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Effects of Ecstasy (MDMA) on the Brain in Abstinent Users: Initial Observations with Diffusion and Perfusion MR Imaging[1]

PURPOSE: To evaluate the effects of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) on the human brain by using diffusion and perfusion magnetic resonance (MR) imaging.

MATERIALS AND METHODS: Eight abstinent ecstasy users and six ecstasy nonusers underwent diffusion and perfusion MR imaging. Apparent diffusion coefficient and relative cerebral volume maps were reconstructed. Differences in apparent diffusion coefficient values and relative cerebral volume ratios between the groups were analyzed with the Mann-Whitney-Wilcoxon test. The relationship between apparent diffusion coefficient and relative cerebral volume and the extent of previous ecstasy use was investigated with Spearman rank correlation.

RESULTS: Apparent diffusion coefficient values (0.84 vs 0.65×10^{-5} cm^2/sec, $P < .025$) and relative cerebral volume ratios (1.22 vs 1.01, $P < .025$) were significantly higher in the globus pallidus of ecstasy users compared with nonusers, respectively. Increases in pallidal relative cerebral volume were positively correlated with the extent of previous use of ecstasy ($\rho = 0.73$, $P < .04$).

CONCLUSION: Ecstasy use is associated with tissue changes in the globus pallidus. These findings are in agreement with findings in case reports, suggesting that the globus pallidus is particularly sensitive to the effects of ecstasy.

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is an amphetamine congener that has gained marked popularity as a recreational drug. MDMA induces release of serotonin (5-hydroxytryptamine) from serotonin neurons. However, it has become increasingly apparent that MDMA use eventually can lead to toxic effects on brain serotonin neurons in animals and humans. In animals, damage to serotonin neurons has been demonstrated by reductions in various markers unique to serotonin axons, and these markers include brain serotonin, 5-hydroxyindoleacetic acid, and the density of serotonin transporters (1–5). Anatomic studies in MDMA-treated animals indicate that these neurochemical changes are secondary to a distal axotomy of serotonin neurons (6,7). Findings in recent positron emission tomography, or PET, and single photon emission computed tomography, or SPECT, studies have shown decreases in the number of central serotonin transporters in human MDMA users, findings which are similar to those observed in MDMA-treated primates (8–10).

Few functional consequences of MDMA-induced neurotoxicity have been identified, however, in either animals or humans (11). Because MDMA-induced serotonergic damage may lead to impairment of functions in which serotonin is involved, it is important to study the potential consequences of MDMA-induced neurotoxicity. The brain microcirculation is of particular interest, since considerable evidence (12,13) has been accumulated in past years that strongly suggests that serotonin is involved in the regulation of brain microcirculation. It is, therefore, of interest to note that findings in several case reports (14–18) have linked the abuse of MDMA to the occurrence of cerebrovascular accidents, as a result of MDMA-induced effects on brain serotonin concentrations.

Diffusion-weighted magnetic resonance (MR) imaging provides a form of contrast that enables the quantitative measurement of diffusional motion of water molecules in biologic tissue, especially axons (19). Cellular structures, such as highly organized myelinated axons in white matter, restrict water molecular motion, and the apparent diffusion coefficient (ADC) is reduced compared with diffusion in bulk water (20–24). Any process that results in changes in structural elements of tissue, such as removal of some of the restricting barriers, can result in increased ADC values. It is, therefore, thought that diffusion-weighted MR imaging is a promising approach for the evaluation of tissue changes in degenerating brain and nerve matter (25–27). Moreover, the use of dynamic contrast-enhanced perfusion-weighted MR imaging has made it possible to study the brain vasculature by means of calculation of relative cerebral blood volume (rCBV) maps (28).

The purpose of our study was to evaluate the effects of ecstasy on the human brain with diffusion and perfusion MR imaging techniques.

MATERIALS AND METHODS

Participants

This study was carried out at the Academic Medical Center in Amsterdam, the Netherlands, from October through December 1998. Eight ecstasy users (seven men, one woman; mean age, 27.6 years ± 4.9 [SD]; age range, 22–35 years) were compared with six ecstasy nonusers (three men, three women; mean age, 22.3 years ± 0.8; age range, 21–23 years) who were using other drugs. Subjects were recruited with flyers distributed at venues associated with the "rave scene" in Amsterdam with the help of UNITY, an agency that provides harm reduction information and advice. Ecstasy user and nonuser groups were thus recruited from the same community sources.

Subjects selected were group-matched for age and sex, were otherwise healthy, and had no history of psychiatric illness. The six ecstasy nonusers reported no prior use of ecstasy. Participants agreed to abstain from use of psychoactive drugs for at least 3 weeks before the study and were asked to undergo a urine test for drug screening (with an enzyme-multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolite, opiates, and *Cannabis* [marijuana]) before enrollment in the study. After urine samples were tested,

subjects were excluded on the basis of the following criteria: positive results of the urine test for drug screening, pregnancy, or a severe medical illness.

Subjects were interviewed with a structured automated diagnostic psychiatric interview, or Composite International Diagnostic Interview (CORE, version 2.1; World Health Organization, Geneva, Switzerland) to screen for current axis I psychiatric diagnoses. A detailed drug history questionnaire was obtained, and in addition, subjects were screened for left- or right-handedness. Written informed consent was obtained from all participants. The institutional medical ethics committee approved the study.

MR Imaging Methods

MR imaging was performed with a 1.5-T machine (Magnetom Vision; Siemens, Erlangen, Germany) with echo-planar imaging capability. Before perfusion and diffusion MR imaging, transverse T1- and T2-weighted standard spin-echo sequences were performed. Imaging parameters were 670/14 (repetition time msec/echo time msec) with one signal acquired for T1-weighted sequences and 3,500/90 with one signal acquired for fast spin-echo T2-weighted sequences. Section thickness was 5 mm; matrix, 256×192; and field of view (FOV), 23 cm. T1- and T2-weighted images were evaluated for the presence of edematous changes.

Diffusion images were obtained by using echo-planar imaging with 700/118 and one signal acquired, an FOV of 23 cm, and a matrix of 96×200. Diffusion gradients were applied independently on each axis of the magnet. Nine diffusion-weighted images were obtained along each axis (b_{xi}, b_{yi}, b_{zi}, where $i = 1.9$). The b value is commonly used to describe the amount of diffusion sensitivity of the sequence.

A baseline image with minimum diffusion weighting was acquired first by using a small b value ($b = 0$ sec/mm^2). Then, a second diffusion-weighted image was acquired with extended diffusion gradients to obtain a larger b value ($b = 1,000$ sec/mm^2). Although signal intensity in the diffusion-weighted imaging is affected by T1 and T2, the ADC map is not. It is obtained by calculating the logarithmic ratio of the signal intensity at each pixel according to the following equation: $ADC = \ln(S_1/S_2)/(b_2 - b_1)$, where S_1 and S_2 are the signal intensity of the baseline and diffusion-weighted images, respectively, and b_1 and b_2 are the b

values for the corresponding pulse sequences.

The ADC value is also dependent on the direction in which diffusion is measured, which makes a comparison of ADC values without taking into account the measurement direction meaningless. By measuring the ADC value in three orthogonal directions and then averaging the results, with the equation $ADC = (ADC_x + ADC_y + ADC_z)/3$, we are able to measure diffusion that is independent of the orientation of structures.

Echo-planar T2*-weighted dynamic contrast-enhanced images (0.8/54, one signal acquired, 23-cm FOV, 128×128 matrix) were obtained in 12 transverse sections at 1.2-second intervals for 64 seconds immediately after intravenous bolus injection of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at 0.1 mmol per kilogram of body weight. The contrast agent was power-injected intravenously at a rate of 5 mL/sec through an 18-gauge antecubital needle with an MR-compatible power injector (Spectris MR injector; Medrad, Indianola, Pa).

Quantitative ADC and rCBV maps were automatically derived on a voxel-by-voxel basis by using software (Massachusetts General Hospital, NMR Center, Charlestown, Mass) (28,29). Regions of interest of various brain regions (left and right frontal cortex, occipital cortex, white matter, putamen, and globus pallidus) were defined on ADC and rCBV maps by a radiologist who was unaware of the participant's history. Mean signal intensities were measured in the region of interest on each ADC (expressed in $\times 10^{-5}$ cm^2/sec) and rCBV (expressed in arbitrary units) map. Since the susceptibility–contrast rCBV mapping method yields a relative rather than an absolute rCBV value, comparison among subjects is facilitated by reference to an internal standard. Analogous to previous studies (30,31), normal white matter was used as this reference. Ratios were calculated by dividing the mean rCBV of the brain region by the mean rCBV of white matter.

Verbal Intelligence Assessment

The Dutch Adult Reading Test (DART) (32) was administered to obtain an estimate of verbal intelligence. The DART is the Dutch adaptation of the National Adult Reading Test (33), a short reading test for the estimation of the premorbid verbal intelligence quotient (IQ) (population mean IQ, 100; SD, 15). Results of this test were used to describe the sample.

TABLE 1
Demographic Data and Characteristics of Ecstasy Nonusers and Users

Demographic Data and Characteristics	Ecstasy Nonusers (n = 6)	Ecstasy Users (n = 8)
Clinical factors		
Mean age (y)	22.3 ± 0.8	27.6 ± 4.9
No. of men/no. of women	3/3	7/1
DART-IQ test results	112.2 ± 5.8	98.3 ± 14.3
Ecstasy use		
Mean duration of use (y)	NA	4.3 (1.4–6.4)*
Usual dose (no. of tablets)	NA	2.4 (0.5–5.0)*
Lifetime dose (no. of tablets)	NA	154 (30–500)*
Time since last dose (wk)	NA	14.6 (3.0–52.0)*
Other drug and alcohol use		
Mean no. of alcohol consumptions per week	7.1 ± 5.9	10.5 ± 17.6
Mean no. of cigarettes smoked per week	1.8 ± 2.4	42.9 ± 58.2
Mean no. of marijuana joints smoked per week	0.3 ± 0.3	4.4 ± 7.6
Mean no. of times amphetamine used in last 3 mo	NA	2.9 ± 4.5[†]

Note.—NA = not applicable. Unless otherwise specified, data are expressed as the mean ± SD.
   * Data in parentheses are ranges.
   [†] Value demonstrates a statistically significant difference ($P < .025$).

TABLE 2
Mean rCBV Ratios and ADC Values in Brain Areas Studied

Diffusion and Perfusion Factors	Ecstasy Nonusers (n = 6)	Ecstasy Users (n = 8)
rCBV ratios		
Frontal cortex	1.90 ± 0.24	1.89 ± 0.20
Occipital cortex	2.93 ± 0.84	2.67 ± 1.28
Putamen	1.48 ± 0.17	1.50 ± 0.27
Globus pallidus	1.01 ± 0.15	1.22 ± 0.14*
ADC values ($\times 10^{-5}$ cm^2/sec)		
Frontal cortex	1.10 ± 0.13	1.23 ± 0.09
Occipital cortex	1.05 ± 0.15	1.01 ± 0.13
White matter	0.81 ± 0.06	0.89 ± 0.15
Putamen	0.72 ± 0.02	0.78 ± 0.12
Globus pallidus	0.65 ± 0.03	0.84 ± 0.22*

Note.—Data are expressed as the mean ± SD.
   * Value demonstrates a statistically significant difference ($P < .025$).

Statistical Analysis

Differences between the two groups with regard to demographic variables and exposure to other drugs were analyzed by using the Mann-Whitney-Wilcoxon test. Differences in ADC values and rCBV ratios between both groups were also analyzed by using the Mann-Whitney-Wilcoxon test. The relationship between ADC values and rCBV ratios in specific brain regions and the extent (lifetime number of ecstasy tablets taken) of previous ecstasy and amphetamine use was investigated with the Spearman rank correlation, since it has the advantage that it is not used to specifically assess a linear association but a more general association. To explore the effects that age, sex, and DART-IQ test results may have on rCBV ratios and ADC values, a correlation analysis was performed between these variables and ADC values and rCBV ratios.

Because of the small sample size, the chance of a type I error was set at α .10, with the use of two-tailed tests of significance. To correct for multiple comparisons, P values less than .025 (.10 ÷ 4, for four different brain regions) were considered significant. All data were analyzed by using computer software (SPSS, version 9.0; SPSS Software, Chicago, Ill).

RESULTS

No statistical differences between any of the demographic variables were found between both groups. Ecstasy users consumed more alcohol and used more tobacco and marijuana than ecstasy nonusers before this investigation (Table 1), though this difference did not reach statistical significance. Ecstasy users ingested more amphetamine compared with ecstasy nonusers, and the difference was

statistically significant. All participants were right handed.

In the ecstasy user group, participants had generally ingested more than 150 tablets of ecstasy during a 2–3-year period. Most of the ecstasy users had not ingested the substance for several weeks, and some indicated that they had not ingested ecstasy for several months (Table 1).

Imaging Findings

The conventional T1- and T2-weighted images showed no edematous changes in the brain of ecstasy users and ecstasy nonusers. In both groups, the differences between the left and right ADC values and rCBV ratios were not statistically significant. Because of this, and because we did not expect left-right differences in the effects of ecstasy, a mean of left and right cerebral ADC values and rCBV ratios was calculated for brain regions studied. Overall, mean ADC values were higher in ecstasy users compared with ecstasy nonusers. This difference was statistically significant only with regard to values in the globus pallidus (0.65×10^{-5} cm^2/sec in ecstasy nonusers vs 0.84×10^{-5} cm^2/sec in ecstasy users) (Table 2) (Figs 1, 2). Similar observations were made for rCBV ratios. Overall, mean rCBV ratios were higher in ecstasy users compared with ecstasy nonusers, although this difference reached statistical significance only in the globus pallidus of ecstasy users (mean, 1.22) compared with nonusers (mean, 1.01) (Table 2) (Fig 3).

Correlations of Findings

No significant correlations were observed between ADC values and extent of previous ecstasy or amphetamine use. Age, sex, and DART-IQ test results were not significantly associated with rCBV ratios or ADC values. However, a significant association was observed between extent of previous ecstasy use and rCBV ratio in the globus pallidus (ρ = 0.73, $P < .04$) (Fig 4). The higher the ecstasy exposure, the higher the rCBV ratio in the globus pallidus.

DISCUSSION

In the present study, we observed increased ADC values and rCBV ratios in the globus pallidus of ecstasy users. As we have previously discussed, diffusion-weighted MR imaging enables evaluation of the random motion of water on a molecular level. ADC values are a rotation-
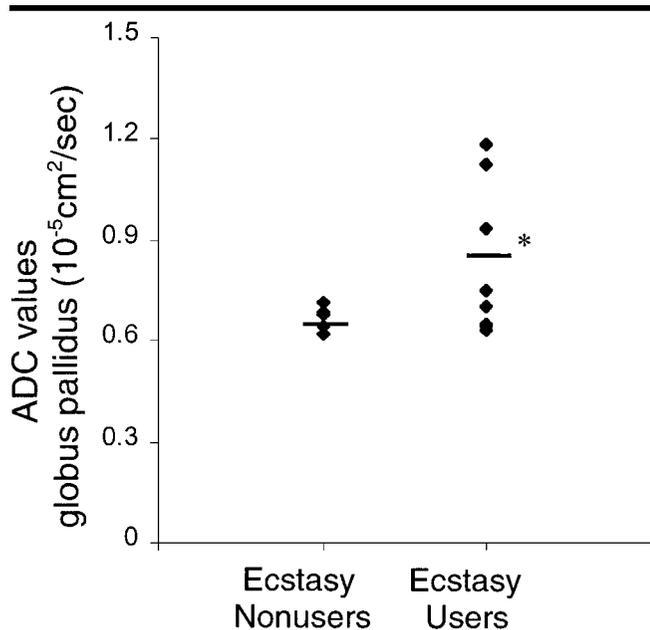
Figure 1. Graph shows the mean (bar) and individual ADC values in the globus pallidus in ecstasy nonusers and ecstasy users. Data show significantly higher ADC values in ecstasy users. ∗ = statistically significant difference in mean binding ratio between ecstasy nonusers and ecstasy users.

Figure 2. Diffusion-weighted MR image obtained after voxel analysis to compare mean ADC values between ecstasy nonusers ($n = 6$) and ecstasy users ($n = 8$). The green regions represent regions with significantly higher ($P < .025$) ADC values in ecstasy users compared with ecstasy nonusers. These regions are located in the bilateral globus pallidus (thick solid arrows), the cingulate gyrus (thin solid arrow), the bilateral temporal cortex (small open arrows), and the left parahippocampal gyrus (large open arrow). Diffusion imaging parameters were obtained by using echo-planar MR imaging (700/118, one signal acquired, 23-cm FOV, 96×200 matrix). After registration in the same orientation, an unpaired Student t test was performed on each voxel of generated ADC maps.

ally invariant measurement of the amount of total diffusion within a tissue (21,23, 34). The in vivo cellular environment contains cell membranes that form a restrictive barrier to water diffusion. Findings in experimental models (19,35) have shown that the axonal cell membrane is sufficient to account for most of the restriction of water diffusion in white matter. Diffusion is much more restricted in a direction perpendicular to the axis of the axon than in a direction parallel to the axon (20–24). It is, therefore, not surprising that any process that disrupts the integrity of the axon or results in axonal loss would change the diffusion of water in this tissue.

The increase in ADC value in the globus pallidus of ecstasy users may be due to axonal injury or loss or increased extracellular fluid (vasogenic edema). T2-weighted MR images are more sensitive to brain edema than are other measurements. However, local brain edema was not detected on the T2-weighted images obtained in the ecstasy users. These results indicate that changes in the globus pallidus of ecstasy users at diffusion-weighted MR imaging are not due to an increased water content in the extracellular space but may reflect axonal loss.
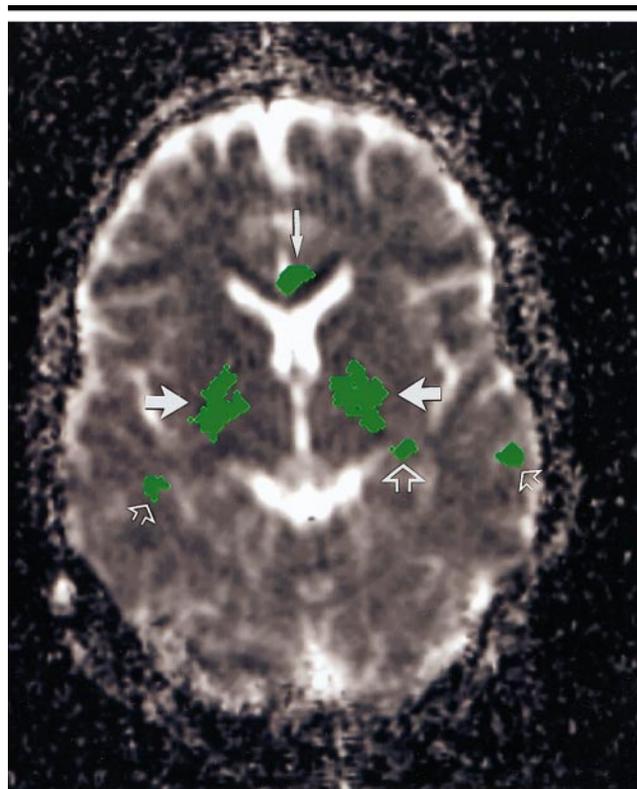
In support of this idea, it is known that extensive serotonergic axonal loss occurs in various brain regions of animals treated with MDMA. These results have been demonstrated anatomically in numerous studies with the use of immunocytochemical methods for visualization of axons that contain serotonin (6,7,36). In MDMA-treated monkeys, serotonergic axons have been shown to be reduced by 80%–90% in cortical brain areas, striatum, and thalamus and by 60% in the globus pallidus 2 weeks after MDMA administration. In time, some axonal sprouting also seems to take place, but reinnervation patterns up to 7 years after treatment are abnormal, with some brain regions remaining denervated and others showing evidence of reinnervation (37).
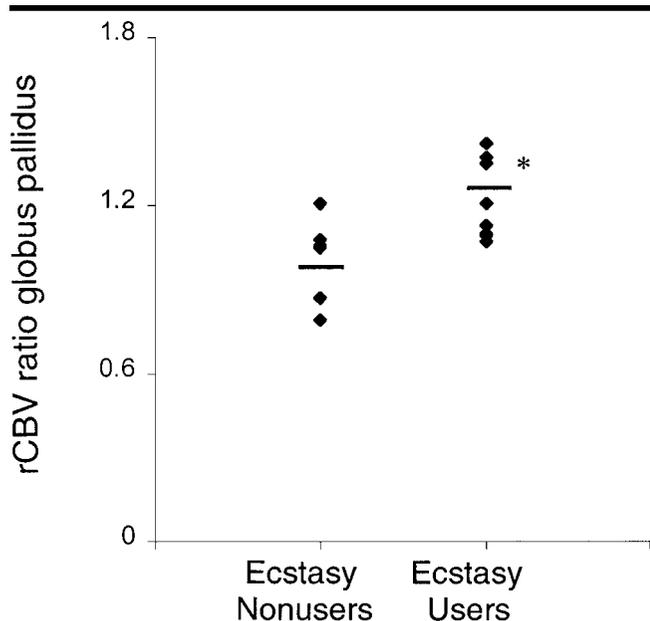
There is suggestive evidence (8,9) that MDMA may also be neurotoxic to serotonin neurons in humans, as well as to serotonin neurons in animals and nonhuman primates. These observations support the suggestion that the increased

ADC values that we observed in the globus pallidus of ecstasy users, compared with ecstasy nonusers, reflect a distal axotomy or axonal injury of ascending serotonergic projections to the globus pallidus. In keeping with this idea, it has been shown (27) that a disturbance in the axonal integrity, produced by the toxic action of dimethylmercury (methylmercury), resulted in increased ADC values in rats treated with methylmercury. Findings in studies in patients with the demyelinating disease multiple sclerosis have shown increased ADC values in multiple sclerosis lesions and increased ADC values sometimes in normal white matter (25,26,38). It is thought (39) that the pronounced increase in diffusion in the chronic stage of multiple sclerosis may represent axonal loss and tissue destruction.

In addition to increased ADC values,

Figure 3. Graph shows the mean (bar) and individual rCBV ratios in the globus pallidus in ecstasy nonusers and ecstasy users. Data show significantly higher rCBV ratios in ecstasy users. ∗ = statistically significant difference in the mean rCBV ratio between ecstasy nonusers and ecstasy users.

Figure 4. Scatterplot with linear regression line shows the correlation between the rCBV ratio in the globus pallidus and the extent of previous ecstasy use, suggesting that the effects of ecstasy on rCBV ratios are dosage-related in this brain region.

we observed increased rCBV ratios in the globus pallidus of ecstasy users. Findings in studies (40,41) have shown that administration of the potent cerebral vasodilator acetazolamide results in large increases in the rCBV ratio. Furthermore, it has been shown (42) that following administration of cocaine, rCBV ratios in brain pial arterioles were consistent with the arteriolar diameter reduction. Thus, a high rCBV ratio implies high regional blood volume, or vasodilatation, whereas a low rCBV ratio implies vasoconstriction (42). Therefore, the increased rCBV ratios in the globus pallidus of ecstasy users in this study most probably reflect vasodilatation.

Considerable evidence (12) has accumulated over the years that strongly points to a vasoconstrictor role of serotonin in the control of brain microcirculation. The remarkable sensitivity of brain vessels to serotonin has been paralleled by visualization, as evidenced with radioautographical, biochemical, and immunocytochemical methods, of a rich network of nerve fibers around major cerebral arteries and pial vessels that contain serotonin. In keeping with this idea, it has been shown (43) that induction of serotonin lesions with systemic administration of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) mediates a vasodilatory response in the cerebrovasculature. It is thought that, because of reduced serotonin content, vasodilatation

occurs due to removal of serotonergic constrictor effects. The increases in rCBV ratios in the globus pallidus of ecstasy users in this study may result from a similar mechanism.

As discussed previously, numerous studies (6,7,36,37,44–46) have shown that in animals and nonhuman primates MDMA administration results in loss of serotonergic axons and terminals, which leads to persistent losses in serotonin. Findings in studies in human ecstasy users have shown selective neurotoxic effects on the serotonergic system, as indicated by decreases in 5-hydroxyindoleacetic acid in cerebrospinal fluid (47,48) and in the number of serotonin transporters (8,9). These findings in human ecstasy users are similar to findings in MDMA-treated animals with documented serotonergic neurotoxic lesions (10,49). There is, therefore, consistent evidence that the increased rCBV ratios in the globus pallidus of the ecstasy users in this study may at least be attributed to MDMA-induced serotonin deficits. In the present study, the positive association between ecstasy exposure and rCBV ratios further supports this finding.

Interestingly, the finding of increased rCBV ratios in the globus pallidus of ecstasy users in this study is in agreement with the finding in a recent study by Reneman and co-workers (50). Findings
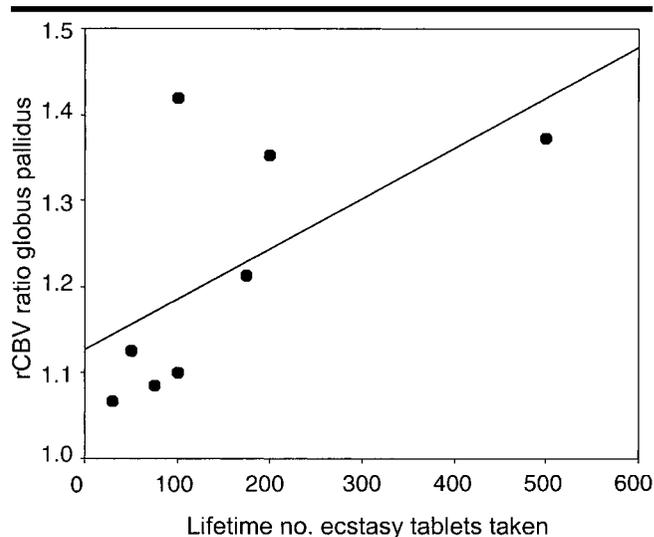
in that study show that in specific brain regions (particularly the globus pallidus) high cortical serotonin 2 receptor densities, which are suggestive of low synaptic serotonin levels, were correlated with high rCBV ratios and implicated vasodilatation. On the other hand, low cortical serotonin 2 receptor densities, which are suggestive of high synaptic serotonin levels, were correlated with low rCBV ratios, indicating vasoconstriction.

Furthermore, findings in a study by Chang and co-workers (51) show that in subjects who received MDMA in a controlled setting, larger decreases in cerebral blood flow, which implicated vasoconstriction, were observed in subjects who received MDMA more recently (on average, 2–3 weeks before the examination). In addition, the authors observed increased cerebral blood flow values, which implicated vasodilatation, in several subjects who underwent imaging after 2–3 months. The short-term effect of MDMA involves excessive release of serotonin. It, therefore, was suggested that, with normalization of the excess of serotonin or depletion of serotonin in some regions at a later time, cerebral blood flow may return to normal or increase to greater than normal values, due to removal of serotonergic constrictive effects. In this study, we observed significant increases in rCBV ratios in the globus pallidus in the ecstasy users with a long period of abstinence from ecstasy use, which was at least 3 weeks but on average was 3½ months.

The ratio obtained in this study between cortical gray and white matter rCBV in ecstasy nonusers, which was approximately 2.5, correlates well with results in other MR rCBV mapping studies (30). The ADC values of approximately 1.1×10^{-5} cm^2/sec in gray matter in this study are in agreement with those in the literature (1.0×10^{-5} cm^2/sec) (52).

As with all retrospective studies, there is a possibility that preexisting differences between ecstasy users and nonusers underlie differences in rCBV ratios and ADC values. Thus, people with high pallidal rCBV ratios and ADC values may be predisposed to use ecstasy. Another potential limitation of the present study may be that the samples were small. Nevertheless, to our knowledge, there have been few studies in which the effects of ecstasy on the central nervous system have been investigated with MR imaging and no studies with diffusion-weighted MR imaging. Age, sex, and results of the DART-IQ test are not likely to have influenced our findings, since they were not significantly related to rCBV ratios or ADC values. Finally, although most of the ecstasy users in our study had more experience with other recreational drugs than did ecstasy nonusers, no statistically significant differences in the use of drugs other than amphetamine and ecstasy were observed between the two groups in this study and were, therefore, not likely to account for changes in rCBV ratios or ADC values.

We cannot, however, completely rule out the possibility that the observed changes in the globus pallidus of ecstasy users were unrelated to amphetamine use. Since amphetamine and the other drugs that ecstasy users reported having used are unknown serotonin neurotoxins in human beings, it seems unlikely that the findings in this study should be attributed to substances other than MDMA.

In conclusion, we provide suggestive evidence that ecstasy use is associated with changes in rCBV ratios and ADC values in the globus pallidus of human ecstasy users. These findings are consistent with findings of serotonergic axonal loss and serotonin depletion in animals treated with MDMA, data in humans from other published reports, and findings of cerebrovascular accidents in medical histories of ecstasy users. Future studies with larger samples of ecstasy users will help in a further evaluation of the association between findings of cerebrovascular accidents in medical histories and findings of MDMA-induced cerebrovascular accidents. Our data indicate that MR imaging may be a valuable tool in the investigation of the consequences of MDMA use in brain tissue and the microvasculature.

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