

Brain Serotonin Transporter Density and Aggression in Abstinent Methamphetamine Abusers

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Context: In animals, methamphetamine is known to have a neurotoxic effect on serotonin neurons, which have been implicated in the regulation of mood, anxiety, and aggression. It remains unknown whether methamphetamine damages serotonin neurons in humans.

Objective: To investigate the status of brain serotonin neurons and their possible relationship with clinical characteristics in currently abstinent methamphetamine abusers.

Design: Case-control analysis.

Setting: A hospital research center.

Participants: Twelve currently abstinent former methamphetamine abusers (5 women and 7 men) and 12 age-, sex-, and education-matched control subjects recruited from the community.

Interventions: The brain regional density of the serotonin transporter, a structural component of serotonin neurons, was estimated using positron emission tomography and *trans*-1,2,3,5,6,10-β-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline ($[^{11}\text{C}](+)\text{McN-5652}$). Estimates were derived from region-of-interest and statistical parametric mapping methods, followed by within-case analysis using the measures of clinical variables.

Main Outcome Measures: The duration of methamphetamine use, the magnitude of aggression and depressive symptoms, and changes in serotonin transporter density represented by the $[^{11}\text{C}](+)\text{McN-5652}$ distribution volume.

Results: Methamphetamine abusers showed increased levels of aggression compared with controls. Region-of-interest and statistical parametric mapping analyses revealed that the serotonin transporter density in global brain regions (eg, the midbrain, thalamus, caudate, putamen, cerebral cortex, and cerebellum) was significantly lower in methamphetamine abusers than in control subjects, and this reduction was significantly inversely correlated with the duration of methamphetamine use. Furthermore, statistical parametric mapping analyses indicated that the density in the orbitofrontal, temporal, and anterior cingulate areas was closely associated with the magnitude of aggression in methamphetamine abusers.

Conclusions: Protracted abuse of methamphetamine may reduce the density of the serotonin transporter in the brain, leading to elevated aggression, even in currently abstinent abusers.

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METHAMPHETAMINE IS A powerfully addictive drug, and the number of its abusers has been steadily increasing worldwide.¹⁻⁵ Long-term methamphetamine abuse can produce various psychiatric symptoms, including psychosis, depression, anxiety, and aggression, under conditions of intoxication and withdrawal.^{6,7} These psychiatric states are sometimes prolonged, in the form of residual symptoms, and are easily exacerbated in some long-term abusers by methamphetamine reuse or by psychological stress.^{3,8-10}

In animal studies, the biochemical effects of the neurotoxicity of methamphetamine on mature neurons, especially on the dopaminergic and serotonergic axon

arbors, are well documented,^{11,12} although neurotoxic methamphetamine may also cause cell death through apoptosis or necrosis.^{12,13} However, methamphetamine-induced neuronal damage is thought to vary across species.^{14,15} For example, in contrast to the findings in rats,¹¹ which indicate that serotonergic neurons are more sensitive to the methamphetamine-induced toxicity than are dopaminergic neurons, recent findings¹⁶ have suggested that serotonergic neurons in non-human primates seem to be less affected by methamphetamine administration than are dopaminergic neurons.

In vivo studies using positron emission tomography (PET) are helpful for understanding the contribution of methamphetamine neurotoxicity and induced

Table 1. Demographic and Clinical Characteristics of the 24 Study Participants

	Control Subjects (n = 12)		Methamphetamine Abusers (n = 12)*	
	Mean ± SD	Range	Mean ± SD	Range
Age, y	31.8 ± 6.6	21-44	31.4 ± 6.8	21-44
Education, y	11.5 ± 1.2	9-12	11.1 ± 2.1	9-12
Duration of methamphetamine use, y	NA	NA	6.7 ± 3.2	1.5-11.0
Duration of methamphetamine abstinence, y	NA	NA	1.6 ± 1.3	0.5-5.0
BPRS positive symptoms subscale score	NA	NA	5.3 ± 3.9	0-14
BPRS negative symptoms subscale score	NA	NA	0.0 ± 0.0	0.0
17-Item HAM-A score	NA	NA	3.8 ± 6.3	0-16
17-Item HAM-D score	NA	NA	4.0 ± 6.3	0-19
Scale for methamphetamine craving score	NA	NA	4.9 ± 3.4	1-10
Aggression Questionnaire score†	30.2 ± 1.7	29-34	75.0 ± 13.9‡	46-97

Abbreviations: BPRS, Brief Psychiatric Rating Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; NA, not applicable.

*All the abusers took methamphetamine intravenously.

†Higher scores represent greater aggression.

‡Significantly difference from control subjects using the *t* test ($P < .001$).

neural damage to the long-term withdrawal syndrome. Recent PET studies have shown that long-term use of methamphetamine decreases the density of DA transporters, which are located on dopaminergic terminals in the human brain^{1-3,17,18}; moreover, long-term use of methamphetamine may cause severe positive symptoms (eg, delusions and hallucinations) and an increased reduction in DA transporter density.^{3,18} However, to date, no studies have addressed the alteration of serotonergic neurons in methamphetamine abusers. In addition, it is not known whether such changes, if found, could be related to the psychiatric symptoms frequently observed in currently abstinent methamphetamine abusers.

We, therefore, examined the possibility of changes in the density of the serotonin transporter, an index of serotonin neuronal damage,¹⁹⁻²⁵ in methamphetamine abusers by means of PET. This information was then considered as part of an evaluation of the potential associations between serotonin transporter density and participant clinical characteristics.

METHODS

PARTICIPANTS

The ethics committees of the Hamamatsu University School of Medicine and Hamamatsu Medical Center approved this study. Written informed consent was obtained from each participant after they were provided an explanation of the study procedures. Twelve currently abstinent methamphetamine abusers who had previously abused only methamphetamine (ie, mono-drug abusers) and 12 age-, sex-, and education-matched control subjects participated in this study (**Table 1**). Potential participants were recruited from the community by means of poster advertisements and word of mouth in and around Hamamatsu City, which is located in the middle of the mainland of Japan. The participants in the methamphetamine group were required to attend a weekly meeting at the Drug Detoxification and Rehabilitation Program Center of Hattori Mental Hospital (Iwata, Japan) to maintain and ensure abstinence until the PET study was conducted.

All the methamphetamine abusers had used the drug recreationally and had no history of toxic or high-dose methamphetamine use. None of the abusers had any history of hospitalization or treatment at psychiatric hospitals. We assessed the participants regarding the use of other illicit drugs, including (±)3,4-methylenedioxymethamphetamine, cocaine, cannabis, heroin, and toluene, because these substances are known to cause psychiatric symptoms and to affect neural transmission in the brain.^{19,26,27} However, none of the methamphetamine abusers recruited for the present study were found to have a history of such illicit drug use. All the methamphetamine abusers were naive to neuropsychiatric medications, such as antipsychotics and antidepressants. None of the methamphetamine abusers had a history of psychiatric disorders, including antisocial or intermittent explosive disorder, or a history of increased aggression before the use of methamphetamine. The controls were healthy and had never used methamphetamine or any other illicit drugs, and none of them met any of the relevant criteria according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.²⁸ The control and methamphetamine groups showed similar habits of occasional drinking and smoking, but none of the participants fulfilled either the alcohol- or the nicotine-related *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. These evaluations were determined using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.²⁹ To increase the accuracy of the abusers' profiles, detailed information on the duration of methamphetamine use and the history of psychiatric symptoms was retrospectively obtained using Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*-based interviews with the abusers and their family members. The period of methamphetamine use was defined as the duration between the first and last use. When intervals of abstinence longer than 1 month occurred during the duration of methamphetamine use as defined, these intervals were subtracted from the total duration value. The methamphetamine abstinence period was arbitrarily defined as the duration between the day of the last use of methamphetamine and that of the PET examination.

DRUG SCREENING

During the weekly meeting at the Drug Detoxification and Rehabilitation Program Center, the absence of recent methamphetamine and other drug use was regularly confirmed using a rapid

immunoassay for the qualitative detection of the metabolites of the following 8 classes of drugs: amphetamines, including methamphetamine and (\pm)-3,4-methylenedioxymethamphetamine; barbiturates; benzodiazepines; cocaine; methadone; opiates; tetrahydrocannabinol; and tricyclic antidepressants (Triage8; Biosite Diagnostics, San Diego, Calif). In addition, the participants were tested for urinary hippuric acid, a biomarker of toluene use, using high-performance liquid chromatography according to the standard diagnostic methods.²⁷ These assessments were also performed on the same day as the PET examination. When necessary, we assessed hair samples using high-performance liquid chromatography, which enabled us to verify long periods of methamphetamine abstinence.³⁰

CLINICAL EVALUATION

The severity of psychiatric symptoms in methamphetamine abusers was evaluated using the Aggression Questionnaire (AQ)³¹; the scores can range from 29 to 145, with higher scores representing greater aggression. In addition, the 17-item Hamilton Rating Scale for Anxiety,³² the 17-item Hamilton Rating Scale for Depression,³³ and positive and negative symptom subscores³⁴ on the Brief Psychiatric Rating Scale³⁵ were included in the evaluation. The Subjective Drug Effect Rating Scale for Cocaine³⁶ was modified and used for the assessment of cravings for methamphetamine. The scores on this assessment can range from 1 to 10, with higher scores representing more intense craving sensations (Table 1). These evaluations were performed on the day of the PET examination by a trained research psychiatrist masked to the PET results.

MAGNETIC RESONANCE IMAGING AND MAGNETIC RESONANCE IMAGING-TO-PET COORDINATE PROCEDURES

Three-dimensional magnetic resonance imaging (MRI) was performed just before the PET examination using a 0.3-T MRI unit (MRP7000AD; Hitachi Medical Corp, Tokyo, Japan) and the following acquisition parameters: repetition time, 200 milliseconds; echo time, 23 milliseconds; flip angle, 75°; slice thickness, 2 mm with no gap; and matrix, 256 × 256. In reference to the measurements of the tilt angle and spatial coordinates obtained in the procedure for determining the anterior-posterior intercommissural line on each participant's sagittal MRIs, a PET gantry was set parallel to the anterior-posterior intercommissural line by tilting and moving the gantry for each participant, which permitted reconstruction of the PET images parallel to the anterior-posterior intercommissural line without reslicing; using this approach, we allocated regions of interest (ROIs) on the target areas of the original PET images.³⁷

PET PROCEDURES

We used a high-resolution brain PET scanner (model SHR12000; Hamamatsu Photonics KK, Hamamatsu, Japan), which was capable of yielding 47 PET images simultaneously.³⁸ Before dynamic scanning, a 20-minute transmission scan was performed for attenuation correction using a germanium Ge 68/gallium Ga 68 source with the participant's head fixed by means of a radiosurgery-purpose thermoplastic face mask. Then, after a bolus intravenous injection of a 370-MBq dose of *trans*-1,2,3,5,6,10- β -hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-*a*]isoquinoline ($[^{11}\text{C}](+)\text{McN-5652}$), a ligand with high specificity to serotonin transporter,^{21,39} 38 serial PET scans (time frames: 4 × 60, 20 × 120, and 14 × 300 seconds) were performed for 92 minutes. A total of 23 arterial blood samples were collected at intervals of 10 seconds to 15 minutes after the tracer

injection. The blood samples were analyzed using thin-layer chromatography (Whatman AL SIL G/UV 20 × 20 cm; Whatman Japan KK, Tokyo) and a storage phosphor screen bioimaging analyzer (model BAS-1500; Fuji Photo Film Co, Tokyo) to determine the levels of unmetabolized tracer.

IMAGE ANALYSIS AND KINETIC MODELING

At the beginning of the study, the MRI voxel size was adjusted to the PET voxel size 3-dimensionally using image processing software (DrView; Asahi Kasei Co, Tokyo) on a Sun workstation (HyperSPARC ss-20; Sun Microsystems, Santa Clara, Calif). These reformatted MRIs with 3-dimensional scales and coordinates identical to those of the PET images were used as anatomic landmarks for the ROI setting, which allowed for minimization of the partial volume effects.^{3,18,40,41} An investigator masked to the participant's condition placed 10 ROIs bilaterally over the midbrain, thalamus, caudate nucleus, putamen, amygdala, anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, temporal cortex, and cerebellar cortex on the MRIs, as previously described.^{40,42,43} After delineation of the ROIs was completed on the reformatted MRIs, the PET images were displayed side-by-side with the MRIs. Then, the determined ROIs were placed on the same area on the MRIs and the corresponding PET images.

To assess the brain serotonin transporter density, we analyzed the $[^{11}\text{C}](+)\text{McN-5652}$ binding data on the basis of a model that described the radioligand kinetics using a single-tissue compartment and 3 parameters—uptake of radioligand in brain tissue (K_1), release of radioligand from brain tissue (k_2), and blood volume—because the regional brain $[^{11}\text{C}](+)\text{McN-5652}$ distribution volume (DV) (ie, the ratio of K_1/k_2) estimated by this model is known to correlate with the known regional brain serotonin transporter density^{21,39,44} and has been reported to be suitable for evaluating amphetamine-induced serotonergic neurotoxicity.²¹ Cerebral radioactivity was corrected for the contribution of plasma radioactivity, assuming a 5% blood volume in the ROIs. The K_1 and k_2 values were estimated by fitting the metabolite-corrected plasma time-radioactivity curves and the blood volume-corrected brain time-radioactivity curves using a nonlinear least squares algorithm.^{3,18,40}

STATISTICAL ANALYSIS

In addition to the ROI method described in the "Methods" section, we also performed a voxel-based whole-brain analysis using statistical parametric mapping (SPM) software (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London). Based on the same kinetic model as that used for the ROI method, absolute parametric $[^{11}\text{C}](+)\text{McN-5652}$ DV images were generated for each participant using biomedical image quantification and kinetic modeling software (PMOD version 2.5; PMOD Technologies Ltd, Zurich, Switzerland) (**Figure 1**).^{45,46} To normalize the absolute DV image to the standard stereotaxic brain atlas,⁴⁷ we used transformation parameters for early integrated images of $[^{11}\text{C}](+)\text{McN-5652}$ (0-20 minutes after injection).^{48,49} Subsequently, *t* statistics were performed on a voxel-by-voxel basis (voxel size: 2.0 × 2.0 × 2.0 mm), resulting in *t* statistic maps. Then, the results were transformed to the unit normal distribution. For the SPM analysis, we assessed both group differences in the regional $[^{11}\text{C}](+)\text{McN-5652}$ DVs and the possible relationship between the regional changes in $[^{11}\text{C}](+)\text{McN-5652}$ DVs and the severity of clinical symptoms in methamphetamine abusers. Age and sex were treated as covariates, and the scores on the clinical measures (AQ, Hamilton Rating Scale for Anxiety, Hamilton Rating Scale for Depression, positive and negative symptoms on

the Brief Psychiatric Rating Scale, and the scale for methamphetamine craving) were considered to be variables of interest. To test hypotheses about the regional specific effects of these variables, the estimates were compared using 2 linear contrasts (positive or negative correlation). According to recently published PET studies^{6,50} of methamphetamine abusers, the level of significance was determined using a voxel height threshold of $P = .05$ (corrected). The cluster significance threshold was also set at $P = .05$ (corrected).

To compare the mean values of the demographic and clinical variables in control subjects and methamphetamine abusers, an unpaired t test was used. We tested the main effect of methamphetamine use on [¹¹C](+)McN-5652 DVs derived from 10 brain regions using multivariate analysis of variance. Statistical significance was set at $P < .05$. To investigate the correlation between the [¹¹C](+)McN-5652 DV and the clinical variables in methamphetamine abusers, including the duration of methamphetamine use and abstinence, the Pearson correlation coefficient was computed, with age and sex adjusted for; after applying the Bonferroni correction, the level of statistical significance was set at $P = .005$ (SPSS version 11.0J; SPSS Japan Inc, Tokyo).

RESULTS

PSYCHIATRIC STATES OF ABSTINENT METHAMPHETAMINE ABUSERS

Methamphetamine abusers showed no apparent negative symptoms as demonstrated by Brief Psychiatric Rating Scale assessment (Table 1). All methamphetamine abusers had previously experienced psychosis during methamphetamine use. Two methamphetamine abusers had persistent psychotic symptoms, such as persecutory delusions and auditory hallucinations; 5 had a depressed mood; 4 had anxiety; 4 showed severe aggression; and 4 had no psychiatric symptoms except for aggressive behavior. The mean AQ score was significantly higher in methamphetamine abusers than in controls ($t = -11.1$; $P < .001$).

ROI ANALYSIS

The traditional ROI-based analysis showed that methamphetamine abusers had significantly decreased [¹¹C](+)McN-5652 DVs in their global brain regions compared with control subjects (Wilks $\Lambda = 0.001$; $P = .003$) (Figure 2). Subsequent univariate analysis of variance revealed that methamphetamine abusers had significantly lower [¹¹C](+)McN-5652 DVs than control subjects in all 10 ROIs studied ($P < .001$ for all). There was no group \times sex interaction effect in the [¹¹C](+)McN-5652 DV, indicating no sex-specific effect in [¹¹C](+)McN-5652 DVs (Wilks $\Lambda = 0.47$; $P = .37$).

Figure 3 shows the correlations between [¹¹C](+)McN-5652 DVs and clinical variables in methamphetamine abusers. The [¹¹C](+)McN-5652 DVs in 5 of the 10 ROIs (ie, the midbrain, thalamus, caudate nucleus, putamen, and orbitofrontal cortex) significantly correlated negatively with the duration of methamphetamine use ($P < .005$ for all by Pearson correlation coefficient) (Figure 3A). There was no correlation in any of the 10 ROIs between [¹¹C](+)McN-5652 DVs and the duration of methamphetamine abstinence, which lasted 6 months to 5 years in our

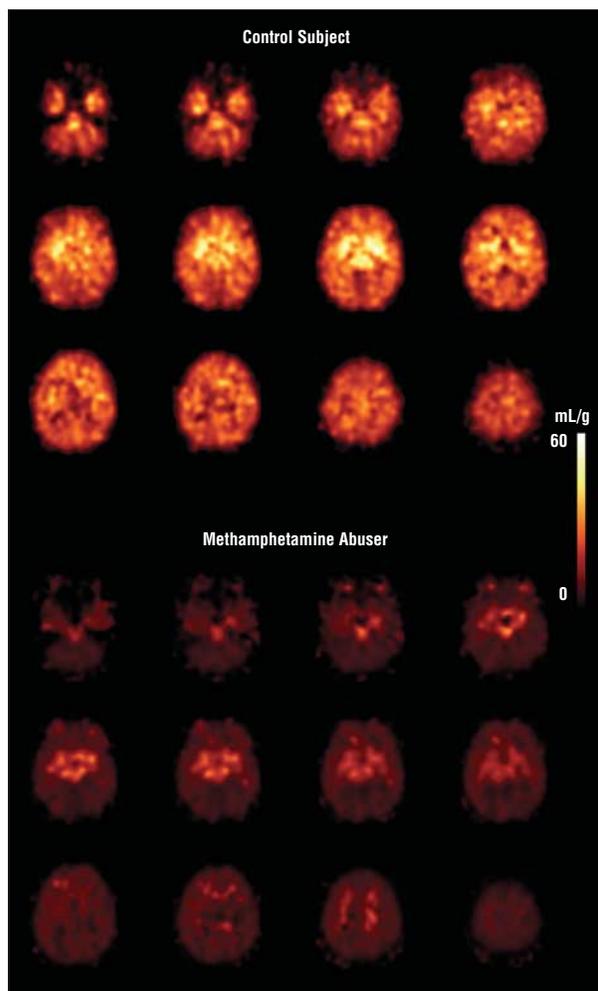


Figure 1. Voxel-based *trans*-1,2,3,5,6,10- β -hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-*a*]isoquinoline ([¹¹C](+)McN-5652) distribution volume images from a control subject and a methamphetamine abuser. These absolute parametric images were normalized to the standard stereotaxic brain atlas using transformation parameters for early integrated images of [¹¹C](+)McN-5652 (0-20 minutes after injection). The [¹¹C](+)McN-5652 distribution volumes in broad areas of the brain of the methamphetamine abuser were lower than those of the control subject.

participants (Figure 3B). The magnitude of aggression, as assessed using the AQ, increased significantly with decreasing [¹¹C](+)McN-5652 DVs in 8 of the 10 ROIs (ie, the thalamus, caudate nucleus, putamen, anterior cingulate cortex, temporal cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, and cerebellar cortex) ($P < .005$ for all by Pearson correlation coefficient) (Figure 3C). Other clinical variables, including craving, were not statistically significantly correlated with changes in [¹¹C](+)McN-5652 DVs (data not shown).

SPM ANALYSIS

Figure 4 illustrates the results of the whole-brain voxel-based SPM analysis of [¹¹C](+)McN-5652 DVs. Figure 4A shows that the methamphetamine group had widely distributed reductions in [¹¹C](+)McN-5652 DVs compared with the control group ($P < .05$, corrected) (Table 2). In accord with the findings derived from the ROI analysis, the SPM analysis revealed an extensive clus-

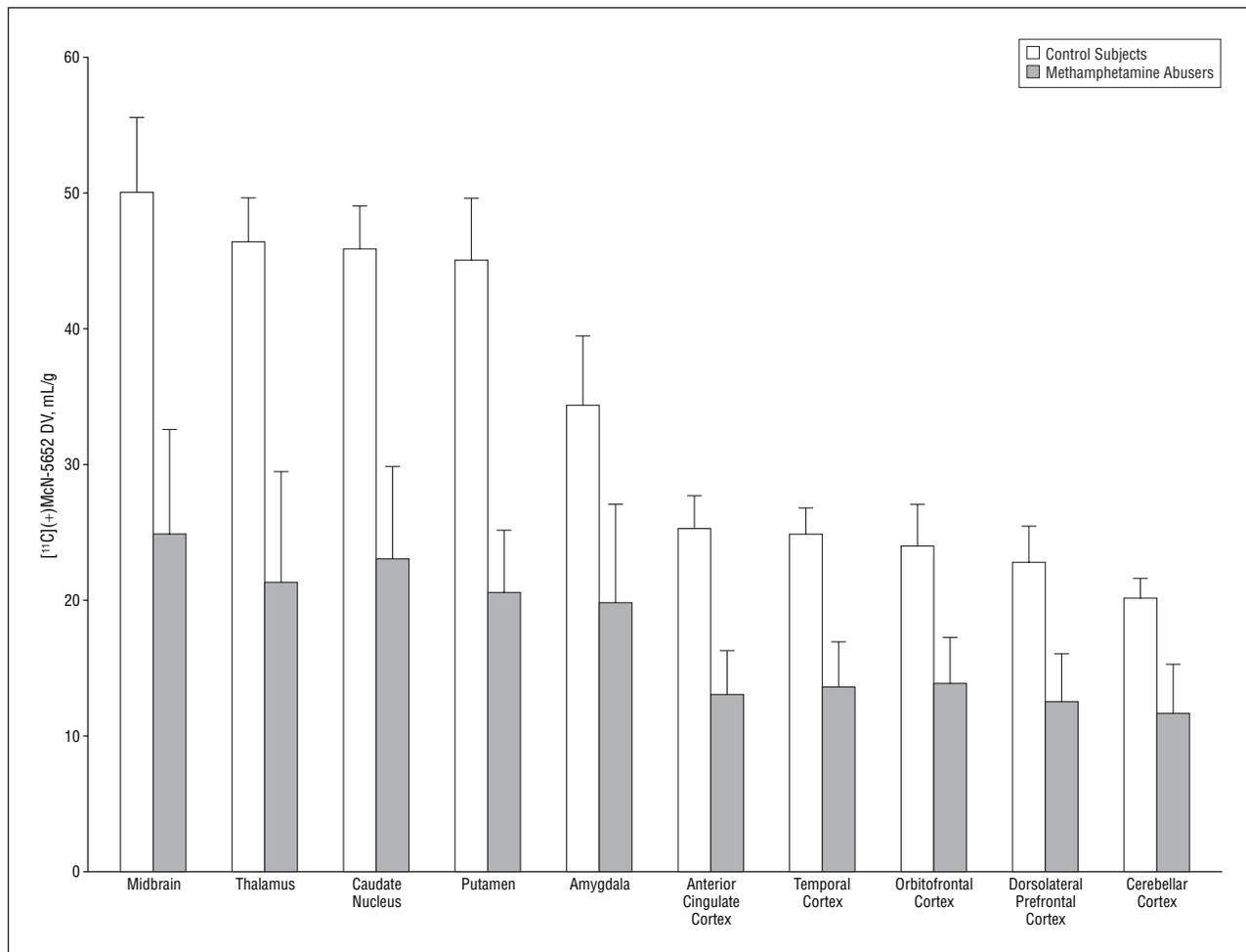


Figure 2. Mean regional brain *trans*-1,2,3,5,6,10- β -hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-*a*]isoquinoline ($[^{11}\text{C}](+)\text{McN-5652}$) distribution volumes (DVs) in control subjects and methamphetamine abusers. Methamphetamine abusers had significantly decreased $[^{11}\text{C}](+)\text{McN-5652}$ DVs in the global regions compared with controls (Wilks $\Lambda=0.001$; $P=.003$, by multivariate analysis of variance). Univariate analysis of variance revealed that methamphetamine users had significantly lower $[^{11}\text{C}](+)\text{McN-5652}$ DVs than controls in all regions studied ($P<.001$ for all). Error bars represent SE.

ter of voxels with reduced $[^{11}\text{C}](+)\text{McN-5652}$ DVs occupying the right insular area and extending out into the bilateral putamen, caudate, thalamus, hypothalamus, midbrain, temporal, parietal, frontal, occipital, cerebellar, anterior cingulate, and posterior cingulate areas. This cluster consisted of 45 315 voxels (363 mL). Figure 4B shows clusters in which the magnitude of aggression increased significantly with decreasing $[^{11}\text{C}](+)\text{McN-5652}$ DVs. These clusters were located on the bilateral orbitofrontal areas ($P\leq.001$), left inferior temporal area ($P<.001$), and right anterior cingulate gyrus area ($P<.001$) (**Table 3**). The other clinical variables did not reach statistical significance (data not shown).

COMMENT

In the present study, methamphetamine abusers had statistically significantly decreased $[^{11}\text{C}](+)\text{McN-5652}$ DVs, a representative measure of serotonin transporter density,^{21,39,44} in their global brain regions compared with control subjects. The finding of significantly reduced $[^{11}\text{C}](+)\text{McN-5652}$ DVs in a several brain regions in methamphetamine abusers, as revealed using the ROI ap-

proach, was in accord with the results of voxel-based SPM analysis. In addition, there was no group \times sex interaction effect in terms of the $[^{11}\text{C}](+)\text{McN-5652}$ DV, indicating that abnormal $[^{11}\text{C}](+)\text{McN-5652}$ DVs in the brains of methamphetamine abusers are observed in both sexes. These findings suggest that the ingestion of methamphetamine leads to a global and severe reduction in the density of human brain serotonin transporters.

The values of the density of serotonin transporters in widely distributed brain regions, including the midbrain, hypothalamus, thalamus, caudate, putamen, amygdala, temporal cortex, and occipital cortex, were found to negatively correlate with the duration of methamphetamine use. This result implies that the longer methamphetamine is used, the more severe the decrease in serotonin transporter density will be. Although the duration of methamphetamine use is viewed as a proxy measure for the actual amount of intake of the drug, such a relationship in a dose-response manner strongly suggests a link between the use of methamphetamine and damage to serotonin neurons. This is compatible with the results of animal experiments⁵¹ demonstrating dose-dependent methamphetamine-induced serotonin transporter reduction.

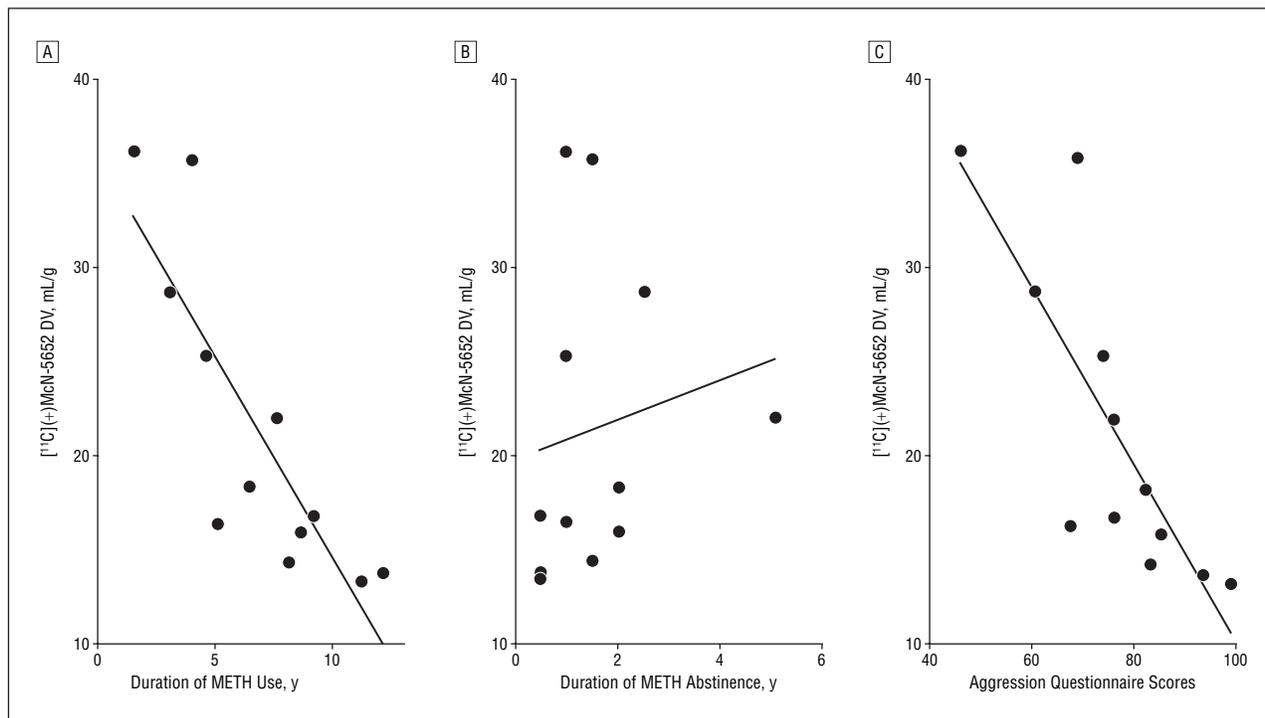


Figure 3. Correlations between *trans*-1,2,3,5,6,10- β -hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-*a*]isoquinoline ($[^{11}\text{C}](+)\text{McN-5652}$) distribution volumes (DV) in a representative brain region (the thalamus) and clinical variables in methamphetamine (METH) abusers. A, Significant negative correlation between $[^{11}\text{C}](+)\text{McN-5652}$ DVs and the duration of METH use ($r = -0.84$; $P = .001$ by Pearson correlation coefficient). B, Correlation between $[^{11}\text{C}](+)\text{McN-5652}$ DVs and the duration of METH abstinence ($r = 0.16$; $P = .61$). C, Correlation between Aggression Questionnaire scores and $[^{11}\text{C}](+)\text{McN-5652}$ DVs ($r = -0.82$; $P = .001$).

Although the present study was not designed to directly assess recovery from brain damage induced by methamphetamine use, there was no correlation between the $[^{11}\text{C}](+)\text{McN-5652}$ DVs and the duration of methamphetamine abstinence. Along with this finding, the result showing that even individuals who had been abstinent for more than 1 year ($n = 9$) had a substantial decrease in serotonin transporter density (approximately a 30% decrease compared with controls) (Figure 3B) suggests that reductions in the density of the serotonin transporter in the brain associated with habitual methamphetamine abuse could persist long after methamphetamine use ceases.

The magnitude of aggression in methamphetamine abusers increased significantly with decreasing serotonin transporter densities in some brain regions. Detoxification from methamphetamine in all the abusers in this study was confirmed by regular urine drug screening as described in the "Drug Screening" subsection, including a test on the day of PET examination; these tests were conducted to establish that the psychiatric symptoms, such as aggression, were residual rather than acute symptoms induced by methamphetamine use. As a result, the relationship between the degree of aggressiveness and the density of serotonin transporter found in this study was not ascribed to the process of detoxification from methamphetamine use. Thus, the present findings indicate that methamphetamine-induced serotonergic disturbances are responsible for the elevated aggressiveness that is frequently observed, as a residual symptom, in abstinent methamphetamine abusers. This contention is consistent with a variety of studies^{52,53} that have documented associations between decreased serotonergic function and increased aggression. For ex-

ample, cerebrospinal fluid 5-hydroxyindoleacetic acid, which is known to reflect presynaptic serotonergic activity in the brain, has been found to be reduced in aggressive psychiatric patients,^{54,55} impulsive violent men,^{56,57} and impulsive violent offenders.⁵⁸

In the correlational region analysis using SPM in the methamphetamine group, the magnitude of aggression was substantially associated with a decrease in serotonin transporter density in the clusters located in the orbitofrontal cortex, anterior cingulate, and temporal cortex, although the clusters were localized to small areas and did not fully occupy the anatomic brain regions. This result suggests that the potential methamphetamine-induced decrease in serotonergic function around these 3 areas may play an important role in the pathogenesis of elevated aggression in methamphetamine abusers. This is supported by several lines of evidence. For example, studies of brain injuries suggest that damage to the orbitofrontal and anterior cingulate areas produces syndromes characterized by aggression and impulsivity.^{52,59} Furthermore, recent PET and postmortem clinicopathologic correlation studies have indicated that low levels of serotonin_{1A} receptors in the orbitofrontal, anterior cingulate gyrus, and temporal areas are related to aggressive behavior.^{60,61}

However, we cannot rule out the possibility that the increased aggression observed in methamphetamine abusers could reflect a preexisting condition, for example, an "addictive personality," which might often involve a tendency toward aggression.⁶² Nevertheless, in the present study, we selected methamphetamine abusers who had no history of abnormal aggression before the use of meth-

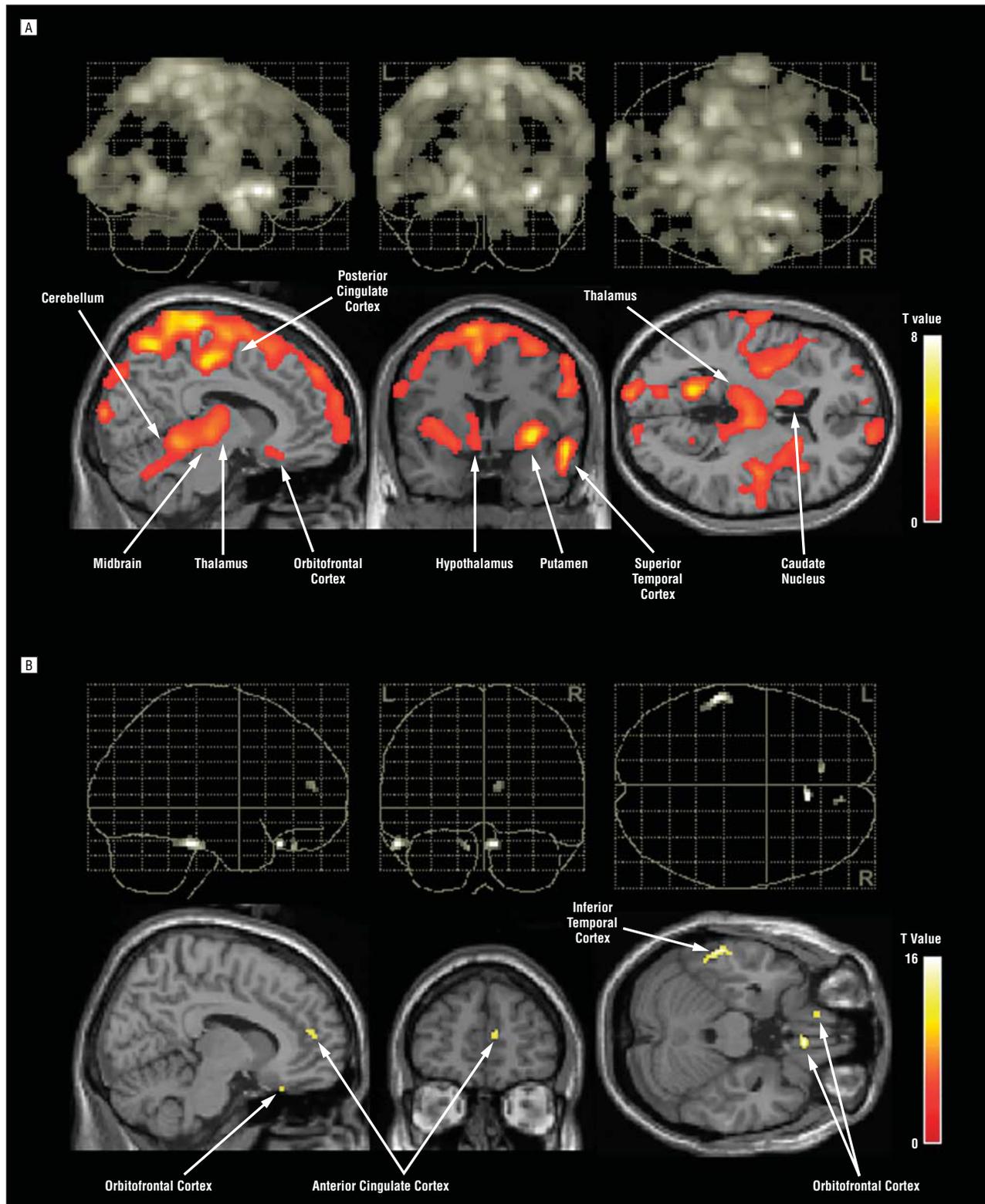


Figure 4. Results of the whole-brain voxel-based statistical parametric mapping analysis of the *trans*-1,2,3,5,6,10-beta-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline ([¹¹C](+)McN-5652) distribution volumes (DVs). A, Locations of methamphetamine abuser and control differences in [¹¹C](+)McN-5652 DVs. Areas with significantly reduced [¹¹C](+)McN-5652 DVs in methamphetamine abusers compared with those in controls ($P < .001$, corrected for cluster level) are given in Table 2. B, Locations of clusters with significant negative correlations between Aggression Questionnaire scores and [¹¹C](+)McN-5652 DVs in methamphetamine abusers ($P < .05$, corrected for voxel level) (Table 3). Each top row shows 3-dimensional glass brain views; each bottom row, detected area superimposed onto normal template magnetic resonance images.

amphetamine, and their histories were retrospectively confirmed by the abusers and their family members through

detailed Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*–

Table 2. Voxel-Based Analysis of Regional Brain [¹¹C](+)McN-5652 Distribution Volume Reductions in 12 Methamphetamine Abusers Compared With 12 Control Subjects*

Location	Cluster-Level Analysis		Voxel-Level Analysis		Talairach Coordinates		
	Corrected P Value	Voxels, No.	Corrected P Value	z Score	x	y	z
Right insular cortex	<.001	45 315	.009	5.33	34	13	-4
Left caudate nucleus	NA	NA	.02	5.12	-10	19	-4
Right claustrum	NA	NA	.03	5.02	32	0	-3

Abbreviations: [¹¹C](+)McN-5652, *trans*-1,2,3,5,6,10-beta-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline; NA, not available.

*The significance threshold was $P < .05$ at the corrected voxel level and $P < .05$ at the corrected cluster level. Coordinates are given in millimeters from the origin at the midpoint of the anterior commissure for voxels of peak significance.

Table 3. Voxel-Based Analysis of Regional Brain [¹¹C](+)McN-5652 Distribution Volumes Negatively Associated With Aggression Questionnaire Scores in 12 Methamphetamine Abusers*

Location	Cluster-Level Analysis		Voxel-Level Analysis		Talairach Coordinates		
	Corrected P Value	Voxels, No.	Corrected P Value	z Score	x	y	z
Right orbitofrontal cortex	<.001	20	.007	5.49	6	26	-21
Left inferior temporal cortex	<.001	38	.007	5.48	-57	-30	-19
Left orbitofrontal cortex	.001	10	.02	5.17	-10	34	-24
Right anterior cingulate cortex	<.001	12	.03	5.13	10	49	10

Abbreviation: [¹¹C](+)McN-5652, *trans*-1,2,3,5,6,10-beta-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline.

*The significance threshold was $P < .05$ at the corrected voxel level and $P < .05$ at the corrected cluster level. Coordinates are given in millimeters from the origin at the midpoint of the anterior commissure for voxels of peak significance.

based interviews. Furthermore, in this study, the severity of aggression clearly paralleled the decreases in serotonin transporter density in the brain, which in turn were found to be associated with the duration of methamphetamine use. Therefore, it seems unlikely that the increased aggression observed in these methamphetamine abusers reflected a preexisting disposition or personality trait.

Except for the scores on the AQ, none of the scores on the clinical rating scales for psychiatric symptoms were correlated with the decrease in serotonin transporter density. Methamphetamine has been reported to affect not only serotonergic neurons but also several other types of neurons, such as the dopaminergic, glutamatergic, and γ -aminobutyric acid (GABA)-ergic neurons, all of which have been implicated in the presence of a variety of psychiatric symptoms (eg, delusions, hallucinations, and anxiety).⁶³ It is possible that changes in various types of neurons might have affected or modified the clinical symptoms evaluated herein. Another plausible interpretation for the negative results is that, as seen in Table 1, the severity of most of the residual symptoms assessed in this study ranged from mild to moderate, and the variances of their distributions were relatively small; together, these factors may have biased the results toward the null hypothesis.

Herein, we recruited methamphetamine abusers from the community; they were recreational abusers of methamphetamine only, and none of them had used other illicit drugs or had taken toxic or high doses of methamphetamine. Although our strategy allowed us to evaluate

the pure effects of methamphetamine on the human brain, the findings may not be generalized to the broad population of methamphetamine abusers. However, the combined use of methamphetamine with other illicit drugs is infrequent in Japan, as indicated by Japanese National Police Agency records in 2002.⁶⁴ One reason for this is that cannabis, cocaine, and major illicit drugs other than methamphetamine are not widely distributed in Japan.⁶⁴ Furthermore, a national survey of 233 methamphetamine abusers reported that only 2.6% of the abusers had undergone methamphetamine intoxication,⁶⁵ suggesting that abusers of an overdose of methamphetamine are rare in Japan. Consequently, our findings are considered to be fairly generalizable to the population of methamphetamine abusers, at least in Japan.

In this study, all the methamphetamine abusers exhibited some psychopathologic symptoms, even in an abstinent state. To our knowledge, no previous studies have examined the incidence of psychopathologic abnormalities in abstinent methamphetamine abusers recruited from the general community. In a study by Wada and Fukui,⁶⁵ who investigated the psychopathologic characteristics of 233 abstinent methamphetamine abusers recruited from hospitals in Japan (the period of abstinence exceeded 1 month; the mean \pm SD duration of methamphetamine use was 11.1 ± 7.9 years), almost all the abusers exhibited some psychopathologic symptoms, such as auditory hallucinations, delusions of reference/persecution, mood disturbances, anxiety, insomnia, irritability, impulsivity, and personality changes, including the antisocial personality type. Such observations cannot be applied to absti-

ment abusers in the community as a whole but may provide some support for the high occurrence of psychopathologic symptoms observed in this study. In Japan, most methamphetamine abusers take the substance intravenously,⁸ whereas in a study⁶⁶ from the United States, approximately 90% of methamphetamine abusers had no history of intravenous or intramuscular injection of methamphetamine. Furthermore, a study by Domier and colleagues⁶⁶ revealed that among recently abstinent methamphetamine abusers who had discontinued its use for several months, the injecting abusers had a significantly higher incidence of psychopathologic symptoms than the noninjecting abusers. These results suggest that in Japan, the intravenous intake of methamphetamine could predispose its abusers to persistent psychiatric problems, even after the cessation of methamphetamine use. Nevertheless, it remains an important and unresolved issue whether a reduction in serotonin transporter could be expected to occur in abusers with no psychopathologic signs or symptoms. To verify our findings that methamphetamine abuse is linked to a reduction in brain serotonin transporters, which in turn underlies persistent psychopathologic symptoms, additional studies that also incorporate a group of methamphetamine abusers with no apparent psychopathologic problems are required.

Wilson and colleagues⁶⁷ examined serotonin concentrations in postmortem tissue samples from human brains with a history of long-term methamphetamine abuse, although they did not study serotonin transporters per se. They concluded that there were no substantial alterations in serotonin concentrations in the global brain except in the medial prefrontal cortex (Brodmann area 11: a reduction of 56% compared with controls) and in the orbitofrontal cortex (Brodmann area 12: a reduction of 61% compared with controls). These results seem to contradict our observation of reductions in serotonin transporters in widely distributed brain regions. The discrepancy between the results of that postmortem study and those of present study is puzzling. However, one possible explanation for this discrepancy could be related to differences in the pattern and amount of drug use between the samples.^{1,16,17} In Western countries, methamphetamine abusers often use other drugs, mainly cocaine or cannabis⁶⁸⁻⁷⁰; however, no information is provided with respect to this issue in the study by Wilson and colleagues.⁶⁷ Because methamphetamine is more likely to produce neurotoxic effects in serotonergic neurons than either cocaine or cannabis,^{71,72} methamphetamine abusers who use this drug only could have experienced more severe damage to serotonergic neurons than abusers who simultaneously use other drugs, such as cocaine or cannabis. Furthermore, similar to most methamphetamine abusers in Japan, those in this study intravenously injected the substance. The intravenous intake may further potentiate the neurotoxic effects of methamphetamine.

To our knowledge, this is the first study to demonstrate a severe and long-lasting reduction in the density of the serotonin transporter in the living brains of methamphetamine abusers. The observed decrease in serotonin transporter density was also found to be associated with elevated levels of aggression. The present findings,

combined with the results of previous animal studies, suggest that those who abuse methamphetamine may be at substantial risk for severe serotonin neuronal damage in the brain, potentially leading to persistently elevated aggression, even in those in a currently abstinent state.

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For details about this new policy see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*.