between right and left hemispheres) in each of the brain regions (ROIs) in both MDMA users and control subjects. Brain regions are defined based on ROIs shown in Fig. 1. Compared to the control subjects, MDMA users show lower, but not significantly different, mean rCBF in most brain regions measured except the visual cortex (VC) and the mid-frontal cortex (MF).

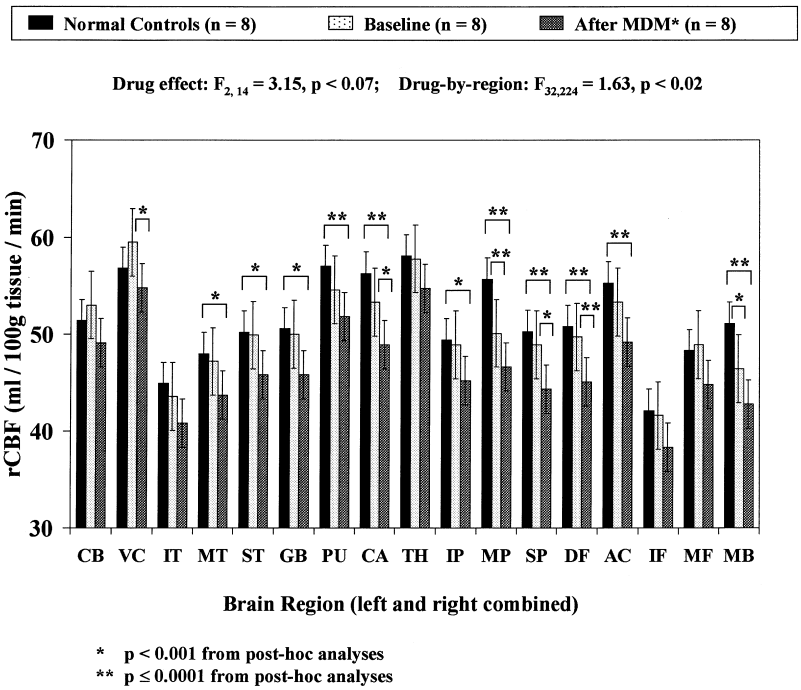


Fig. 3. Bar graphs showing rCBF (averaged between right and left hemispheres) in the eight MDMA subjects who had repeat SPECT scans 2–3 weeks after receiving two doses of MDMA. The rCBF of the corresponding eight age- and gender-matched healthy control subjects is also shown for comparison. Brain regions are defined based on ROIs shown in Fig. 1 (see also Table 2).

Table 2
Brain volume, global %CSF, global and regional CBF in MDMA users at baseline and post-MDMA[a]

| Region of interest | | Matched comparison subjects ($n = 8$) | Baseline MDMA users ($n = 8$) | Post-MDMA[b] administration (pre–post difference) ($n = 8$) | *P*-values[c] Pre MDMA vs. controls | *P*-values[c] Baseline vs. post-MDMA | *P*-values[c] Post MDMA vs. controls |
|---|---|---|---|---|---|---|---|
| Brain volume ($cm^3$) | | 1394 ± 149 | 1374 ± 122 | 1393 ± 115 (+1.4%) | n.s. | n.s. | n.s. |
| Global CSF ($cm^3$) | | 149 ± 58 | 127 ± 33 | 128 ± 30 (+0.8%) | n.s. | n.s. | n.s. |
| Global CSF (%) | | 9.7 ± 3.7 | 8.4 ± 1.8 | 8.4 ± 1.8 (0%) | n.s. | n.s. | n.s. |
| Global CBF (ml/100 g per min) | | 45.9 ± 6.5 | 46.1 ± 11.6 | 42.6 ± 8.3 (−7.6%) | n.s. | n.s. | n.s. |
| Cerebellum | R | 51.6 ± 7.7 | 53.1 ± 12.9 | 49.2 ± 8.8 (7.3%) | n.s. | n.s. | n.s. |
| | L | 51.3 ± 7.7 | 52.8 ± 13.2 | 49.2 ± 8.5 (−6.8%) | | | |
| Visual cortex | R | 57.1 ± 7.9 | 59.2 ± 12.8 | 53.9 ± 9.2 (−9.0%) | n.s. | 0.0004 | n.s. |
| | L | 56.6 ± 7.8 | 59.8 ± 13.6 | 54.5 ± 9.8 (−8.9%) | | | |
| Inferior temporal | R | 45.9 ± 4.6 | 43.5 ± 11.6 | 40.8 ± 9.2 (−6.2%) | n.s. | n.s. | n.s. |
| | L | 43.8 ± 5.4 | 43.7 ± 11.8 | 40.8 ± 8.6 (−6.6) | | | |
| Middle temporal | R | 49.1 ± 6.4 | 47.4 ± 11.6 | 44.1 ± 8.7 (−6.7%) | n.s. | n.s. | 0.001 |
| | L | 47.1 ± 6.9 | 46.9 ± 10.5 | 43.4 ± 7.7 (−7.5%) | | | |
| Superior temporal | R | 49.9 ± 6.9 | 49.8 ± 11.9 | 45.7 ± 8.8 (−8.2%) | n.s. | n.s. | 0.001 |
| | L | 50.5 ± 6.5 | 50.0 ± 12.4 | 45.9 ± 9.0 (−8.2%) | | | |
| Globus pallidus | R | 50.6 ± 7.5 | 49.9 ± 13.0 | 45.8 ± 9.9 (−8.2%) | n.s. | n.s. | 0.0003 |
| | L | 50.7 ± 6.5 | 50.1 ± 11.1 | 45.9 ± 7.3 (−8.4%) | | | |
| Putamen | R | 57.1 ± 9.2 | 54.0 ± 14.3 | 51.4 ± 9.2 (−4.8%) | n.s. | n.s. | 0.0001 |
| | L | 56.9 ± 7.9 | 55.2 ± 13.8 | 52.2 ± 9.7 (−5.4%) | | | |
| Caudate | R | 55.9 ± 7.8 | 52.5 ± 12.9 | 47.7 ± 9.3 (−9.1%) | n.s. | 0.001 | < 0.0001 |
| | L | 56.8 ± 7.5 | 54.2 ± 11.9 | 49.2 ± 7.8 (−9.2%) | | | |
| Thalamus | R | 57.2 ± 8.6 | 57.0 ± 11.8 | 54.0 ± 8.6 (−5.3%) | n.s. | n.s. | n.s. |
| | L | 59.1 ± 9.1 | 58.5 ± 12.3 | 55.4 ± 8.6 (−5.3%) | | | |
| Inferior parietal | R | 49.7 ± 5.9 | 49.2 ± 10.6 | 45.5 ± 7.9 (−7.5%) | n.s. | n.s. | 0.001 |
| | L | 49.1 ± 6.9 | 48.6 ± 10.2 | 44.8 ± 7.4 (−7.8%) | | | |
| Middle parietal | R | 56.2 ± 6.5 | 50.0 ± 11.2 | 46.9 ± 7.9 (−6.2%) | < 0.0001 | n.s. | < 0.0001 |
| | L | 55.2 ± 5.2 | 50.2 ± 11.3 | 46.4 ± 7.7 (−7.6%) | | | |
| Superior parietal | R | 50.0 ± 8.8 | 48.9 ± 10.8 | 44.0 ± 6.2 (−10%) | n.s. | 0.0005 | < 0.0001 |
| | L | 50.7 ± 7.6 | 48.9 ± 11.5 | 44.5 ± 7.1 (−9.0%) | | | |
| Dorsal/lat frontal | R | 51.2 ± 8.4 | 49.2 ± 12.4 | 44.3 ± 8.6 (−10%) | n.s. | 0.0001 | < 0.0001 |
| | L | 50.4 ± 8.3 | 50.2 ± 12.2 | 46.0 ± 8.2 (−8.4%) | | | |
| Ant cingulum | R | 54.8 ± 8.1 | 53.4 ± 14.1 | 49.2 ± 9.2 (−7.9%) | n.s. | n.s. | < 0.0001 |
| | L | 55.8 ± 9.1 | 53.1 ± 16.3 | 49.3 ± 9.8 (−7.2%) | | | |
| Inf frontal | R | 42.3 ± 8.6 | 41.8 ± 14.6 | 38.5 ± 9.9 (−7.9%) | n.s. | n.s. | n.s. |
| | L | 41.9 ± 8.7 | 41.5 ± 13.2 | 38.2 ± 9.1 (−8.0%) | | | |
| Mid frontal | R | 49.4 ± 7.9 | 48.5 ± 14.9 | 44.8 ± 11.2 (−7.6) | n.s. | n.s. | n.s. |
| | L | 47.2 ± 9.9 | 49.2 ± 15.5 | 44.9 ± 9.7 (−8.7%) | | | |
| Midbrain | R | 51.8 ± 9.4 | 46.4 ± 11.1 | 42.9 ± 7.6 (−7.5%) | 0.0004 | n.s. | < 0.0001 |
| | L | 50.3 ± 7.6 | 46.3 ± 11.1 | 42.4 ± 7.4 (−8.4%) | | | |

[a] R, right hemisphere; and L, left hemisphere.
[b] Subjects were scanned 16.3 ± 4.3 days after MDMA.
[c] *P*-values are from post-hoc analyses.

were decreased in most regions compared to the baseline values and to the matched-control subjects (Table 2, Fig. 3). Although there was only a trend for an overall drug effect ($F_{2,14} = 3.15$; $P < 0.07$), a group (MDMA)-by-brain region interaction effect was observed ($F_{32,224} = 1.63$; $P = 0.02$). Furthermore, there was a significant interaction between drug status and hemisphere ($F_{2,14} = 6.6$; $P = 0.01$). Post-hoc analyses showed a significant effect of MDMA on rCBF in some of the brain

Table 3
MDMA dosages received and corresponding changes in rCBF

| Subject | Gender | MDMA dose (mg/kg) | Body weight (kg) | Total dose received (mg) | Days to post-MDMA SPECT | Changes in global CBF (ml/100 g per min) | Changes in rCBF in caudate[a] (ml/100 g per min) | Changes in rCBF in globus pallidus[a] (ml/100 g per min) |
|---|---|---|---|---|---|---|---|---|
| 1 | Female | 2.25 | 88 | 198 | 14 | −6.28 | −3.10 | −0.86 |
| 2 | Male | 2.25 | 97 | 218.25 | 16 | −0.41 | −1.09 | −1.67 |
| 3 | Male | 2.75 | 57 | 156.75 | 21 | −0.75 | −1.19 | −1.26 |
| 4 | Male | 3.25 | 77 | 250.25 | 14 | −3.15 | −1.35 | −3.96 |
| 5 | Male | 3.75 | 68 | 255 | 10 | −3.50 | −5.02 | −6.77 |
| 6 | Male | 4.25 | 82 | 348.5 | 17 | −1.40 | −9.53 | −7.85 |
| 7 | Male | 4.75 | 80 | 380 | 19 | −12.38 | −16.30 | −14.93 |
| 8 | Female | 4.75 | 57 | 270.75 | 21 | −6.26 | −4.50 | −7.54 |
| 9 | Female | 3.75 | 56 | 210 | 80 | 5.84 | 8.20 | 7.90 |
| 10 | Male | 4.25 | 74 | 314.5 | 43 | 3.64 | 3.20 | 5.00 |

[a]Changes in rCBF in caudate and globus pallidus are averaged between the left and right sides.

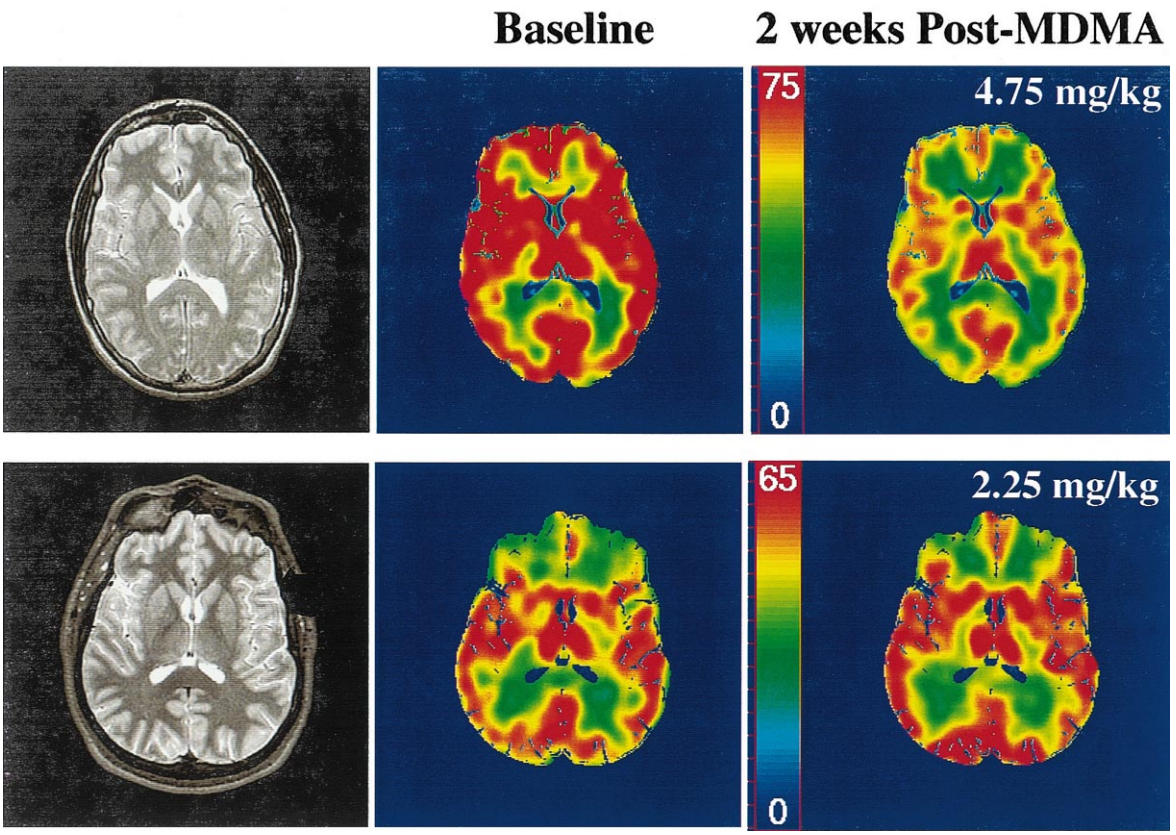


Fig. 4. Axial MRI and $^{133}$Xe-calibrated $^{99m}$Tc-HMPAO SPECT in MDMA users at baseline and after MDMA administration. The top row shows images from a male subject who received the highest dosage (4.75 mg/kg) of MDMA and the bottom row shows images from a male subject who received the lowest MDMA dosage. Color scales denote range of CBF (ml/100 g tissue per min). Note decrease in global and rCBF only in the subject who received the larger dose of MDMA.

regions evaluated (Table 2). Compared to the eight age- and gender-matched control subjects, the eight subjects who received MDMA also showed significantly decreased rCBF in most of the brain regions (Table 2, Fig. 3). The largest reductions were observed in the caudate ($-9.1\%$ and $-9.2\%$), the superior parietal cortices ($-10.0\%$ and $-9.0\%$), and the right dorsolateral frontal cortex ($-10\%$). Global CSF volume and %CSF showed no significant changes following MDMA administration.

The decreases in the rCBF after MDMA administration were generally more pronounced in subjects who received higher doses of MDMA (Fig. 4) and in those with more recent MDMA administration. The total MDMA dose received correlated negatively with the change of rCBF in left globus pallidus ($r = +0.66$, $P = 0.04$) and in the right caudate ($r = +0.78$, $P = 0.009$); however, after correction for multiple correlations, these $P$-values were not significant. Two of the 10 subjects who received MDMA were scanned more than 2 months later; increased global CBF was observed in both the younger female subject ($+13.6\%$) who received 3.75 mg/kg and the older male subject ($+8.6\%$) who received 4.25 mg/kg (Table 3).

## 4. Discussion

We found low normal ranges of rCBF in abstinent recreational MDMA users compared to age- and gender-matched normal subjects, but

subacute decreases in rCBF in subjects given MDMA in a controlled clinical setting. The relatively normal baseline rCBF values observed indicate that either long-term recreational use of MDMA does not substantially alter 5-HT regulation of rCBF, or the neuronal networks involved in CBF regulation gradually adapt to long-term serotonergic abnormalities.

In rodents and non-human primates, MDMA causes lasting effects in some brain regions and recovery with resprouting in other regions (Ricaurte et al., 1992; Scanzello et al., 1993). MDMA produces lasting serotonergic deficits, up to 18 months; however, some brain regions, showed reinnervation and hyperinnervation (Ricaurte et al., 1992; Fisher et al., 1995). Since our subjects were studied on the average 4 months after their last MDMA use, the relatively normal baseline rCBF observed in our subjects may be due to neuronal recovery or serotonergic axonal sprouting as seen in rodents and non-human primates. A recent PET study, however, found decreased regional and global 5-HT transporter in brains of MDMA users who had been abstinent for an average of 19 weeks (McCann et al., 1998). Therefore, either deficits in the serotonergic system may not be sufficient to alter rCBF or compensatory responses from other neurotransmitter systems may be maintaining the relatively normal long-term rCBF observed in our subjects.

Serotonin is a potent vasoconstrictor of cerebrovascular smooth muscle in rats (Sharma et al., 1990; McBean et al., 1991). Therefore, our findings of persistent decreases in rCBF in subjects who received MDMA may be related to the effects of metabolites from MDMA, which may have prolonged the 5-HT induced vasoconstrictive effects on the smooth muscles of the cerebral blood vessels. Studies in both rodents and primates also showed marked reduction in serotonergic axonal markers two weeks after MDMA treatment (Fisher et al., 1995); these subacute effects of MDMA on the serotonergic nerve endings could lead to increased extracellular 5-HT due to release of 5-HT from the terminals, and the subsequent increase in monoamine metabolites. Since the microcirculation of the fronto-parietal cortex has a preferential relationship with 5-HT terminals (Cohen et al., 1996), MDMA-mediated increases in 5-HT would have the most profound effects in these brain regions. Our finding of the largest decrease in rCBF in the parietal and dorsolateral frontal brain regions of these subjects after MDMA administration is consistent with a serotonergically mediated vasoconstrictive effect, either due to the direct effect of 5-HT or the monoamine metabolites of 5-HT. Due to the small number of subjects who were approved to receive MDMA, however, these findings should be considered preliminary.

Compared to the baseline rCBF, larger decreases in rCBF were observed in subjects who received MDMA more recently. Since MDMA decreases rCBF acutely in preclinical studies, our findings suggest that the initially decreased rCBF normalizes with time and may even increase above baseline at later time points. In rodents, activation of the dorsal raphe nucleus can evoke both increases and decreases in CBF (Underwood et al., 1992). McBean et al. also showed that 6–9 weeks after treatment with MDA, a demethylated form of MDMA and also a 5-HT-specific neurotoxin, rats showed focal increases in CBF in excess of metabolic demand (McBean et al., 1990). Similarly, in our human study, the decreased rCBF suggests subacute vasoconstriction due to an MDMA-mediated serotonergic effect; with normalization of the excess 5-HT or depletion of 5-HT in some regions at later time points, rCBF may return to normal or increase above normal.

In comparison to the rCBF abnormalities observed in these MDMA users, a recent report showed that 20/21 (95%) of amphetamine abusers had relative 'focal defects' by visual inspection of $^{99m}$Tc-HMPAO SPECT (Kao et al., 1994); no data were available regarding the time since last use of amphetamines in these subjects. In addition, global decreases in CBF of normal volunteers acutely after intravenous amphetamine or methylphenidate were observed on $^{133}$Xe SPECT (Kahn et al., 1989) and $^{15}$O–water PET studies (Wang et al., 1994), respectively. However, the mechanism of action of MDMA differs from that of amphetamine. MDMA affects serotonergic nerve endings specifically while most other amphetamine compounds affect both dopaminergic

and serotonergic pathways. Some studies, however, indicate that MDMA also alters dopamine release and the levels of dopamine metabolites (Schmidt, 1987; Johnson et al., 1991; Colado and Green, 1994). Therefore, it is possible that subacutely, the metabolites of MDMA, although undetectable with urine toxicology screen, may increase dopamine or other monoamines and cause regional hypoperfusion. Similar subacute effects on glucose metabolism have been observed during early cocaine withdrawal (Volkow et al., 1991). Furthermore, apomorphine, a dopamine agonist, may cause acute increases in rCBF in the caudate-putamen and globus pallidus (Ingvar et al., 1983), as well as the anterior cingulate, ventral motor cortex and the dorsolateral prefrontal cortex (Kapur et al., 1994). The dosage-related hypoperfusion observed in the basal ganglia regions, which are rich in dopaminergic receptors, may be related to the indirect effect of MDMA on the dopaminergic system.

The rCBF measurements in our study are not affected by potential volume dilution due to increased CSF in atrophied brain regions with wider sulci, because our co-registration program corrects for CSF content (Itti et al., 1997a,b). However, we did find decreased global brain volume and increased %CSF in MDMA users with longer duration of MDMA use. This finding suggests that brain atrophy might occur in association with chronic MDMA abuse.

The relatively normal rCBF in these abstinent recreational MDMA users in comparison with age- and gender-matched control subjects suggests that low dose recreational MDMA does not alter rCBF significantly in the long-term. However, the neuronal networks involved in autoregulation might have considerable flexibility in adapting to chronic abnormalities in the serotonergic system. Our study also found that regional hypoperfusion may be observed for 2–3 weeks after administration of MDMA, especially with the higher dosages. The spatial and temporal patterns of the hypoperfusion are consistent with those observed in preclinical studies. Lastly, with only four female subjects, we did not evaluate for possible gender effects on rCBF in these MDMA users. Future studies with larger sample size, evaluating for both acute and long-term effects with longitudinal follow-up evaluations, will help to determine whether the regional hypoperfusion is a transient effect, and whether a gender interaction effect may exist.

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