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ORIGINAL INVESTIGATION

Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (±)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance

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Abstract
Background (±)3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a recreational drug and brain serotonin (5-HT) neurotoxin. Under certain conditions, MDMA can also damage brain dopamine (DA) neurons, at least in rodents. Human MDMA users have been found to have reduced brain 5-HT transporter (SERT) density and cognitive deficits, although it is not known whether these are related. This study sought to determine whether MDMA users who take closely spaced sequential doses, which engender high plasma MDMA concentrations, develop DA transporter (DAT) deficits, in addition to SERT deficits, and whether there is a relationship between transporter binding and cognitive performance.
Materials and methods Sixteen abstinent MDMA users with a history of using sequential MDMA doses (two or more doses over a 3- to 12-h period) and 16 age-, gender-, and education-matched controls participated. Subjects underwent positron emission tomography with the DAT and SERT radioligands, [^{11}C]WIN 35,428 and [^{11}C]DASB, respectively. Subjects also underwent formal neuropsychiatric testing.
Results MDMA users had reductions in SERT binding in multiple brain regions but no reductions in striatal DAT binding. Memory performance in the aggregate subject population was correlated with SERT binding in the dorsolateral prefrontal cortex, orbitofrontal cortex, and parietal cortex, brain regions implicated in memory function. Prior exposure to MDMA significantly diminished the strength of this relationship.
Conclusions Use of sequential MDMA doses is associated with lasting decreases in brain SERT, but not DAT. Memory performance is associated with SERT binding in brain regions involved in memory function. Prior MDMA exposure appears to disrupt this relationship. These data are the first to directly relate memory performance to brain SERT density.

Keywords Positron emission tomography · Amphetamines · Pharmacokinetics · Neurotoxicity · Serotonin · Dopamine · Memory

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Introduction

(±)3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a popular recreational drug in western countries (El-Mallakh and Abraham 2007). Frequently, MDMA is used in dance club settings where experienced users often take several dosages at spaced intervals during a given evening (i.e., "stacking"; Parrott 2005). In addition to its use as a recreational drug, MDMA is also a well-documented brain serotonin (5-HT) neurotoxin in animals (Green et al. 2003). There is increasing evidence that some recreational MDMA users, like animals treated with MDMA, develop a persistent reduction in brain 5-HT axonal markers (McCann et al. 1998, 2005; Semple et al. 1999; Reneman et al. 2001; Buchert et al. 2003, 2004; Thomasius et al. 2006). In animals, the neurotoxic effects of MDMA are dose-related and are generally selective toward brain 5-HT neurons, leaving other neuronal systems intact (Steele et al. 1994; Green et al. 2003). However, when given at high dosage (Commins et al. 1987) or when given at high ambient temperature (Yuan et al. 2002), MDMA can also damage brain DA systems in rats. In mice, for reasons that are not clear, MDMA preferentially damages dopamine (DA) neurons, producing modest 5-HT neurotoxicity only at very high dosage (Easton and Marsden 2006). Results from a recent study in squirrel monkeys given three closely spaced sequential doses of MDMA showed no evidence of DA neurotoxicity (Mechan et al. 2006). However, it is not known which animal model is best for determining the risks of MDMA-induced neurotoxicity in humans.

Studies in animals and humans suggest that the pharmacokinetics of MDMA may be nonlinear with plasma concentrations of MDMA rising out of proportion to increases in dose (Chu et al. 1996; de la Torre et al. 2000; Mechan et al. 2006). In particular, plasma MDMA concentrations rise to a greater extent than would be predicted by the increase in dose. Therefore, MDMA users who take either high doses or several closely spaced sequential doses (two or more doses within a 3- to 12-h period) would be anticipated to develop disproportionately high plasma MDMA concentrations. This raises the possibility that MDMA users who take closely spaced sequential doses, like rats treated with high doses of MDMA (Commins et al. 1987), develop toxic effects in both 5-HT and DA systems.

Despite strong evidence that MDMA is a 5-HT neurotoxin, it has been difficult to identify functional consequences directly linked to serotonergic neural injury. One of the most frequently reported abnormalities in abstinent MDMA users is that of subtle cognitive dysfunction, particularly in the area of short-term memory (Kalechstein et al. 2007). A recent prospective study in MDMA-naïve subjects revealed deficits in verbal memory after low cumulative exposure to MDMA (mean cumulative dose of 3.2 tablets; Schilt et al. 2007). However, a number of factors, including the fact that most MDMA users have been exposed to a variety of other recreational drugs in addition to MDMA, make it difficult to unambiguously attribute cognitive deficits in MDMA users to MDMA-induced 5-HT neurotoxicity. Indeed, to date, only one study has reported a validated marker of MDMA-induced neurotoxicity, cerebrospinal fluid concentrations of 5-hydroxyindole acetic acid (5-HIAA, the major metabolite of 5-HT), to be related to cognitive deficits in the same individuals (Bolla et al. 1998).

The purpose of this study was twofold. First, we sought to determine whether MDMA users who use closely spaced sequential doses of MDMA (and are thus at risk for developing high plasma MDMA concentrations) develop signs of brain DA neurotoxicity, in addition to brain 5-HT neurotoxicity. Second, we wished to explore the possibility that monoamine transporter binding (either DAT or SERT) in brain regions where differences in binding are present is related to measures of cognitive function. To this end, abstinent recreational MDMA users underwent quantitative positron emission tomographic (PET) studies with selective DAT and SERT radioligands, [^{11}C]WIN 35,428 and [^{11}C] DASB, respectively, and formal neuropsychiatric testing. In preplanned regions of interest (ROI) analyses, we included cortical brain regions known to be involved in memory function (dorsolateral prefrontal cortex, orbitofrontal cortex, and parietal cortex) with relatively low SERT density, along with subcortical regions (hippocampus, amygdala) with more dense 5-HT innervation.

Materials and methods

Subjects Subjects were medically healthy individuals who responded to advertisements placed in newspapers or posted fliers. After undergoing a phone screen involving questions about medical, psychiatric, and drug use histories, individuals who appeared to meet the inclusion criteria were invited for a face-to-face screening including blood sampling for routine blood chemistries, complete blood counts, and clotting studies. Urine samples were also collected from all subjects for screening of illicit drugs including amphetamines, cannabinoids, cocaine metabolites, and opiates. On the same day as these medical tests, subjects underwent structured diagnostic psychiatric interviews using the SCID-I (First et al. 1997).

The inclusion criteria for all subjects included willingness to remain drug-free for 2 weeks prior to study, normal results from blood screens and clotting tests, negative drug screens (with the exception of marijuana, which can be detected in urine screens for three or more weeks after the last use) prior to PET scanning, and for female subjects,

negative pregnancy tests on the day of scanning. Drug screens were conducted in both groups at the time of the initial screen (and neuropsychiatric testing) and again on the day of scanning. The inclusion criteria for the MDMA group included self-reported use of MDMA on at least 25 separate occasions. Information about MDMA use was obtained by: (1) a preliminary telephone interview; (2) an MDMA questionnaire that asked about the number of times MDMA had been used, the usual amount of MDMA taken, the frequency of MDMA use, the last time MDMA had been used, and the highest dose of MDMA ever taken; (3) a standardized drug history questionnaire; and (4) the Scheduled Interview for DSM-III-R. Subjects were excluded if they were taking prescribed psychotropic medications, had a major medical illness, history of significant head injury, or met lifetime criteria for an Axis I psychiatric condition in which brain 5-HT or DA has been implicated (i.e., major depression, bipolar affective disorder, psychosis, panic disorder, generalized social phobia, obsessive compulsive disorder). Subjects in the control group were excluded if they had ever used MDMA. As above, all subjects agreed to refrain from use of psychotropic drugs (defined as any drug that could influence brain function) for at least 2 weeks prior to study participation.

Imaging procedures MRI and PET procedures were similar to those used recently (McCann et al. 2005), except that the two radioligands employed were [^{11}C] DASB and [^{11}C] WIN 35,428, rather than [^{11}C] DASB and [^{11}C] McN5652. Briefly, [^{11}C] WIN 35,428 and [^{11}C] DASB were prepared according to published methods (Dannals et al. 1993; Wilson et al. 2000). Two PET studies were performed for each subject: one study employed [^{11}C] DASB at 694± 40 MBq and the second study employed [^{11}C] WIN 35,428 at 709±51 MBq. The time difference between the injections was approximately 135 min. At the time of injection, specific activity for [^{11}C] DASB was 296 GBq/μmol (median 186 GBq/μmol) and that of [^{11}C] WIN was 355 GBq/μmol (median 296 GBq/μmol). A total of 18 serial dynamic PET images were acquired during the first 95 min after the injection of both radioligands. PET scans were reconstructed using ramp-filtered back projection in a 128×128 matrix with a transaxial pixel size of 2×2 mm. Subjects were not allowed to smoke prior to scanning procedures to avoid potential effects of nicotine on tracer binding.

Input function Repeated arterial blood samples were collected to obtain the input function for compartmental analysis. The input function was corrected for metabolized radioligand activity, as previously described (McCann et al. 2005).

Regions of interest Regions of interest for both radioligands were drawn by an investigator (MV) who was blind to the group designation of the subject, using multiple coregistered SPGR MRI scan slice pairs and previously described methods (McCann et al. 2005). PET and MRI images were coregistered before the regions of interest were drawn using a software package developed at our institution. Fifteen regions of interest for [^{11}C] DASB included in our analyses were: amygdala, hippocampus, midbrain, ventral pons, dorsal pons, anterior cingulate gyrus, posterior cingulate gyrus, orbitofrontal cortex, dorsolateral frontal cortex, parietal cortex, occipital cortex, temporal cortex, thalamus, head of caudate, and putamen. Based upon previous results with [^{11}C] DASB (McCann et al. 2005), it was predicted that binding parameters would be decreased in the cortical brain regions, hippocampus and amygdala and that binding in the striatum, midbrain, thalamus, and pons would not differ between MDMA users and controls. For [^{11}C] WIN 35,428, regions of interest included the caudate (left and right combined) and putamen (left and right combined). The hypothesis to be tested was that sequential dosing regimens of MDMA would be associated with decreased [^{11}C] WIN 35,428 binding potential in these striatal structures.

Tracer kinetic modeling As before (McCann et al. 2005), [^{11}C]DASB binding was quantified by the (apparent) total distribution volume (V_T) represented by the ratio $V_T=K_1/k_2$ where K_1 represented radioligand uptake into brain tissue and k_2 represented radioligand release from the brain tissue (one-tissue compartment model). K_1 and k_2 were estimated using the Marquardt error minimization algorithm and a single-tissue compartmental model (Szabo et al. 1999; Marquardt 1963). The impulse response function that builds the kernel of this model is described by a blood volume component B_V and the two parameters K_1 and k_2. To increase the stability of estimating K_1 and k_2, B_V was preset to 0.05 to correspond to an average blood volume of 5% in brain tissue. V_T was expressed in units of ml (virtual ligand binding space)/ml (tissue space). In an effort to correct for nonspecific binding, specific distribution volume V_S and distribution volume ratio D_{VR} were also determined. V_S was calculated as V_T ROI minus V_T cerebellum. The distribution volume ratio D_{VR}, which is identical to BPND+1 (Innis et al. 2007) was calculated as V_T ROI divided by V_T cerebellum. These binding parameters are both calculated based upon the assumption that cerebellar SERT binding is relatively low and does not differ between groups. Striatal binding of [^{11}C] WIN 35,428 was expressed by the ROI/cerebellum tissue activity ratio between 75 and 95 min after tracer injection, assuming that the majority of cerebellar tissue activity is nonspecific (Kerenyi et al. 2003). The specific-to-nonspecific binding

ratio correlates well with the binding potential (k_3/k_4) derived from tracer studies of the DA transporter (Laruelle 2000). In addition, [^{11}C] WIN 35,428 binding was also estimated by the rate constant K_i obtained with the Patlak graphical method, using metabolite-corrected arterial plasma time–activity curves as input function.

Cognitive testing Subjects underwent formal neurocognitive testing using a structured standardized neuropsychiatric battery that included tests of memory, attention, and executive function, cognitive spheres previously reported to be impaired in MDMA users. The cognitive battery used included the Wisconsin Card Sorting Test (Berg 1948), the Stroop Color–Word Test (Stroop 1935), the Trail Making Test (A and B; Reitan and Wolfson 1993), the Wechsler Memory Scale-III (Wechsler 1987), the Rey Auditory Verbal Learning Test (Rey 1964), and the Rey Osterrieth Complex Figure Test (Rey 1964). In addition, the Wechsler Adult Intelligence Scales-III Vocabulary subtest and the New Adult Reading Test-Revised were administered as estimates of verbal intelligence that are better predictors of neurobehavioral performance than level of education (Bolla et al. 1998).

Statistical methods To test the hypothesis that MDMA use leads to decreased binding parameters in regions of interest previously identified, analyses of covariance were conducted with group (MDMA versus control) and brain region (each of the predesignated regions of interest) as fixed variables, age as the covariate, and SERT or DAT binding as dependent variables. Significance level was set at $p=0.025$ (or 0.05 after Bonferroni correction for simultaneous testing of two hypotheses). To explore the potential relationship between global and regional SERT and DAT binding parameters and MDMA use parameters (total dose in any 24-h period, estimated lifetime dose, duration of use, duration since last MDMA use), Pearson's product moment correlations covarying for age were performed. Notably, all subjects had used MDMA sequentially. Because some subjects continued to use sequential dosing beyond the 12-h time-point, a 24-h cutoff for total (sequential) dose was employed in the analysis. The significance level for these analyses was set at $p=0.025$ (0.05 after Bonferroni correction for simultaneous testing of two hypotheses). Additionally, for [^{11}C] WIN 35,428, additional exploratory correlational analyses were conducted to assess the possibility that the maximum dose of MDMA used in a single session (which in all cases was taken in a sequential dosing pattern) was inversely correlated with striatal DAT density. In brain regions where significant differences between groups were found for measures of the SERT, exploratory Pearson's partial correlation analyses covarying for age were conducted to test the hypothesis that lower binding in those regions is associated with lower scores on neuropsychiatric testing measures. Because of the large number of correlations, the relationship between SERT BP and memory performance were not considered significant unless SERT BP in a particular brain region was found to be correlated ($p<0.05$) with performance on five or more memory tasks in the aggregated subject groups (i.e., MDMA users plus controls). If a significant relationship between SERT BP and performance was found in a particular brain region for the aggregated group, then the relationship between SERT BP and performance was also investigated in the two individual groups (i.e., MDMA users alone, control subjects alone). Also, in MDMA subjects, the relationship between MDMA use patterns and test scores was explored to test the hypothesis that lower exposure or a longer duration of abstinence is associated with higher test scores. Statistical tests were conducted using SPSS (Chicago, IL, USA) and Matlab (Mathworks, Natick, MA, USA).

Results

Sixteen MDMA subjects (eight males and eight females) and 16 control subjects (ten males and six females) participated in this study. All MDMA subjects reported having used sequential doses of MDMA (i.e., two or more doses over a 3- to 12-h period). As shown in Tables 1 and 2, subjects were well-matched with regard to age, education level, and estimated IQ. MDMA users, as a group, had previously used more types of recreational drugs than the control subjects. One MDMA subject did not undergo neuropsychiatric testing. Two subjects (one MDMA user, one control) had positive marijuana screens at the time of scanning. However, both subjects reported (consistently and on a variety of different screening instruments) that their last use of marijuana was more than 2 weeks prior to study. Since marijuana can sometimes be detected in urine screens for 3 weeks or more following cessation of use, the two positive drug screens were consistent with these subjects' self-reports. Drug screens for all other subjects were negative at the time of study participation. Three MDMA users had used single doses of a prescription formulation of amphetamine salts (commonly used for the treatment of attention deficit hyperactivity disorder) within 6 months of study participation with their lifetime separate exposures ranging from two to 25. Of the 14 females who participated in the study, six were using oral contraceptives (four controls and two MDMA subjects).

PET measures As found previously (McCann et al. 2005), MDMA users were found to have significant reductions in

Table 1 Subject demographics

	MDMA (n=16)	Control (n=16)
Gender	10 male, 6 female	8 male, 8 female
Average age	23.5±5.3	23.0±2.9
Average years of education	13.3±1.2	13.8±2.2
Average MDMA exposure		
Usual total dose (tabs/caps)	2.25±1.40 (range 0.5–5.0)	N/A
Number of separate uses	193.5±246.01 (range 30–1000)	N/A
Duration of use (months)	55.25±38.44 (range 14–168)	N/A
Frequency of use (separate uses/month)	3.46±2.57 (range 0.75–8.33)	N/A
Maximum total dose in 24 h (tabs/caps)	6.81±4.32 (range 2.0–17.0)	N/A
Time since last use (months)	2.75±1.76 (range 0.5–7.0)	N/A

[^{11}C] DASB binding parameters in multiple brain regions (using both methods for calculating binding potential) when compared to the controls (Fig. 1). There were no significant differences in cerebellar V_T (control=9.13±1.39; MDMA=8.875±1.91), supporting the use of cerebellar binding as an indicator of "nonspecific" binding. Furthermore, there were no significant differences in the plasma-free fraction of [^{11}C] DASB in the two groups (control=0.167±0.048; MDMA=0.156±0.019), mitigating concerns that this might confound the use of V_S as a binding parameter. Indeed, results are nearly identical to those obtained previously using the same ligand in a different cohort of MDMA users (McCann et al. 2005). Percent reductions of [^{11}C] DASB V_S were greatest in cortical brain regions (up to a maximum reduction of 59% in the occipital cortex) with no significant differences in the subcortical regions (Table 3).

In contrast, for [^{11}C] WIN 35,428 binding to the DAT, no differences were found between MDMA users and controls, either the caudate or putamen (Fig. 2), whether or not arterial input function was used to calculate binding potential (i.e., Patlak plots). Differences in K_1 between groups were not significant for either tracer.

Exploratory correlations In the MDMA group, there was a significant negative correlation between duration of MDMA use and hippocampal [^{11}C] DASB D_{VR} (r=−0.55, p=0.03), and a near-significant negative correlation between duration of MDMA use and thalamic D_{VR} (r=−0.50, p=0.06) and hippocampal V_S (r=−0.47, p=0.08). No significant correlations were found between SERT binding parameters and number of occasions MDMA was used or duration since last MDMA use, although r values were negative between measures of use intensity and SERT binding for nearly all brain regions (data not shown).

No significant relationships between any MDMA use parameter and [^{11}C] WIN 35,428 binding to the DA transporter was found. MDMA use parameters considered were: (1) total (sequential) dose in a 24-h period, (2) estimated lifetime dose, (3) duration of use, and (4) duration since last MDMA use.

Cognitive measures Although MDMA users tended to perform more poorly on most tasks compared to the controls, these differences did not reach statistical significance. This is likely due, in part, to the relatively small

Table 2 Other drug use

	MDMA (n=16)		Control (n=16)	
Other drug exposure	Lifetime, n (%)	Past 6 months, n (%)	Lifetime, n (%)	Past 6 months, n (%)
Other amphetamines	11 (69)	3 (19)	0 (0.00)	0 (0)
Marijuana	15 (94)	12 (75)	11 (69)	8 (50)
Hallucinogens	15 (94)	8 (50)	3 (19)	0
Cocaine	13 (81)	8 (50)	0	0
Opioids	13 (81)	5 (31)	1 (6)	0
Ketamine	8 (50)	3 (19)	0	0
Inhalants	8 (50)	1 (6)	1 (6)	0
Alcohol	16 (100)	14 (88)	11 (69)	9 (56)
Tobacco	13 (81)	13 (81)	8 (50)	5 (31)

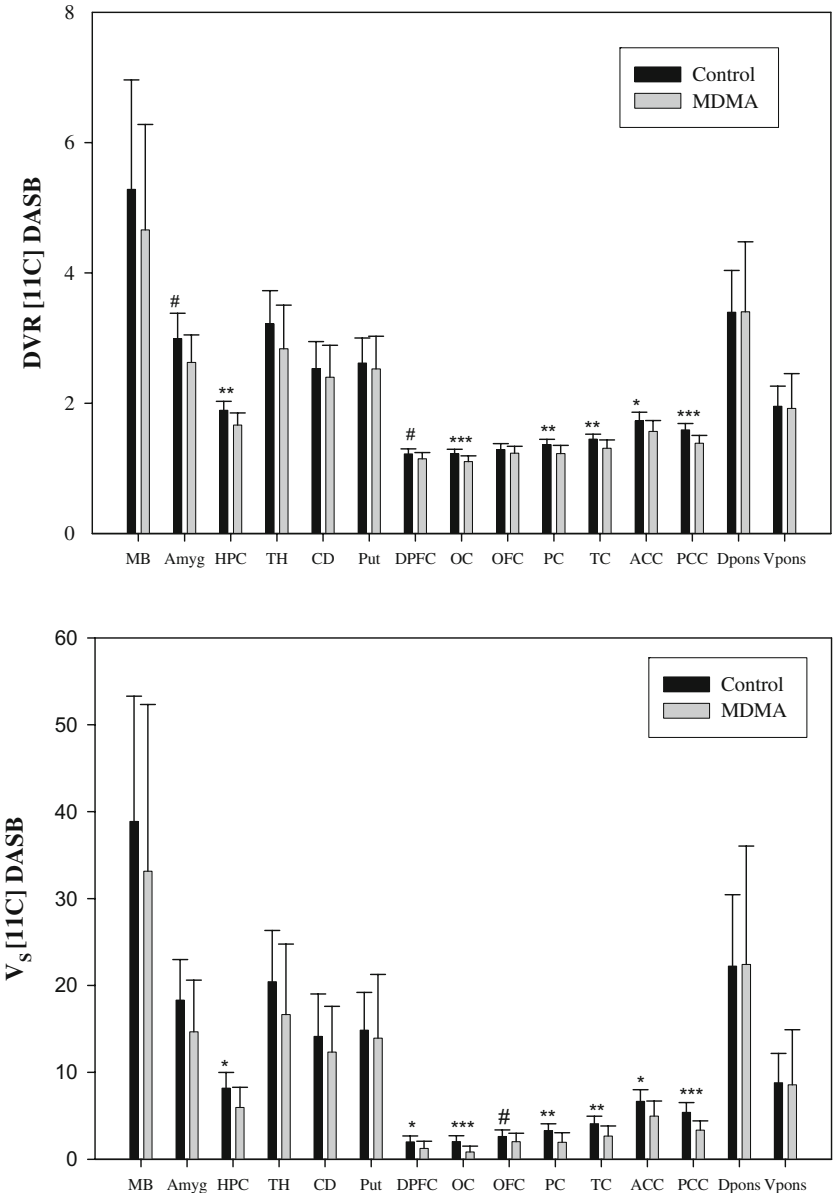

Fig. 1 Serotonin transporter binding parameters in abstinent MDMA users and controls, as measured by PET imaging with [^{11}C]DASB, DVspec (ml/ml±SD), and D_{VR}±SD. #$p \leq 0.05$; *$p \leq 0.01$; **$p \leq 0.001$; ***$p \leq 0.0001$. The brain regions are as follows: *MB* midbrain, *Amyg* amygdala, *HPC* hippocampus, *TH* thalamus, *CD* caudate, *Put* putamen, *DPFC* dorsolateral prefrontal cortex, *OC* occipital cortex, *OFC* orbitofrontal cortex, *PC* parietal cortex, *TC* temporal cortex, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *Dpons* dorsal pons, *Vpons* ventral pons

sample size in the present study and an associated lack of power. Correlation analyses examining the relationship between SERT binding (in brain areas where significant group differences had been found) and neuropsychiatric testing performance revealed a number of significant relationships. For example, when all subjects were included in the analysis, lower [^{11}C] DASB D_{VR} in the dorsolateral prefrontal cortex and parietal cortex were associated with poorer performance on a variety of verbal memory tasks in the Wechsler Memory Scale-III (WMS-III), as well as digit span (forward and backward), also from the WMS-III (Table 4). Similar findings were seen for [^{11}C] DASB V_S with lower binding in the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the parietal cortex significantly related to a variety of memory tasks (data not shown). Some significant relationships between SERT binding parameters and cognitive performance were also seen when MDMA subjects and control subjects were considered separately (Fig. 3; Table 4). However, the number and strength of the relationships were markedly diminished in MDMA users, whereas with control subjects, the strength of the relationship was similar despite a smaller "*n*," suggesting that MDMA exposure may have disrupted the normal relationship between serotonin neuronal function and memory function in the MDMA group (Table 4).

Correlation analyses between MDMA use parameters (in the MDMA users group) and neuropsychiatric testing performance also revealed several significant relationships. Specifically, duration of MDMA use was found to be

Table 3 V_S of [^{11}C]DASB in MDMA users and controls

Brain region	V_S [^{11}C]DASB (ml/ml)		
	Mean control (SD)	Mean user (SD)	Percent difference (from control)
Midbrain	38.88 (14.41)	33.14 (19.19)	−14.76
Amygdala	18.32 (4.67)	14.67 (5.94)	−19.93
Hippocampus**	8.19 (1.80)	5.96 (2.31)	−27.30
Thalamus	20.43 (5.90)	16.66 (8.10)	−18.43
Caudate	14.14 (4.88)	12.34 (5.25)	−12.72
Putamen	14.86 (4.34)	13.93 (7.35)	−6.24
DLPF cortex**	2 (0.69)	1.25 (0.82)	−37.62
Occipital cortex****	2.04 (0.65)	0.83 (0.66)	−59.05
Orbitofrontal cortex*	2.62 (0.75)	2.02 (0.96)	−22.80
Parietal cortex***	3.3 (0.77)	1.95 (1.08)	−40.90
Temporal cortex***	4.09 (0.85)	2.67 (1.16)	−34.76
Ant. cingulate cortex**	6.66 (1.34)	4.97 (1.73)	−25.40
Post. cingulate cortex****	5.39 (1.14)	3.36 (1.06)	−37.70
Dorsal pons	22.22 (8.23)	22.42 (13.62)	+0.90
Ventral pons	8.81 (3.38)	8.57 (6.34)	−2.69

Ant.: signifies anterior, *Post.*: signifies posterior, *DLPF*: dorsolateral prefrontal
*$p\leq0.05$; **$p\leq0.01$; ***$p\leq0.001$; ****$p\leq0.0001$

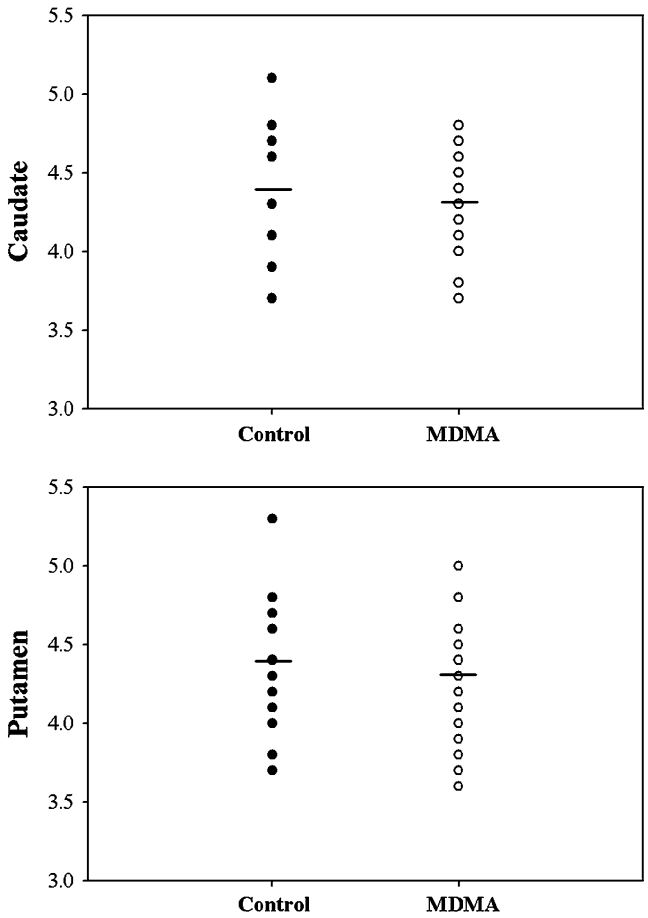

Fig. 2 Dopamine transporter binding potential (BP) in the caudate nuclei (left and right combined) and putamens (left and right combined) of abstinent MDMA users and controls, as measured by PET imaging with [^{11}C] WIN 35,428. Individual data points represent BP values for individual subjects. *Horizontal lines* in the columns of data points indicate group means

Table 4 Correlations between memory performance and SERT D_{VR} in abstinent MDMA users and controls*

	D_{VR} DLPFC MDMA+control	D_{VR} DLPFC Control	D_{VR} DLPFC MDMA	D_{VR} Parietal MDMA+control	D_{VR} Parietal Control	D_{VR} Parietal MDMA
WMS story A recall unit	**r = 0.37**	**r = 0.57**	r = 0.33	r = 0.16	r = 0.41	r = 0.15
	p = 0.04	**p = 0.03**	p = 0.25	p = 0.40	p = 0.13	p = 0.61
WMS story B 1st recall unit	**r = 0.38**	r = 0.50	r = 0.21	**r = 0.41**	**r = 0.69**	r = 0.24
	p = 0.04	p = 0.06	p = 0.48	**p = 0.03**	**p = 0.00**	p = 0.40
WMS story B 1st recall thematic	r = 0.15	r = 0.40	r = −0.15	r = 0.27	**r = 0.64**	r = −0.20
	p = 0.44	p = 0.14	p = 0.62	p = 0.15	**p = 0.01**	p = 0.61
1st recall total score	**r = 0.46**	**r = 0.57**	r = 0.30	**r = 0.36**	**r = 0.59**	r = 0.23
	p = 0.01	**p = 0.03**	p = 0.29	**p = 0.05**	**p = 0.02**	p = 0.42
WMS story B 2nd recall unit	**r = 0.41**	**r = 0.51**	r = 0.51	**r = 0.39**	**r = 0.62**	**r = 0.55**
	p = 0.02	**p = 0.05**	p = 0.06	**p = 0.03**	**p = 0.01**	**p = 0.04**
WMS recall total	**r = 0.46**	**r = 0.63**	r = 0.41	**r = 0.38**	**r = 0.69**	r = 0.38
	p = 0.01	**p = 0.01**	p = 0.14	**p = 0.04**	**p = 0.00**	p = 0.18
WMS thematic total	r = 0.11	r = 0.46	r = −0.15	r = 0.20	**r = 0.57**	r = −0.03
	p = 0.55	p = 0.08	p = −0.62	p = 0.30	**p = 0.03**	p = 0.91
WMS logical memory II story B recall	**r = 0.47**	**r = 0.69**	r = 0.39	**r = 0.40**	**r = 0.65**	r = 0.42
	p = 0.01	**p = 0.00**	p = 0.16	**p = 0.03**	**p = 0.01**	p = 0.13
WMS logical memory II recall total	**r = 0.44**	**r = 0.63**	r = 0.28	**r = 0.38**	**r = 0.60**	r = 0.30
	p = 0.02	**p = 0.01**	p = 0.34	**p = 0.04**	**p = 0.02**	p = 0.29
WMS logical memory II recognition	**r = 0.44**	**r = 0.54**	**r = 0.54**	r = 0.29	r = 0.46	r = 0.47
	p = 0.02	**p = 0.04**	**p = 0.05**	p = 0.13	p = 0.10	p = 0.09
Digits forward	**r = 0.43**	**r = 0.62**	r = 0.35	r = 0.34	**r = 0.51**	r = 0.30
	p = 0.02	**p = 0.01**	p = 0.22	p = 0.06	**p = 0.05**	p = 0.16
Digits backward	**r = 0.36**	r = 0.39	r = 0.32	**r = 0.44**	r = 0.47	r = 0.46
	p = 0.05	p = 0.16	p = 0.27	**p = 0.02**	p = 0.08	p = 0.09
Digits total	**r = 0.44**	**r = 0.51**	r = 0.40	**r = 0.44**	**r = 0.51**	**r = 0.52**
	p = 0.02	**p = 0.05**	p = 0.15	**p = 0.01**	**p = 0.05**	**p = 0.05**

Only correlations involving brain regions in which significant differences in SERT D_{VR} were found between groups are shown

negatively correlated with four tests of immediate and delayed recall of themes in stories included in the Wechsler Memory Scale-III (story A thematic unit score $r=-0.64$, $p=0.01$; story B first recall thematic unit score $r=-0.71$, $p=0.004$; delayed recall of story A thematic unit score $r=-0.52$, $p=0.01$; delayed thematic total score $r=-0.70$; $p=0.01$) as well as the Trail Making Test A ($r=-0.72$, $p=0.004$). Similarly, the total estimated lifetime MDMA dose was negatively associated with delayed recognition of items contained in stories (i.e., logical memory II total recognition scores; $r=-0.6$, $p=0.02$), as well as immediate and delayed performance on the Rey Osterrieth Complex Figure Test ($r=-0.62$, $p=0.02$; $r=-0.68$, $p=0.01$, respectively).

A high proportion of MDMA users also report using marijuana, which is reported to lead to cognitive deficits (at least in the short-term). Therefore, correlations between neurocognitive testing measures and marijuana use parameters (total estimated number of uses, lifetime duration of marijuana use) were also assessed. Interestingly, significant correlations were found on three tests, but these differed from those found to be related to MDMA use. Also, in two of the three tests, correlations were paradoxical (i.e., marijuana use was associated with improved performance). In particular, the total number of lifetime exposures was negatively associated with immediate recall on one test of

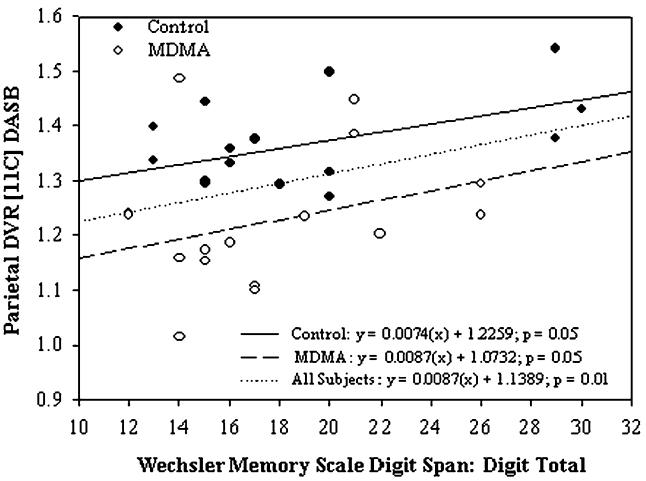

Fig. 3 Relationship between serotonin transporter number in the parietal cortex, as reflected by D_{VR} [^{11}C]DASB, to performance on a working memory digit span task

the Wechsler Memory Scale-III (story A recall; $r=-0.53$, $p=0.05$) and no measures of delayed recall. In addition, lifetime duration of marijuana use was associated with improved performance on the Rey Auditory Verbal Learning Test ($r=0.54$, $p=0.04$) and the Finger Tapping Test (nondominant hand; $r=0.64$, $p=0.01$). There was no overlap in the tasks found to be associated with MDMA use and marijuana use.

Discussion

No previous studies have evaluated the possibility that humans who use high or closely spaced sequential doses of MDMA (and thus likely develop high plasma MDMA concentrations; Chu et al. 1996; de la Torre et al. 2000; Mechan et al. 2006) incur brain DA neurotoxicity, as do rodents under certain conditions (Commins et al. 1987; Yuan et al. 2002; also see Easton and Marsden 2006). Results from the present study indicate that while high and sequential doses of MDMA lead to lasting decreases in SERT binding, they do not produce enduring alterations in DAT binding in humans. In particular, while abstinent MDMA users who participated in this study had global reductions in SERT binding, as reflected by PET studies with [^{11}C] DASB, they had normal brain DAT binding, as reflected by PET studies with [^{11}C] WIN 35,428. These findings suggest that lasting effects of recreational dose regimens of MDMA in humans are selective for brain 5-HT neurons and that rodent models of MDMA neurotoxicity demonstrating that high doses (and plasma levels) of MDMA can lead to loss of brain DA axonal terminals do not generalize to humans. Furthermore, they underscore the fact that the mouse, in which MDMA-induced DA neurotoxicity is the rule, may not be a good model for human MDMA neurotoxicity studies. Differences in the pharmacokinetics and pharmacodynamics of MDMA in preclinical models, when compared to humans, could shed light on the mechanisms of MDMA-induced neurotoxicity. Specifically, differences in the disposition and physiological effects of MDMA (or its metabolites) in species with different neurotoxic profiles could point to particular metabolites or physiological processes that promote the development of serotonergic versus dopaminergic injury.

These present data are the first to demonstrate a relationship between brain SERT binding and performance on verbal memory and attention tasks in any species. Interestingly, the strength of the relationship between verbal memory function and serotonin transporters was greater in controls than MDMA users, suggesting a disruption in the normal relationship between serotonin neurons and memory function (e.g., it is possible that compensatory brain mechanisms or other brain systems may be recruited to perform memory tasks in MDMA users). While many researchers have found that MDMA users have lasting subtle cognitive deficits and that these deficits often correlate with MDMA exposure patterns (Bolla et al. 1998; McCann et al. 2007; Gouzoulis-Mayfrank et al. 2000; Bhattachary and Powell 2001; Fox et al. 2001; Morgan et al. 2002; current study), no previous research has linked cognitive function to SERT binding alterations in the same subjects. The fact that there were positive correlations between SERT binding and verbal memory in brain areas known to be important in working and short-term memory (e.g., dorsolateral prefrontal cortex, parietal cortex, orbitofrontal cortex) suggests that MDMA-induced reductions of the SERT in those brain regions may be involved in memory impairments that have been previously noted in MDMA users. The present results are consistent with those of previous reports indicating that altered 5-HT neuronal function, as indicated by reduced CSF-5HIAA concentrations (Bolla et al. 1998) or 5-HT$_{2A}$ receptor binding (Reneman et al. 2000), is correlated with subtle memory impairment in abstinent MDMA users.

One previous study used SPECT with [^{123}I]β-CIT and found no relationship between cortical [^{123}I]β-CIT binding and scores on the Rey Auditory Verbal Learning Test (Reneman et al. 2001). However, as noted previously (McCann et al. 2001; Heinz and Jones 2000), the ability for [^{123}I]β-CIT to measure cortical SERT binding sites is controversial, with studies in a nonhuman primate, demonstrating no change in the level of cortical [^{123}I]β-CIT binding following the administration of the 5-HT reuptake inhibitor, citalopram (Laruelle et al. 1993). Another study conducted PET and cognitive studies in MDMA users (Thomasius et al. 2003), but did not report whether the two were related. Notably, although the current study found a significant positive relationship between verbal memory performance and SERT binding in controls (and, to a lesser degree, MDMA consumers), this correlation does not prove that MDMA-induced 5-HT neurotoxicity is the basis for cognitive deficits that have been found in MDMA users. For example, as recently discussed (McCann et al. 2007), it is possible that other factors (e.g., MDMA-related sleep abnormalities) contribute to cognitive deficits in MDMA users. Nevertheless, the current findings raise the possibility that MDMA-induced brain 5-HT neurotoxicity may play a role in memory deficits in MDMA users, whether directly or indirectly.

The present finding of reduced SERT binding potential in MDMA users are consistent with an earlier study with the same ligand (McCann et al. 2005), as well as other imaging studies with different radioligands demonstrating a reduction in brain 5-HT transporter binding in abstinent MDMA users (McCann et al. 1998; Reneman et al. 2001; Buchert et al. 2003, 2004; Thomasius et al. 2006). Binding

parameters were negatively correlated with the duration of MDMA use in some brain regions, supporting the view that reductions in binding are related to MDMA use. There was no relationship between duration of abstinence and binding parameters, in contrast to previous findings (McCann et al. 2005; Buchert et al. 2003; Thomasius et al. 2006). However, most subjects in the present study had used MDMA within the previous 6 months prior to scanning, and the failure to find evidence for recovery of ligand binding might be related to the relatively short duration of abstinence. Alternatively, it is possible that the number of subjects in the MDMA group (n=16) was not sufficiently large to detect a small degree of recovery, even if it occurred.

Notably, although the ability for [^{11}C] DASB to detect differences in cortical serotonin binding potential may not be adequate if reductions in the SERT are not sufficiently large (Frankle et al. 2006), it has been validated as a method for detecting MDMA-induced loss of cortical SERT. In particular, [^{11}C]DASB has been shown to be capable of detecting MDMA-induced reductions in the SERT in both cortical and subcortical brain regions in a baboon that underwent PET before and after treatment with MDMA (Szabo et al. 2002). Postmortem brain analysis of the SERT in cortical brain regions was highly correlated with PET measures of [^{11}C]DASB (although tended to underestimate the extent of the lesion). Therefore, although binding of [^{11}C]DASB to the SERT is relatively low in cortical brain regions, if the size of the reduction is sufficiently large, differences in cortical regions can still be detected in cortical regions using [^{11}C]DASB.

Several limitations of this study exist, including the fact that MDMA users, as a group, used more recreational drugs than control subjects and exposure to other drugs could have played a role in the cognitive or SERT deficits found in the present study. However, aside from certain amphetamines, none of these other recreational drugs are known to be toxic toward brain 5-HT or DA systems or to produce lasting (>2 weeks) changes in DAT or SERT binding. Importantly, previous studies have raised the question that recent marijuana use may confound cognitive studies of MDMA users (Dafters et al. 2004; Lamers et al. 2006). However, in the present study, only two subjects had positive urine marijuana screens (one control and one MDMA user) and neither of these subjects reported use of marijuana in the 2 weeks prior to study participation. Furthermore, lifetime marijuana use parameters were associated with decreased performance on only one memory task in the present study. Although the two groups were well-matched with regard to premorbid intelligence, it is possible that MDMA users had preexisting reductions in SERT binding and that loss of the normal relationship between cortical SERT density and verbal memory performance preceded MDMA use. Nevertheless, given the compelling preclinical literature demonstrating MDMA-induced reductions in brain SERT binding in animals, concerns about premorbid 5-HT lesions are diminished. Also, given the recent report by Schilt et al. (2007) demonstrating prospective decline in verbal memory after low cumulative doses of MDMA, it does not appear likely that the memory deficits that have been reported in MDMA users are preexisting. In the present study, all accounts of drug use were retrospective and self-reported and, therefore, subject to error. Finally, it is possible that the number of subjects used in the current study did not provide sufficient power to detect differences in DAT binding or that MDMA users included in the study did not develop sufficiently high MDMA levels to produce DAT binding changes.

In conclusion, results from the present study indicate that MDMA users who employ common sequential dosing regimens develop selective brain SERT deficits with no evidence of brain DAT deficits. The present study also provides the first indication of a relationship between brain SERT density and memory function in control subjects and a disruption of this relationship in MDMA users, raising the possibility that SERT reductions play a role in memory deficits in individuals with a history of recreational MDMA use. Although the present findings implicate brain 5-HT neurotoxicity in MDMA-related memory deficits, additional research is needed to determine whether MDMA-induced 5-HT injury and cognitive deficits in MDMA users are causally related or whether other intercurrent factors (e.g., MDMA-induced sleep disruption) play a role in cognitive dysfunction in MDMA users.

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