In vivo evidence for long-term CNS toxicity, associated with chronic binge use of methamphetamine

Yong An Chung[a], Bradley S. Peterson[b], Sujung J. Yoon[c], Sung-Nam Cho[d], Sukhi Chai[e], Jaeseung Jeong[b,f,*], Dai Jin Kim[c,**]

[a] Department of Radiology and Biomedical Engineering, The Catholic University of Korea, Seoul 420-717, South Korea
[b] Department of Psychiatry, Columbia College of Physicians and Surgeons, and the New York State Psychiatric Institute, New York, NY 10032, USA
[c] Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul 420-717, South Korea
[d] Bugok National Hospital, 70 Bugok-ri, Bugok-myon, Changnyung-gun, Gyeongnam, South Korea
[e] Department of Addiction Rehabilitation and Welfare Study, Eulji University, South Korea
[f] Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, South Korea

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ABSTRACT

Objective: The aim of this study was to examine disturbances in regional cerebral blood flow (rCBF) associated with methamphetamine abuse.

Methods: Using Single Photon Emission Computed Tomography (SPECT), rCBF was measured in 20 men who had previously injected methamphetamine intravenously for over 30 months and who were now abstinent for a minimum of 9 months and for an average of 2 years. Values were compared with those in 12 healthy men who had never injected methamphetamine.

Results: While rCBF was significantly and disproportionately reduced in subcortical and dorsal cortical brain regions, including the striatum, thalamus, cingulum, mesiodorsal prefrontal cortex, and pons (all t's > 8.3 after global normalization, corrected p's < 0.001), whole brain CBF was also significantly reduced in the former methamphetamine users. Binge use of methamphetamine is associated with long-term changes in both global and regional blood flows, likely representing severe and enduring neural toxicity of monoaminergic neurotransmitter systems in the brain, producing a pattern of hypoperfusion that resembles patterns reported previously for persons with atypical Parkinson's disease.

Conclusions: These findings suggest that methamphetamine abusers may be possibly at increased risk for neurodegenerative diseases later in life.

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1. Introduction

The abuse of methamphetamine ("speed") and its pure crystalline form ("crystal meth", "ice", or "glass") has reached epidemic proportions. The estimated lifetime prevalence of methamphetamine abuse is 5.3% across the United States (Substance Abuse and Mental Health Services Administration (SAMHSA), 2002). Between the years of 1992 and 2001, 33 states in the United States reported a 100% increase in admissions to treatment centers for abuse of methamphetamine (SAMHSA, 2002). According to a United Nations report, approximately 33.4 million people use methamphetamine in Asian countries, particularly in eastern and southeast Asia, where its abuse is among the most pressing of societal concerns (Chung et al., 2004; Kulsudjarit, 2004). The abuse of methamphetamine has had profoundly harmful social and public health consequences (Cohen et al., 2003; London et al., 2004). Despite the high prevalence and destructive effects of methamphetamine abuse, the long-term effects of methamphetamine on neural functioning are still poorly understood.

Methamphetamine has strong addictive characteristics and is a potent neurotoxin (Woolverton et al., 1984). Animal models suggest that continuous administration of methamphetamine produces long-lasting reductions in striatal dopamine concentrations, dopamine transporter levels, and rate-limiting synthetic enzymes as well as autophagocytosis of the neurites and apoptosis of dopaminergic neurons in the striatum (Ricaurte et al., 1980; Villemagne et al., 1998; Wagner et al., 1980). In vivo studies of the acute neurobiological effects of methamphetamine in humans have documented alterations in dopamine neurotransmitter systems and neural metabolism across the cerebrum, but particularly in the basal ganglia (Alhassoon et al., 2001; Doudet and Holden,

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* Corresponding author at: Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, South Korea.
** Corresponding author.
E-mail addresses: jsjeong@kaist.ac.kr (J. Jeong), KDJ922@chollian.net (D.J. Kim).

2003; Gouzoulis-Mayfrank et al., 1999; Hwang et al., 2006; Iyo et al., 1997; Kao et al., 1994; London et al., 2004; Pontieri et al., 1990; Volkow et al., 2001; Vollm et al., 2004; Wang et al., 2004). Studies on abstinent methamphetamine abusers using Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) have shown decreased cerebral blood flow (CBF) both in cortical and subcortical regions, particularly the cerebral cortex (Iyo et al., 1997; Alhassoon et al., 2001), the right anterior cingulate cortex (Hwang et al., 2006), or putamen/insular cortices and the right lateral parietal brain regions (Chang et al., 2002, 2007). More interestingly, studies of abstinent, former methamphetamine abusers suggest that regions that are most sensitive to the acute effects of methamphetamine administration differ from those that are most sensitive to its long-term effects, although the longest average duration of abstinence studied thus far has been 19 months (Kim et al., 2005). Here, we use the SPECT to examine brain perfusion in persons who were formerly chronic binge users of methamphetamine and who at the time of imaging had abstained from methamphetamine use for an average of 2 years.

2. Methods

2.1. Subject recruitment and participation criteria

Members of the methamphetamine group met Diagnostic and Statistical Manual-IV (DSM-IV) criteria for methamphetamine dependence based on a consensus procedure involving two board-certified psychiatrists using all available clinical material, including a semi-structured interview. They all have used intravenous methamphetamine regularly in their lifetime for at least 30 months, but have been abstinent for at least 9 months at the time of the study (an average of 2 years). The period of the methamphetamine use was designated as the period between the initial use and the last use. Intervals of abstinence longer than 1 month during the duration of methamphetamine use were subtracted from the calculated total duration of use. Methamphetamine users were recruited from the Incheon Court Drug Rehabilitation Program, a long-term treatment program that included an inpatient stay of 2–11 months and subsequent weekly drug monitoring to ensure abstinence based on urinalysis and self-report. All of the patients were inpatients in the hospital according to the Korean Law of Drug Addiction, thus they had no chance to take drugs during staying the hospital. Patients were excluded from the study if they were seropositive for HIV or if they had a history of comorbid psychiatric illness, seizures or any other neurological disorder, abnormal results on laboratory screening tests, addiction to drugs other than methamphetamine, or head trauma with loss of consciousness for more than 30 min. We studied men only because of extensive prior evidence that methamphetamine-induced neurotoxicity is sex-specific, particularly greater in men than in women (D'Astous et al., 2005; Dluzen et al., 2002; Kim et al., 2005; Wagner et al., 1993).

Controls were randomly selected healthy individuals who visited the Korea University Ansan Hospital for regular health screenings. They were group-matched with the patient group by age, sex, and socioeconomic status. They had no history of methamphetamine use or abuse of other substances. None had a personal or familial history of psychiatric illness based on an unstructured interview conducted by a trained psychiatrist.

No subjects could be taking medication at the time of the study, and all had negative urine toxin screens to ensure the absence of psychoactive drug use. Subjects in both groups were excluded if they reported drinking alcohol more than once per day or >40 g per week or reported smoking more than 10 cigarettes per day. All provided written, informed consent to participate in the study.

2.2. SPECT Imaging

The scans of patients and controls were interleaved in time. Images were obtained 40 min after intravenous injection of 1110 MBq of Tc-99m ECD using a dual-head gamma camera (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. Subjects were supine with eyes open during the scan. The room was dimly lit, and noise was kept to a minimum. Gathered data were reconstructed in a 128 × 128 matrix with a pixel size of 3.9 mm × 3.9 mm × 3.9 mm (FOV = 240 mm, slices thickness = 7 mm), and a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after back-projection with a Butterworth filter (cutoff frequency 0.4 cycles/pixel, order 5) to reduce noise. Tc-99m ECD images were corrected for tissue attenuation using a standard commercial correction routine (Siemens, Erlangen, Germany).

Image analyses were performed on an IBM PC running Windows XP operating system. SPM99 software (Friston et al., 1995) based on MatLab version 5.3 was used for image analyses. The SPECT data with attenuation and scatter correction were converted into ANALYZE format. The mean pixel intensity across all slices of the imaging volume was calculated. Each pixel was then thresholded at 80% of this value to eliminate background noise and partial volume effects at the edge of the brain. Each SPECT scan was then spatially normalized using a 12-parameter affine warping and sinc-linear interpolation to the SPECT template brain from the Montreal Neurological Institute and reformatted to a 16-bit image of $79 \times 95 \times 68$ voxels, each 2 mm × 2 mm × 2 mm in size. These images were spatially smoothed with a Gaussian filter of 16 mm full-width at half maximum. Normalized rCBF values were calculated by dividing CBF at each voxel by global CBF in each individual (Aguirre et al., 1998; Desjardins et al., 2001). The t-statistic image was thresholded at $t = 7.75$, corresponding to a Bonferroni corrected p-value < 0.001, in conjunction with a cluster filter of 200 voxels. This combined application of a statistical threshold and cluster filter has previously been shown to reduce substantially the false positive identification of activated pixels at any given threshold (Forman et al., 1995). The t-score clusters were projected onto the standard high-resolution T1-weighted MRI for anatomic localization and visualization.

Finally, in exploratory analyses, we assessed the correlations of normalized rCBF in each of the regions that differed significantly across groups with measures of methamphetamine use. We also assessed the intercorrelations of rCBF across regions that differed significantly across groups.

3. Results

3.1. Subject sample

The methamphetamine group consisted of 20 men (mean age: 41.2 ± 8.3 years, range: 31–58; years of education: 12.6 ± 3.1) who had all repeatedly injected methamphetamine intravenously for an average of 142 ± 89 (range: 36–360) months, but who had been abstinent an average of 24 ± 18 (range: 9–65) months prior to the study. They began use at a mean age of 27.2 ± 6.7 (range: 19–47) years and averaged 0.48 ± 0.49 (range: 0.08–2.00) g of methamphetamine each week, for an average cumulative, self-reported lifetime dose of 563 ± 581 (range: 50–2080) g. Controls consisted of 12 healthy men (mean age: 44.0 ± 9.4 years, range 30–58; years of education: 14.3 ± 2.3). Both groups had similar patterns of occa-

Table 1
Locations of disproportionately decreased rCBF in Methamphetamine abusers.

Cluster level Equivalent K	Voxel T	Talairach coordinates			Region
		x	y	z	
14783	14.52	4	−8	44	Right Cingulate Gyrus BA 24
14783	10.21	−4	4	42	Left cingulate gyrus BA 24
14783	8.75	−28	2	60	Left middle frontal gyrus, BA 6
14783	8.39	24	4	64	Right superior frontal gyrus, BA 6
1836	15.79	12	−20	10	Right thalamus
1836	12.72	−12	−24	4	Left thalamus
504	11.50	20	10	4	Right striatum
626	9.68	−20	12	4	Left striatum
309	10.46	−2	−30	−30	Right pons

T-Values were calculated for data normalized by global CBF, which was significantly lower in the methamphetamine group than in control subjects.
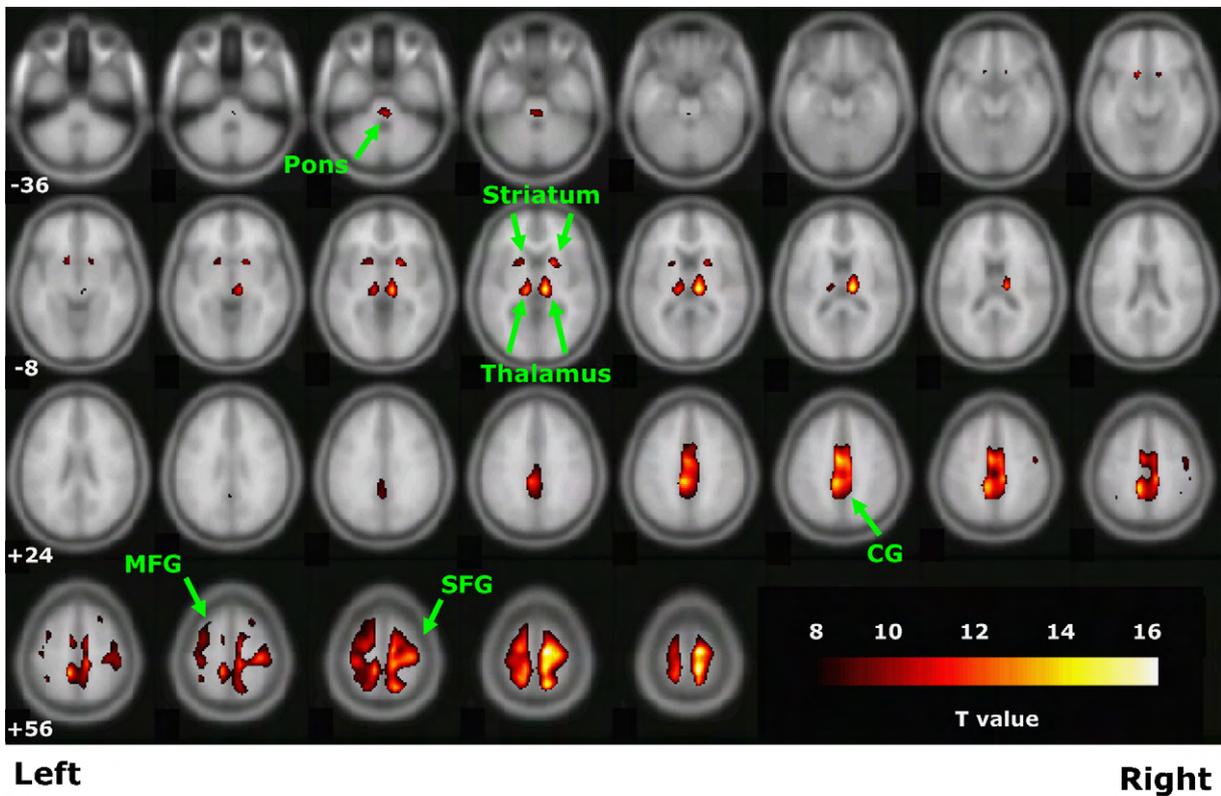Magnitude threshold: $T = 7.75$, $p < 0.001$.
BA: Brodmann's Area.

Fig. 1. Group differences in normalized rCBF. The brain regions are shown where normalized rCBF values are disproportionately reduced in the methamphetamine abusers compared with the healthy control subjects. The numbers on the left-most margin of each row are locations of the axial slices (z-levels) in the Talairach atlas. *T*-Values are color-coded according to the color bar in the lower right corner of the figure. Magnitude threshold $T = 7.75$, $p < 0.001$, and cluster filter = 200 voxels, each 2 mm × 2 mm × 2 mm in size after spatial normalization.
MFG: middle frontal gyrus; SFG: superior frontal gyrus; CG: cingulate gyrus.

sional smoking (below 10 cigarettes/day) and drinking (<40 g of alcohol per week).

3.2. SPECT findings

The mean global count was significantly decreased in the methamphetamine group (85.0 ± 11.6, dimensionless unit) compared with that of control group (120.4 ± 11.1) ($p < 0.0001$). After global normalization, rCBF in methamphetamine user group compared with the control group was significantly disproportionately reduced in the striatum, thalamus, cingulum, mesiodorsal prefrontal cortex, and pons (all t's > 8.3 after global normalization, corrected p's < 0.001) (Table 1, Fig. 1).

In the methamphetamine group, the duration of use correlated strongly and significantly with global CBF ($r = 0.51$, $p < 0.03$) and with normalized rCBF in all regions of disproportionate hypoperfusion, including the striatum ($r = 0.62$, $p < 0.004$), thalamus ($r = 0.60$, $p < 0.01$), cingulum ($r = 0.44$, $p < 0.05$), and pons ($r = 0.51$, $p < 0.02$); rCBF did not correlate significantly, however, with age at first use, duration of abstinence, lifetime cumulative dose, the number of cigarettes per day, or the amount of alcohol per week, for any region. Furthermore, normalized rCBF was strongly intercorrelated across all regions where disproportionate hypoperfusion was identified, including striatum and thalamus ($r = 0.90$), thalamus and cingulum ($r = 0.91$), thalamus and pons ($r = 0.89$), and striatum and pons ($r = 0.94$) (all p's < 0.0001) (Fig. 2).
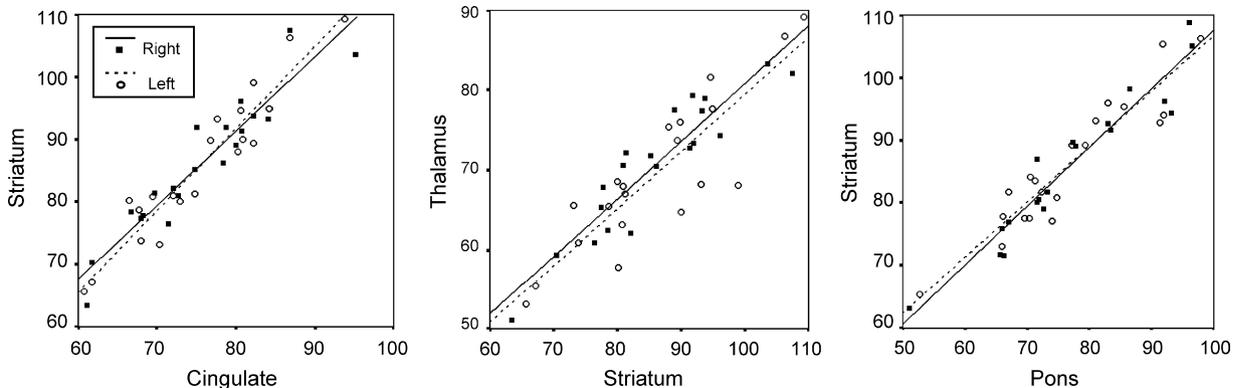

Fig. 2. Interregional correlations of rCBF. Representative correlations in only methamphetamine users are shown in scatter-plots with left and right hemispheres (cingulate (left), striatum (center), and pons (right)) plotted separately. These are rCBF measures normalized by global CBF, and therefore the measures are in dimensionless units.

4. Discussion

We detected significantly reduced global CBF in former methamphetamine abusers who had been abstinent for an average of nearly 2 years and for a minimum of 9 months. We also detected disproportionate reductions in flow to the striatum, thalamus, cingulum, mesiodorsal prefrontal cortex, and pons. The striatum, cingulum, and prefrontal cortex are all important projection sites for midbrain dopaminergic neurons, which are highly sensitive to the neurotoxic effects of methamphetamine (Cubells et al., 1994; Fornai et al., 2004; McCann et al., 1998; Preston et al., 1985; Wilson et al., 1996). The thalamus mainly receives glutamatergic signals from the striatum, and therefore the lower thalamic blood flow could reflect either a downstream effect of reduced neural activity within the striatum, or methamphetamine-induced damage to glutamatergic neurons projecting from the striatum to the thalamus, both of which are documented effects of methamphetamine (Burrows and Meshul, 1999; Mark et al., 2004; Nash and Yamamoto, 1992; Rocher and Gardier, 2001; Stephans and Yamamoto, 1994). The upper pons is the location of the raphe nuclei containing the cell bodies of the majority of the brain's serotonergic neurons, which project primarily to the frontal cortex and striatum; it also contains the locus ceruleus, an origin of noradrenergic neurons that project widely to the neocortex, diencephalon, and cerebellum. In addition to its most prominent toxic effects on the neurites of dopaminergic neurons in the striatum, methamphetamine has increasingly been implicated as toxic to serotonergic neurons (Kita et al., 2003; Kraemer and Maurer, 2002), consistent with the pontine hypometabolism observed here.

We speculate that the vast expanse of cortical and subcortical brain regions to which these monoaminergic systems project account for the reductions in global CBF observed in the former methamphetamine abusers of our study. If toxicity across these monoaminergic systems does account for global reductions in flow, then the high correlations of blood flow across the regions exhibiting disproportionately reduced flow compared with control values may suggest that the toxicity of methamphetamine to the various monoamine systems of the brain is reasonably consistent within individuals compared with its variable degree of toxicity to these systems across individuals. Although the determinants of this variable individual vulnerability are unknown, it is consistent with the known variability in the severity of neural toxicity of methamphetamine across the sexes (i.e. male is more vulnerable) (D'Astous et al., 2005; Dluzen et al., 2002; Kim et al., 2005; Wagner et al., 1993) and therefore could include genetic, hormonal, or environmental effects that disturb these various monoamine systems to a similar degree. Alternatively, the interregional correlations in rCBF in the methamphetamine group may reflect the effects of anatomical and functional connectivity among the regions most affected by the long-term toxicity of methamphetamine. Indeed, the striatum, thalamus, and cingulum within the frontal cortex – the regions most associated with the long-term toxicity of methamphetamine in this study – are likely components of neural systems commonly regarded as subserving habit learning, executive functioning, and impulse control (Marsh et al., 2006; Packard and Knowlton, 2002), functions previously found to be impaired in current and former methamphetamine abusers (Barr et al., 2006; Johanson et al., 2006; Verdejo-Garcia et al., 2006). Regardless of whether the interregional correlations are a consequence of the comparable effects of methamphetamine on multiple monoamine systems or its effects on a functionally coupled neural system, the estimated duration of methamphetamine use correlated strongly with global and normalized rCBF values across all portions of these monoaminergic and functional networks, possibly suggesting a hypothesis that the duration of exposure to methamphetamine accounts for a substantial portion of variance in the severity of its long-term, system-wide neurotoxic effects observed across individuals.

Our findings following long-term abstinence from methamphetamine are consistent with and extend those of prior imaging studies of the effects of methamphetamine, particularly prior studies of cerebral metabolism and blood flow. During acute methamphetamine intoxication in animals and humans, previous studies demonstrated sustained and stable increases in synaptic dopamine (Doudet and Holden, 2003) and widespread dose-dependent increases in glucose utilization within structures of the extrapyramidal motor system, particularly in basal ganglia and ventral striatum, thalamus, and cerebellum (Gouzoulis-Mayfrank et al., 1999; Vollm et al., 2004). Chronic administration of methamphetamine then depleted dopamine and serotonin in these same regions (Pontieri et al., 1990). In the first week of abstinence from chronic methamphetamine use, glucose metabolism was reduced in anterior cingulate and insular cortices but increased in orbitofrontal, posterior cingulate, amygdala, ventral striatum, and cerebellum (London et al., 2004). One to five months following the initiation of abstinence, metabolism was reduced in the striatum and thalamus but increased in parietal cortex (Volkow et al., 2001). An average of 19 months of abstinence was associated with reduced metabolism in frontal white matter (Kim et al., 2005). In addition, several studies suggested the possibility that disturbances in metabolism and blood flow may improve with the duration of abstinence, although abnormalities in the striatum and anterior cingulate persist even after prolonged abstinence (Hwang et al., 2006; Wang et al., 2004). Together, these studies suggest that the regions most sensitive to the acute effects of methamphetamine administration differ from those that are most sensitive to its long-term effects, and our study may suggest that those long-term effects in males are profound throughout the cerebrum, particularly so in subcortical nuclei and in the cingulate cortex.

Our findings must be interpreted in light of the limitations of this study. The duration and amounts of methamphetamine use were determined by retrospective self-reports, which have limited validity and precision. Detailed neuropsychological testing was not conducted, and therefore the functional correlates of the altered perfusion detected in this study could not be assessed. The decision to study only males, who likely are more susceptible than are women to the neurotoxic effects of methamphetamine, limited the generalizability of our findings to men only. Finally, although we excluded subjects with extensive nicotine, alcohol use, or other drugs, the methamphetamine abusers likely consumed larger amounts of other drugs during their lifetimes than did the comparison group, thereby confounding our ability to attribute the causes of hypoperfusion to methamphetamine alone.

We should note that the recent study of Renshaw and his colleagues (Hwang et al., 2006) demonstrated that abstinent MA users only had decreased rCBF in the anterior cingulated cortex. We speculate that this discrepancy might be arisen from the fact that their study examined the methamphetamine patients with abstinence period of 6 months, which is quite different from the abstinence period of our patients (i.e. 2 years on average in our study). We speculate that our result may be originated from a relatively long-term effect of methamphetamine on the cortex, compared with the Renshaw study.

Because of the potency and regional specificity of its neurotoxic effects, methamphetamine is commonly used to generate experimental models of Parkinson's disease in animals (Garcia de Yebenes et al., 2000; Romero et al., 2006; Walsh and Wagner, 1992), and indeed the pattern of chronic abnormalities of blood flow detected in this study after prolonged remission is reminiscent of the reduced striatal and thalamic metabolism reported in patients with atypical Parkinson's disease (Antonini et al., 1998). Patients with more typical Parkinson's disease, however, have either nor-

mal or increased striatal and thalamic metabolism (Brooks, 1998; Eidelberg et al., 1994). Whether methamphetamine predisposes to long-term neurological or neuropsychological deterioration is unknown; nevertheless, chronic methamphetamine administration has been shown to produce motor disturbances in animals (Walsh and Wagner, 1992; Woolverton et al., 1984). The magnitude and regional distribution of blood flow abnormalities detected in this study despite the prolonged period of abstinence, together with the similarity of that regional distribution to the abnormalities associated with atypical Parkinson's, may suggest that prospective longitudinal studies are needed to determine whether methamphetamine users are predisposed to developing neurodegenerative diseases. Based on our findings together with those reported in previous animal and human studies, we suggest with caution that the growing pandemic of methamphetamine abuse may forebode a future pandemic of neurodegenerative illnesses.

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Contributors

Authors Yong An Chung and Dai Jin Kim designed the study and wrote the protocol. Jaeseung Jeong and Bradley S. Peterson managed the literature searches and summaries of previous related work. Sujung J. Yoon and Sung-Nam Cho undertook the statistical analysis, and author Yong An Chung wrote the first draft of the manuscript and Jaeseung Jeong and Bradley S. Peterson revised the manuscript to the current form. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

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