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ORIGINAL INVESTIGATION

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Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers

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Abstract *Objective:* Preclinical investigations have established that methamphetamine (MA) produces long-term changes in dopamine (DA) neurons in the striatum. Human studies have suggested similar effects and correlated motor and cognitive deficits. The present study was designed to further our understanding of changes in brain function in humans that might result from chronic high dose use of MA after at least 3 months of abstinence. *Method:* Brain function in abstinent users was compared to controls using neuroimaging of monoamine transporters and cognitive assessment. Striatal levels of DA transporter (DAT) and vesicular monoamine transporter type-2 (VMAT2) were determined using [^{11}C] methylphenidate and [^{11}C]dihydrotetrabenazine positron emission tomography, respectively. Cognitive function was evaluated using tests of motor function, memory, learning, attention, and executive function. *Results:* Striatal DAT was approximately 15% lower and VMAT2 was 10% lower in MA abusers across striatal subregions. The MA abusers performed within the normal range but performed more poorly compared to controls on three of the 12 tasks. *Conclusions:* Failure to find more substantial changes in transporter levels and neurocognitive function may be attributed to the length of time that MA users were abstinent (ranging from 3 months to more than 10 years, mean 3 years), although there were no correlations with length of abstinence. Persistent VMAT2 reductions support the animal literature indicating a toxic effect of MA on nigrostriatal nerve terminals. However, the magnitude of the MA effects on nigrostriatal projection integrity is sufficiently small that it is questionable whether clinical signs of DA deficiency are likely to develop.

Keywords Methamphetamine · Human · Neurocognitive function · PET · Neuroimaging · Dopamine transporter · DAT · VMAT2

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Introduction

Laboratory investigations conducted over the past 25 years in nonhumans have clearly established that administration of amphetamines can produce long-term neurochemical and structural changes in dopamine (DA) and serotonin (5-HT) neurons in certain brain regions (Lew and Malberg 1997). Specifically, it was shown that high dose methamphetamine (MA) produces long-lasting decreases in the brain levels of DA and serotonin; plasmalemmal reuptake transporters for dopamine (DAT) and serotonin; and the rate-limiting neurotransmitter synthesizing enzymes, tyro-

sine hydroxylase, and tryptophan hydroxylase (Hotchkiss and Gibb 1980; Ricaurte et al. 1982; Seiden et al. 1976; Seiden and Ricaurte 1987; Wagner et al. 1980). Further, there is morphological evidence of neurotoxicity on DA nerve terminals (Lorez 1981). On the other hand, there is histological evidence that indicates there is no degeneration of the axon trunks or somata of the DA and 5-HT neurons, which makes it likely that regeneration of the axon terminals could take place (Ricaurte et al. 1982).

Human neuroimaging studies have also reported long-term neurochemical differences when former high dose MA abusers were compared to nondrug-abusing age- and sex-matched controls. Ernst et al. (2000) using a magnetic resonance (MR) scan, found decrease in concentrations of *N*-acetylaspartate (NAA) in the basal ganglia and frontal white matter of individuals in treatment for MA dependence relative to matched controls. Nordahl et al. (2002) reported decrease in concentrations of NAA in cerebral cortical regions of the brain rich in DA innervation (e.g., anterior cingulate) in individuals who were abstinent for 4 to 13 weeks compared to age-matched controls. A study by Thompson et al. (2004) in current MA users using high-resolution (3 Tesla) structural MR imaging showed atrophy of the cingulate, limbic, paralimbic cortices and hippocampus, and white matter hypertrophy. While the mechanism underlying these structural abnormalities cannot be determined from these data with certainty, the investigators suggested cell death as a possibility.

Positron emission tomography (PET) studies investigating the consequences of high dose amphetamine abuse in humans have utilized ligands that bind to DAT. McCann et al. (1998) studied individuals who had abused high doses of MA for long periods of time but were abstinent for an average of 3 years. Relative to controls, DAT binding in the caudate and putamen were reduced 23 and 25%, respectively. Volkow et al. (2001b) also demonstrated significantly lower DAT binding in the caudate and putamen, 28 and 21%, respectively, of MA abusers who were abstinent from 2 weeks to 36 months (average of 6 months) relative to controls. These researchers (Volkow et al. 2001a) conducted further evaluations on a subgroup of five MA users from the previous study. These individuals were abstinent on an average of 3 months in the first study but were abstinent for at least nine more months. Results of the second PET scan demonstrated partial recovery in DAT binding with degree of recovery related to length of abstinence. Sekine and colleagues (Sekine et al. 2001, 2003) also demonstrated decreases in DAT binding in the striatum and nucleus accumbens in MA users abstinent for 7 days to 1.5 years (average 6 months) compared to controls. The decreases were correlated with duration of use and to some extent, with psychiatric symptoms but not duration of abstinence. Unlike previous studies, these MA users recruited from hospital centers in Japan were not polydrug users except for nicotine and alcohol.

The decrease in levels of DAT binding seen in these studies could result from a decrease in the expression level of the protein within DA terminals, a subcellular relocation of the protein or DA neuron terminal degeneration. A postmortem study of the striata of active MA abusers found reductions in the concentrations of DA, tyrosine hydroxylase, and DAT but not in levels of aromatic amino acid decarboxylase (AADC), or VMAT2 (Wilson et al. 1996). These investigators argued that because AADC and VMAT2 concentrations are more stable indicators of the structural integrity of nerve terminals than the DAT, this evidence indicates that the DA nerve terminals are biochemically altered by acute effects of MA but remain structurally intact. A subsequent study in rats demonstrated that a neurotoxic dose regimen of MA can produce a decrease in both DAT and VMAT2 throughout the striatal complex (Frey et al. 1997), indicating that VMAT2 binding assays are able to reveal nerve terminal damage induced by MA. Thus, Frey et al. (1997) concluded that their data and the results obtained by Wilson et al. (1996) suggest that long-term high dose MA abuse in humans does not necessarily produce structural damage to nigrostriatal nerve endings.

In addition to the evidence in humans for MA induced neurochemical changes, several studies also reported functional deficits in cognitive and motor functions. However, many of these studies were conducted with active users (Simon et al. 2000, 2002; Ornstein et al. 2000). To evaluate whether deficits persist, designs employing testing after a period of abstinence are required. Testing after a period of drug abstinence also decreases the likelihood that the observed cognitive impairment is due to residual drug or withdrawal effects. Kalechstein et al. (2003) found that the MA users who were abstinent for 5–14 days still performed significantly worse than controls on measures of attention/psychomotor speed (Symbol Digit Modalities Test), learning/memory (Rey Auditory Verbal Learning Test, Wechsler Memory Scale-III Logical Memory), and executive function (Controlled Oral Word Association, Ruff Figural Fluency Test). On the other hand, there were no differences in the performance between the MA users and control group on many other measures of attention/psychomotor speed, visuospatial skills, learning/memory, or executive functioning.

In a study conducted by Salo et al. (2002), individuals who were MA-dependent but were abstinent for a period of 2–4 months were compared to normal controls on a computerized single-trial version of the Stroop Test, which is thought to assess selective attention. Results indicated that the MA group had greater rates of interference despite intact priming, which the authors interpreted as indicating an impaired ability to suppress irrelevant information. Clinically, this reduced cognitive inhibition may present as increased distractibility and difficulty with concentration.

Chang et al. (2002) administered a computerized cognitive test of reaction time and working memory [California Computerized Assessment Package (CalCAP)], as well as measures of psychomotor speed, fine and gross motor function, and verbal memory and executive function to 20 MA users who were abstinent for a minimum of 2 weeks (range 2 weeks to 36 months). They reported that although the MA users exhibited performance deficits

relative to controls on several CalCAP tasks that involve reaction time and working memory, the MA users as a group performed similarly to the controls on many other measures of cognitive function. Furthermore, the magnitude of the observed deficits was not correlated with any aspect of MA use.

In the study by Volkow et al. (2001b) that demonstrated decrease in levels of DAT binding after 2 weeks to 36 months of abstinence, the MA users were also evaluated with a battery of cognitive tests. The magnitude of the striatal decrease in DAT binding was inversely correlated with motor speed and memory performance but there was no correlation with measures of attention (CalCAP, Symbol Digit Modalities Test, Trail Making Test, and Stroop Interference Test). In the second study by Volkow et al. (2001a) demonstrating partial recovery in DAT binding with longer periods of MA abstinence, there were also improvement trends in one measure of motor (timed gait) and memory function (delayed recall), but these were not statistically significant.

The human studies reviewed above, in combination with laboratory animal studies, allow the conclusion that high dose MA abuse leads to neurochemical changes in DA systems in the brain. It is important to note, however, that it is not clear whether these changes are due to structural damage to DA neuron terminals or to regulatory adaptations in an intact population of nerve terminals. The present study was designed to investigate this issue by using the PET ligand (+)-α-[^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) that binds selectively to the vesicular monoamine transporter (VMAT2), which is a more stable marker of the integrity of DA nerve terminals than DAT. [^{11}C]DTBZ binding cannot differentiate DA and 5-HT terminals, however, over 95% of its striatal binding is attributable to the dopaminergic nigrostriatal pathway. To compare results with previous studies, PET scans were also done on each participant using the DAT ligand, [^{11}C]methylphenidate ([^{11}C]MPH). If decrease in concentrations of both DAT and VMAT2 were found in the nigrostriatal pathway of former MA abusers in comparison to matched controls, this would support the hypothesis that there are long-term structural changes in DA neuron terminals in that brain region. Furthermore, to evaluate the functional consequences of any changes, both the MA users and controls were assessed with a cognitive test battery that incorporated a wide variety of measures designed to assess motor function, memory, learning ability, and reasoning.

Materials and methods

Participants

All participants had to be in good health, be between 18 and 55 years of age, have a high school education, and an estimated IQ of 85 or greater according to the Revised Shipley Institute of Living Scale (Zachary 1986). Participants who had experienced head trauma, had a history of a seizure disorder, met the criteria for bipolar disorder or schizophrenia, or were taking a proscribed medication (e.g., antidepressants) were excluded. Female subjects could not be pregnant or lactating.

MA users were recruited from sites in the San Francisco, Los Angeles, and Detroit areas through advertisements in newspapers and word-of-mouth. MA participants met the above criteria and additionally had to have negative urine drug tests for stimulants, opiates, benzodiazepines, and cocaine at screening and before all assessments. All MA users had to report heavily using MA for at least a 3-month period with toxic effects, which included agitation, sleeplessness, paranoia, and tremors and had to meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for Amphetamine Dependence in the past, but had to be in at least early partial remission (i.e., only one or two of the criteria for dependence were met for at least 1 month but less than 12 months) with no MA use for a minimum of 3 months. Previous abuse of or dependence on other drugs was allowed as long as the diagnosis was not current (at least 1 year without meeting DSM-IV criteria). Nicotine dependence was allowed.

Control participants who were recruited from the Detroit area only had to report not to have used any illegal drug more than 50 times except marijuana, no history of drug dependence, and not used any illegal drug except marijuana within the past year. They also had to provide a urine sample that tested negative for stimulants, opiates, benzodiazepines, and cocaine at screening and before all assessments. Control participants were matched on a one-to-one basis to MA users in age, sex, ethnicity, and estimated IQ scores.

Eligibility was determined during a screening interview either at the site of origin for those from Los Angeles and San Francisco or in Detroit. Occasionally, some of the screening tests could not be performed at the remote site and were completed in Detroit. Screening evaluations included obtaining drug use and medical history; a pregnancy test for females; electrocardiogram, physical, blood, and urine analysis; urine drug screen; a psychiatric interview using the Structured Clinical Interview for DSM-IV (First et al. 1996); and administration of the Shipley Scale. MA users resided on a locked inpatient research unit for 3 to 4 days while the procedures were being completed whereas control participants resided at home and came to the laboratory on study days.

After complete description of the study to the participants, written informed consent was obtained. Participants were paid for their time and inconvenience. The study was carried out in accordance with the Declaration of Helsinki and regulations of the United States Department of Health and Human Services and was approved by the Wayne State University Institutional Review Board.

Procedures

Eligible participants were assessed with two procedures. These included determination of striatal VMAT2 and DAT binding site densities using [^{11}C]DTBZ and [^{11}C]MPH,

respectively, and PET and a battery of neurocognitive tests. The scheduling of these two evaluations was determined by the availability of PET scanner time. For all MA users, evaluations were conducted within a 3-day period. This was also true for most control participants but for some, the interval was longer but never more than 30 days. Smoking was allowed up to the time that sessions began and for the neuropsychological testing, there was a break during which smokers could smoke.

Positron emission tomography of neurotransmitter transporter binding

The distribution and density of VMAT2 binding sites was determined with the use of PET and the radioligand [^{11}C]DTBZ as described previously (Koeppe et al. 1997). Subjects were positioned supine in the PET scanner (Seimens/CTI Exact HR^{+} tomograph) gantry with eyes and ears unoccluded. A transmission scan was obtained for attenuation correction immediately before radiotracer administration. In determinations of VMAT2 binding, a bolus injection was given followed by a 59-minute continuous intravenous infusion of [^{11}C]DTBZ (containing 10–18 mCi and less than 50 μg mass). Prior studies have demonstrated that administration of 55% of the total dosage as a bolus over 1 min followed by the remaining 45% administered as a continuous infusion over 59 min produces constant arterial and brain tracer levels after 30 min (Koeppe et al. 1997). After a 60-min period to allow the further decay and elimination of [^{11}C]DTBZ activity, determinations of DAT binding site density were made with the use of MPH. An imaging protocol similar to that of the DTBZ study was used, employing approximately 18 mCi of [^{11}C]MPH administered as a loading bolus (60% of the dose) over the first minute followed by a constant infusion of the remaining 40% of the dose over the next 79 min.

In [^{11}C]DTBZ binding scans, dynamic brain imaging was obtained over 60 min. Early image frames (0 to 4 min postinjection of the [^{11}C]DTBZ bolus) were used to estimate the blood-brain barrier (BBB) transport rate and were employed in voxel-based analyses requiring gray matter structural delineations. Three frames acquired for 10 min each between 30 and 60 min postinjection were used to estimate VMAT2 binding site density (Koeppe et al. 1997). In [^{11}C]MPH scans, early image frames (0 to 4 min postinjection) were again used for BBB transport and anatomic registration, while two 10-min frames from 60 to 80 min post injection were used to estimate [^{11}C]MPH binding (Volkow et al. 1995; Sossi et al. 2000).

Images were reconstructed by filtered backprojection with a Hanning 0.5 filter using the measured tissue attenuation coefficients and calculated scatter correction. Summed reconstructed images from 30 to 60 min for [^{11}C]DTBZ or 60 to 80 min for MPH, which depicted the total tissue equilibrium tracer distribution volumes (DV_{TOT}), were employed to calculate striatal VMAT2 or DAT binding site densities. Volumes-of-interest (VOI) were extracted from the striatum in each subject's parametric DV maps, delineating the maximal activity in each of three rostrocaudal regions (dimensions 2.25 mm craniocaudal×9 mm anteroposterior×4.5 mm mediolateral) representing the caudate nucleus, the anterior putamen, and the posterior putamen in each hemisphere. We estimated the nonsaturable components of [^{11}C]DTBZ or [^{11}C]MPH DV_{TOT} (DV_{REF} representing nonspecific binding and free ligand contributions) from the occipital cortex (Brodmann areas 17, 18, and 19) as a reference region known to be free of detectable VMAT2 binding sites in [^{11}C]DTBZ PET (Koeppe et al. 1999) and of very low DAT expression (Volkow et al. 1995; Sossi et al. 2000). Our measure of specific [^{11}C]DTBZ or [^{11}C]MPH bindings, the binding potential (BP) was calculated as follows:

$$BP = (DT_{TOT} - DV_{REF})/DV_{REF}$$

Neurocognitive examination

The neurocognitive test battery included tests of general cognitive ability for IQ estimates, motor performance, explicit memory that assesses both encoding and retrieval components, working memory, and executive function. The battery also included tests from the Cambridge Automated Neuropsychological Assessment Battery (CANTAB) that are performed by the participant on a computer terminal using a touch screen or button press (Robbins et al. 1994, 1998).

Estimated IQ was based on scale scores obtained on the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler 1997). The Vocabulary/Block Design dyad was shown to yield estimated IQs that correlated highly with the WAIS-III Full Scale IQ using data both from the WAIS-III standardization sample (r=0.88; Sattler and Ryan 2001) and from a clinical sample (r=0.91; Ringe et al. 2002). Motor performance was measured using the finger-tapping task (Reitan 1969), grooved pegboard (Klove 1964), and the Digit Symbol Substitution test (DSST) (Wechsler 1997).

The California Verbal Learning Test (CVLT) and the Paired Associates Learning (PAL) Task (CANTAB) were used to measure explicit memory. The CVLT (Delis et al. 1987) involves learning a "shopping" list of 16 items over five trials. After five trials, an interference list of 16 words is presented for one trial immediately followed by free recall and category-cued recall of the first list. After a 20-min delay during which nonverbal testing is conducted, free recall, cued recall, and recognition of the first list are tested. The PAL is a form of a visuospatial memory procedure of explicit memory. The computer screen contains 6 to 8 boxes and one by one in a random sequence these are "opened," revealing the location of a pattern. The participant is asked to remember the location. The number of patterns is increased to two, then three, then six and finally eight. Advancement to a new set cannot occur until the previous set is completed correctly. Total and average errors prior to successful completion, number

of sets successfully completed on the first try, and number of sets completed correctly are measured.

Working memory was evaluated using three tasks from the CANTAB. In the Spatial Working Memory (SWM) task, a trial begins with a number of colored squares (boxes) shown on a computer screen. The goal is to find a blue "counter" in one of the boxes and "transfer" it to fill up an empty column on the right hand side of the screen. The participant must touch each box in turn until one opens with a blue counter inside (a search). The number of boxes appearing on the screen increases from three (practice) to four, to six, and to eight. Returning to an empty box already sampled (within error) or returning to a box where a counter was already found (between error) constitutes an error. In the Delayed Match to Sample (DMS) task, participants are asked to choose the correct stimulus out of four that was presented 0, 4, or 12 s previously. Percent correct under each condition is measured. Finally, the Rapid Visual Information Processing (RVIP) is a test of sustained attention with a small working memory component. A white box appears in the center of the computer screen, inside which digits from numbers 2 to 9 appear in a pseudorandom order at the rate of 100 digits/min. Participants are asked to monitor the changing digits for predefined number sequences and to press a button upon presentation of the final digit of a sequence. Total hits (correct button press), total false alarms (incorrect button press), and total misses (failure to press button after target sequences) are measured.

Executive function was measured using the standard Trail Making Test (parts A and B; Reitan 1958) and two word list generation tasks. In the first word list generation task, the participant is asked to name as many words as possible that begin with a designated letter (F, A, or S) within 60 s. The score is the total number of words (excluding duplicates and changes of suffix) named across letters. The second word list generation task is similar except the participant is asked to name as many animals as possible within 60 s.

Two additional measures of executive function were tasks from the CANTAB. The intradimensional/extradimensional (ID/ED) shift task is a computer version of the Wisconsin Card Sorting Task. This test measures ability to attend to the specific attributes of compound stimuli and to shift that attention when required. The first seven stages (early stages) only require intradimensional shifts whereas at stage 8, an extradimensional shift is required and stage 9 requires a reversal. Stages completed, errors when the shift required is intradimensional (ID shift errors), and errors when the shift required is extradimensional (ED shift errors) are measured. In addition, the percentage of individuals who reached the criterion at each of the nine stages in each group was also calculated. The Stockings of Cambridge test requires spatial planning and is based upon the Tower of London. The participant is shown two displays containing three colored balls. The participant must move the balls in the lower display to copy the pattern shown in the upper one. Participants are encouraged to plan their moves carefully. The minimum number of moves required increases from 2 to 5 and mean initial thinking time (i.e., time until first move), subsequent thinking time (i.e., time from first move to completion), and number of moves for each display are measured.

Data analyses

The BP of [^{11}C]DTBZ and [^{11}C]MPH in the striatal VOI were compared across the MA and control groups using unpaired t tests. In addition, Pearson product–moment coefficient correlations among striatal [^{11}C]DTBZ and [^{11}C]MPH BPs and between these levels and drug use were computed.

Except for comparing the percentage of individuals in each group who completed the criterion for each stage of the ID/ED shift test, the neurocognitive data were analyzed using two-factor univariate ANOVAs with each group (user or control) as the between-subject factor. The percent completion of ID/ED shift stages was analyzed by a chi-square. In addition, correlations between performance measures and drug use measures were computed.

Two sets of exploratory correlational analyses were done in MA users. The BP of [^{11}C]DTBZ and [^{11}C]MPH in the caudate, putamen, and striatum and the motor function measures (Finger Tapping and Grooved Peg Board) were correlated as previous studies showed significant correlations in former MA users (Volkow et al. 2001a). The second set were correlational analyses between the BP of both ligands in these same areas and any neurocognitive measure that showed the MA users performing worse than controls.

Results

Participants

There were 16 MA users and 18 controls for a total of 34 participants. The neuroimaging data for one of the MA users (white woman, 38) and one of the controls (white man, 25) could not be obtained because of radiotracer synthesis problems. Data from another control participant (white man, 38) was not used in the analyses because of movement artifact. Thus, for the neuroimaging results, the total number of participants was 31 (15 MA users and 16 controls) whereas there were 34 participants tested on the neurocognitive measures. Age, IQ, and gender/race distribution are shown in Table 1. Most participants were white and there were more men than women. There were no significant differences in these demographics across groups.

Although bipolar disorder and schizophrenia were exclusionary, other Axis 1 disorders were not. Whereas nine of the MA users had no other DSM-IV diagnoses, six met the criteria for Major Depressive disorder (MDD) with five in full and one in partial remission. Two MA users met the criteria for a specific phobia, two for social phobia, and one for panic disorder. Except for the individual who met

Table 1 Participant characteristics

	MA (n=16)	Controls (n=18)
Age	32 (21–48)	31 (18–48)
IQ*	101.81	105.61
Ethnicity/Gender		
White/Male	9 (56%)	10 (56%)
Black/Male	2 (13%)	2 (11%)
White/Female	5 (31%)	6 (33%)

*Based on summed scale scores on WAIS-III vocabulary and block design subtests

Table 3 Other lifetime drug use (controls) or abuse/dependence (MA users)

MA			Controls
Drug	Abuse (%)	Dependence (%)	Use (%) any/current
Stimulants		100	11/0
Alcohol	31	31	100/78
Cocaine	0	31	11/0
Marijuana	0	38	78/0
Opioids	0	19	0/0
Sedatives	0	19	0/0

the criteria for panic disorder, those with these other diagnoses also had MDD.

All MA users met the DSM-IV criteria for Amphetamine Dependence. The average years of regular use (defined as three or more times per week) of MA was 10.3 years, but this ranged from 1 to 30 years with a median of 10 years. Participants used MA either by snorting or smoking (or both) with only one individual reporting using it intravenously. Average years since last regular use was 3.4 with a range of 3 months to 18 years and a median of 1 year. To be eligible, participants had to have a drug-free urine for opiates, benzodiazepines, or cocaine at the time of screening and testing. While they could have used recreational drugs recently, this, to a large extent was not the case as seen in Table 2. Except for one person who used cocaine, one who used marijuana, and four who drank alcohol within the last 30 days, participants had almost totally abstained from any drug use for at least that time and in many cases longer (Table 2). However, all MA users had a history of abuse and dependence on other drugs as seen in Table 3. None of these diagnoses were current except nicotine dependence. Control participants had used minimal recreational drugs as shown in Table 3 and were required to report no use of illegal drugs except marijuana for a year. Most were current users of alcohol but none met the criteria for any current drug abuse or dependence. Eleven of the MA users and two of the controls were current smokers.

To qualify for the study, MA participants had to report at least one 3-month period when they experienced MA-induced toxic symptoms (agitation, sleeplessness, paranoia, or tremors). Table 4 shows the number of participants who met this three-month criterion for each symptom and the mean and median number of months the symptom was experienced. Participants were also asked whether they had experienced 16 other types of consequences but they were not asked to indicate for how long. These are listed in Table 5 with incidence noted.

Table 2 Number of MA participants who reported they did *not* use any of the listed recreational drugs even once at various time periods

Had not used in less than	1 month	3 months	6 months	1 year
Methamphetamine	16/16	16/16	8/16	8/16
Other stimulants	10/10	9/10	9/10	7/10
Cocaine	14/15	14/15	13/15	11/15
Marijuana	15/16	12/16	11/16	7/16
Alcohol	11/14	7/14	6/14	5/14
Opioids	10/10	9/10	9/10	6/10
Sedatives	9/9	9/9	9/9	8/9

The denominator indicates the number of individuals who ever had used the drug lifetime

Neuroimaging results

There were statistically significant differences in VMAT2 binding in the caudate nucleus, anterior putamen, and striatum with the MA group having about 10–11% lower levels (Table 6 and Fig. 1). In addition, DAT binding was also significantly lower (12–16%) for the MA group in all regions of the striatum (Fig. 2). While the decreases were greater for DAT, the differences compared to VMAT2 were not statistically significant.

VMAT2 concentrations were highly correlated across all striatal brain regions. There were no consistent correlations in either MA use parameter (i.e., duration of regular use and time since last regular use) and the levels of availability of DAT or VMAT2.

Neurocognitive effects

Analyses of results failed to reveal statistically significant group differences on the following tasks: Finger Tapping, Grooved Pegboard, PAL, Trail Making A and B, Phonemic Verbal Fluency (FAS) and Animal Fluency, Intra/Extra-dimensional Shift, Stockings of Cambridge, SWM, and DMS (Table 7).

As also shown in Table 7, MA users performed significantly more poorly than controls on the DSST and all measures of the CVLT. On the RVIP, MA users performed less well on number of hits, misses, correct rejections, and probability of a hit. None of these significant differences were correlated with years of regular use or years since regular use with one exception. There was a significant correlation between CVLT trial 5 raw scores and years since regular use but this correlation was negative indicating that the longer the abstinence, the lower the scores (r=−0.051, p<0.042). A scatter plot of the data

Table 4 Consequences of MA use

	Met 3 month criterion (n=15)*	Duration of recurring symptom in months (mean, median)
Agitation	11	69, 48
Paranoia	14	63, 24
Disrupted sleep	14	67, 42
Shakes/ tremors	8	85, 78

*Data not available for one of the 16 participants.

revealed an outlier, someone who had not used drugs in 14 years but did very poorly on all measures of the CVLT. When this participant's data were removed from the analyses, the correlation was no longer significant (r=−0.014; p<0.962).

Exploratory correlational analyses in methamphetamine users

There were no significant correlations between [^{11}C]DTBZ or [^{11}C]MPH bindings and any of the measures of motor function. There were significant positive correlations between the BP of [^{11}C]DTBZ in caudate nucleus (r=0.53, p<044), putamen (r=0.57, p<0.026), and striatum (r=0.57, p<0.026) with only CVLT short delay recall, indicating that lower BP was associated with impaired performance. For [^{11}C]MPH binding levels, there were no significant correlations.

Discussion

There is ongoing controversy concerning the potential neurotoxicity of MA at the dosages and exposure frequencies employed by human psychostimulant abusers. While experimental animal models of MA effects permit detailed, mechanistic approaches to the study of its pharmacological and toxic effects, interspecies differences and other aspects of drug dosage and exposure patterns may confer important distinctions in the case of human psychostimulant users. To directly explore the issue of human MA toxicity, we conducted PET measurement imaging of DAT and VMAT2 together with neurocognitive assessments in abstinent MA users. The current study is the first to use VMAT2 PET to investigate in vivo the integrity of DA nerve terminals in the striatum of abstinent MA abusers. In the present study, statistically significant lower levels of both VMAT2 and DAT binding sites were found in the former MA users, indicating the possibility of nerve terminal degeneration.

Table 5 Other self-reported symptoms

Symptom	# out of 15
Overdose	3
Blackout	7
Seizures	2
Craving	14
Tolerance	14
Unable to stop	14
Lack of appetite	15
Accident/injury	6
High on job	14
Missed work	15
Lost job	10
Suspended/expelled	3
Fight or quarrel	13
Drove under influence	15
Family problems	14
Financial problems	14

Our present finding of decrease in availability of striatal DAT binding sites in former MA abusers is consistent with previous PET studies of abstinent MA abusers (McCann et al. 1998; Volkow et al. 2001b). It is of interest to note that the magnitude of the decrease in availability of DAT in the present study was smaller than in the previous two studies. The reason for this discrepancy is not apparent. However, the failure to find correlations between BP and duration of use and abstinence rules out these potential differences from other studies.

Despite the relatively small magnitude of the lower levels of availability, the fact that both DAT and VMAT2 were decreased in former MA abusers strongly supports the hypothesis that there are long-term structural changes in the DA nerve terminals in these regions. It was argued that reductions in DAT levels may reflect changes in its expression or subcellular trafficking rather than indicating structural damage to DA nerve terminals (Harvey et al. 2000). In the present study, the finding that both VMAT2 and DAT binding levels were significantly decreased in individuals who have not used MA for as long as 30 years and that BP was not correlated with years of abstinence are strongly suggestive of irreversible structural changes, at least in a fraction of striatal DA nerve terminals. As opposed to possible regulatory and subcellular localization influences on DAT binding, VMAT2 binding is relatively unaltered by nontoxic pharmacological interventions that alter DA signaling and tracks closely with lesion intensity in preclinical neurotoxin lesion studies (Vander Borght et al. 1995a,b). While the present results therefore support a long-lasting depletion of nigrostriatal DA terminals in former MA users, the magnitude of the reduction (10–15%) is unlikely to lead directly to clinical symptoms of DA deficiency. Parallel studies of [^{11}C]DTBZ PET imaging in hemi-Parkinson disease (PD) patients (Bohnen et al. 1996) indicate that more than 75% of VMAT2 sites in the posterior putamen are lost before clinical signs and symptoms develop.

Because of the role of the striatal DA system in motor function, investigators were concerned that MA-induced toxicity in this area might predispose previous users to develop symptoms of PD. However, studies in rhesus monkeys failed to show any deficits in motor function as

Table 6 Striatal VMAT2 and DAT binding potentials

	Caudate nucleus	Anterior putamen	Posterior putamen	Putamen	Striatum
[^{11}C]DTBZ					
MA (n=15)	2.20 (0.25)*	2.60 (0.26)*	2.66 (0.28)	2.63 (0.26)	2.48 (0.25)*
Controls (n=16)	2.48 (0.40)	2.91 (0.42)	2.95 (0.51)	2.93 (0.46)	2.78 (0.42)
MA/Controls %	89	89	90	90	89
[^{11}C]MP					
MA (n=15)	1.56 (0.15)**	1.81 (0.15)*	1.77 (0.19)*	1.79 (0.16)*	1.72 (0.15)**
Controls (n=16)	1.85 (0.30)	2.04 (0.32)	2.01 (0.35)	2.03 (0.33)	1.97 (0.32)
MA/Controls %	84	89	88	88	87

*p<0.05
**p<0.01

measured by hand-steadiness (Johanson et al. 1979) or visual pursuit tracking (Ando et al. 1986) after a high dose regimen of MA that produced large decreases in DA neuronal markers but with an intervening period of abstinence. In contrast, studies in short-term abstinent MA abusers reported that the magnitude of the striatal decrease in DAT binding was inversely correlated with motor speed both in the Timed Gait and the Grooved Pegboard tasks (Volkow et al. 2001b). However, a subsequent study by Chang et al. (2002) did not show any deficits in MA users abstinent for on average of 8 months in either Timed Gait or Grooved Pegboard in comparison to normative values. The present investigation also failed to show any motor deficits in rate of Finger Tapping or speed in completing the Grooved Pegboard. Thus, it does not appear that there are motor function deficits suggestive of early PD in either recent or long-term abstinent MA abusers. It remains possible that previous MA exposure may increase the risk of PD later in life, but the magnitude of this contribution is likely to be minor in comparison to yet undetermined genetic or other environmental factors.

Of equal concern is whether neurotoxic changes in the caudate nucleus may result in long-term, possibly irreversible deficits in cognitive function as suggested by Moszczynska et al. (2004). In the present study, MA users showed deficits in the DSST of the WAIS-III relative to the controls. However, neither the mean standard score (9.63) nor individual scores were greater than one SD (3) below the age-controlled norm (10.0). This finding suggests that although MA may produce long-term, possibly irreversible deficits in speed and accuracy of information manipulation, these deficits are relatively small and for some may not reach clinical significance.

Using a task of attentional set-shifting ID/ED from the CANTAB, Ornstein et al. (2000) found that a larger percentage of current amphetamine abusers were less likely to learn discrimination when an extradimensional shift was required compared to controls. In the present investigation using the same test battery, no differences between MA users and matched controls were found. The failure to replicate the results by Ornstein et al. (2000) may be due to the length of abstinence from MA and perhaps, lack of comorbidity or other recent drug use.

A few investigators reported that MA abusers show memory deficits even after periods of abstinence (e.g., Kalechstein et al. 2003). In the present investigation, MA users showed significantly poorer performance on several of the subtests of the CVLT including both cued and noncued short and long delayed recall. However, despite this statistically significant difference compared to controls, their performance was not outside the normal range

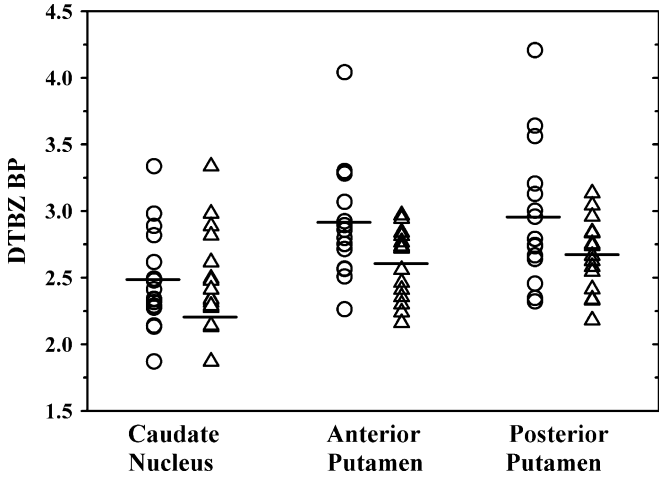

Fig. 1 Scatter plot of [^{11}C]DTBZ binding potential in the caudate nucleus and anterior and posterior putamen. The *open circles* represent individuals in the control group (n=16) and *triangles* represent individuals in the methamphetamine group (n=15)

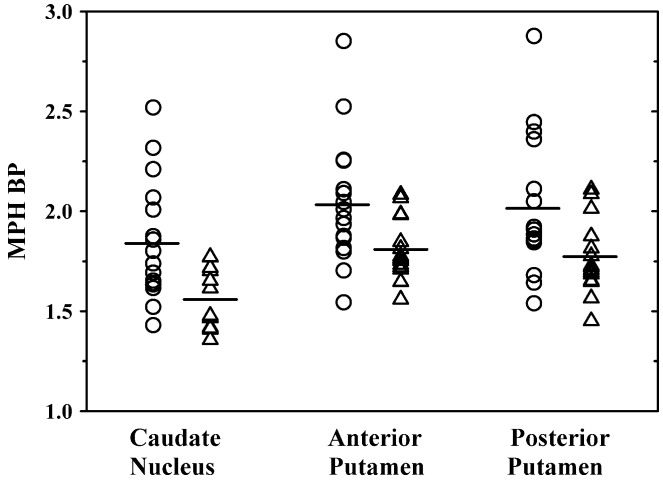

Fig. 2 Scatter plot of [^{11}C]MPH binding potential in the caudate nucleus and anterior and posterior putamen. The *open circles* represent individuals in the control group (n=16) and *triangles* represent individuals in the methamphetamine group (n=15)

Table 7 Neurocognitive test results [mean (SE)]

	Controls (*n*=18)	MA (*n*=16)
Psychomotor function		
Finger Tapping		
Dominant hand	53.19 (9.03)	48.63 (5.40)
Non-dominant hand	48.77 (7.07)	46.04 (8.13)
Grooved Pegboard		
Dominant hand	66.44 (9.73)	67.06 (9.84)
Non-dominant hand	70.72 (16.44)	76.25 (10.80)
WAIS-III digit symbol (standard score)	11.17 (1.42)	9.63 (2.16)*
Explicit memory		
CVLT		
Trial 1	8.39 (2.12)	6.94 (1.81)*
Trial 5	13.44 (1.82)	11.75 (1.53)*
Short delay free recall	12.61 (2.28)	9.94 (2.35)*
Short delay cued recall	12.94 (2.24)	11.25 (2.18)*
Long delay free recall	12.44 (2.38)	10.38 (2.58)*
Long delay cued recall	13.00 (2.03)	11.13 (1.93)*
PAL		
Total errors	8.22 (10.84)	12.00 (11.96)
Mean errors to success	1.03 (1.36)	1.50 (1.50)
Stages completed 1st trial	6.44 (0.92)	5.88 (1.20)
Stages completed	8.00 (0.00)	8.00 (0.00)
Executive function		
Trails		
Trail A time (s)	28.00 (8.94)	30.81 (12.68)
Trail B time (s)	65.94 (37.18)	63.25 (18.31)
Word List		
FAS (number)	39.39 (12.65)	40.75 (9.18)
Animal Fluency (number)	22.06 (6.31)	21.69 (5.59)
Intra/Extradimensional Shift (CANTAB)		
Stages completed	8.44 (0.86)	8.13 (1.02)
Pre-extradimensional shift errors	5.50 (1.89)	8.06 (5.98)
Extradimensional shift errors	11.72 (11.16)	13.50 (12.07)
Total errors	22.26	22.63
Completed stage errors	13.22	11.25
Stockings of Cambridge (CANTAB)		
Moves (2 move solutions)	2.00 (0.00)	2.00 (0.00)
Moves (3 move solutions)	3.28 (0.49)	3.03 (0.13)
Moves (4 move solutions)	4.96 (1.17)	5.11 (1.30)
Moves (5 move solutions)	6.68 (1.48)	6.77 (1.31)
Initial time (s; 2 moves)	2.81 (2.05)	2.45 (0.89)
Initial time (s; 3 moves)	7.46 (3.32)	7.00 (4.05)
Initial time (s; 4 moves)	8.46 (3.57	9.03 (6.49)
Initial time (s; 5 moves)	9.89 (4.49)	10.52 (6.15)
Subsequent time (s; 2 moves)	0.42 (0.85)	0.34 (1.16)
Subsequent time (s; 3 moves)	0.54 (0.82)	0.11 (0.22)
Subsequent time (s; 4 moves)	0.94 (0.97)	0.99 (1.09)
Subsequent Time (s; 5 moves)	1.05 (0.97)	0.95 (0.91)
Working memory		
Spatial Working Memory (CANTAB)		
Between errors (4 boxes)	0.94 (2.10)	1.13 (2.09)
Within errors (4 boxes)	0.61 (1.91)	0.13 (0.50)
Between errors (6 boxes)	7.22 (8.08)	6.56 (7.15)
Within errors (6 boxes)	0.78 (1.63)	0.81 (1.87)
Between errors (8 boxes)	18.28 (12.60)	16.69 (10.53)

Table 7 (continued)

	Controls (n=18)	MA (n=16)
Within errors (8 boxes)	1.78 (2.51)	0.81 (1.56)
Delayed Matching to Sample (CANTAB)		
Percent correct (short delay)	88.33 (12.95)	88.75 (8.85)
Percent correct (medium delay)	92.22 (11.66)	90.00 (7.30)
Percent correct (long delay)	83.89 (15.39)	82.50 (12.91)
Rapid Visual Information Processing (CANTAB)		
Total hits	18.06 (4.71)	14.50 (3.29)*
Total misses	8.94 (4.71)	12.50 (3.29)*
Total correct rejections	251.11 (10.81)	243.44 (8.03)*
Probability of hit	0.67 (0.17)	0.54 (0.12)*

*p<0.05 control group performed better

for their age group. Thus, the functional significance of these differences in memory function is questionable. Nevertheless, it seems likely that these deficits are permanent because they were not correlated with duration of abstinence. It is obvious that the possibility remains that these deficits predated drug use but the present study cannot address this possibility.

On the RVIP of the CANTAB, which is thought to assess attentional function and distractibility, MA abusers showed significantly poorer performance in all measures. Several investigators found out that MA abusers show increased interference on the Stroop Color Word Interference Test. For instance, Simon et al. (2000) found that individuals who had used MA for an average of 11 years and were currently using were significantly impaired in their ability to ignore irrelevant information (Stroop Color-Word Interference Test). Salo et al. (2002) using a single trial version of the Stroop Test also showed greater rates of interference in individuals who were abstinent from MA for 2–4 months. This attentional deficit seen in the MA abusers and our findings on the RVIP may be related to the distractibility described by clinicians treating MA abusers.

Although MA users showed poorer performance on several tests on the neurocognitive test battery, in most cases their performance was no different than controls. There were no differences in measures of motor function (Finger Tapping and Grooved Pegboard), one of the two measures of explicit memory (PAL), executive function (Trails A and B, FAS and Animal Fluency, Intra/Extradimensional Shift, and Stockings of Cambridge), or working memory (SWM and Delayed Matching to Sample). While previous studies showed a greater degree of cognitive impairment even in those studies, many functions remained intact.

There are a number of caveats for this and other studies attempting to determine the long-term neurochemical and functional consequences of high dose MA abuse in humans. First, with very few exceptions, MA abusers in these studies were polydrug abusers. Where differences in brain chemistry and motor or cognitive functions are found, it is necessary to use a control group that is matched in other drug use. This was not done in any of the studies to date and would be an extremely difficult undertaking because investigators would also have to control for amount of use and length of abstinence. However, in the present study, participants did not report extensive drug use in the last 3 months and for many, they did not use drugs for years. A second caveat is that comorbid disorders could have affected the results. However, few comorbid disorders were diagnosed and of those participants with MDD, all but one of the six were in full remission. Unfortunately in this study, and most of those finding cognitive deficits in former MA abusers, no attempt was made to determine whether the participants met the criteria for Attention Deficit Hyperactivity disorder (ADHD). This is important because the prevalence of ADHD is high in substance-abusing populations (Biederman et al. 1995). Future studies should make every attempt to control for the presence of ADHD in studies comparing the cognitive status of controls and MA abusing research participants.

In conclusion, decreases were noted in the BPs of DAT and VMAT2 and several measures of cognitive function in former MA users compared to controls. Fortunately, the magnitude of the differences was small and may not have major functional significance. This finding, if confirmed by others, should lead to a more optimistic attitude on the part of treatment practitioners and those in recovery from MA abuse/dependence.

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