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Cocaine Dependence and D_2 Receptor Availability in the Functional Subdivisions of the Striatum: Relationship with Cocaine-Seeking Behavior

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Striatal dopamine D_2 receptors have been implicated in the neurobiology of cocaine addiction. Previous imaging studies showed reduced striatal D_2 receptor availability in chronic cocaine abusers, and animal studies suggested that low D_2 receptor availability promotes cocaine self-administration. Here, D_2 receptor availability was assessed with positron emission tomography (PET) and [^{11}C]raclopride in the limbic, associative, and sensori-motor subdivisions of the striatum in 17 recently detoxified chronic cocaine-dependent (CCD) subjects and 17 matched healthy control (HC) subjects. In addition, the relationship between regional D_2 receptor availability and behavioral measures obtained in cocaine self-administration sessions was investigated in CCD subjects. [^{11}C]Raclopride binding potential was significantly reduced by 15.2% in the limbic striatum, 15.0% in the associative striatum, and 17.1% in the sensori-motor striatum in CCD subjects compared to HC subjects. In CCD subjects, no relationship was detected between D_2 availability in striatal regions and either the positive effects of smoked cocaine or the choice of cocaine over an alternative reinforcer (money) following a priming dose of cocaine (a laboratory model of relapse). Thus, this study confirms previous reports of a modest decrease in D_2 receptor availability in CCD subjects, and establishes that this decrease is generalized throughout the striatum. However, this study failed to demonstrate a relationship between D_2 receptor availability and cocaine-induced cocaine-taking behavior. Additional research is warranted to unravel potential neurobiological traits that might confer vulnerability to relapse in detoxified CCD subjects.
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INTRODUCTION

Over the last decade, imaging studies using positron emission tomography (PET) have suggested that alterations in the density of striatal dopamine (DA) D_2 receptors might be involved in the initiation or maintenance of cocaine abuse and dependence. First, three studies from one laboratory have observed reduced striatal D_2 receptor availability in detoxified cocaine-dependent subjects compared to healthy subjects (Volkow *et al*, 1990, 1993, 1997). Second, studies from the same laboratory reported that, in healthy subjects, low striatal D_2 receptor availability was predictive of a pleasurable experience following administration of the psychostimulant methylphenidate (Volkow *et al*, 1999, 2002). Third, studies in nonhuman primates demonstrated that low striatal D_2 receptor availability was predictive of increased propensity to self-administer cocaine (Morgan *et al*, 2002). Together, these studies suggest that a low expression of D_2 receptors in the striatum might constitute a risk factor for the development of cocaine dependence, and that this neurobiological trait is associated a decreased sensitivity to natural reinforcers (Volkow *et al*, 2002).

The present study was designed to further evaluate the potential involvement of D_2 receptor expression in cocaine dependence. Recently detoxified chronic cocaine-dependent (CCD) subjects and matched healthy control (HC) subjects underwent a PET study with the D_2/D_3 receptor radiolabeled antagonist [^{11}C]raclopride. PET studies were acquired on the high-resolution camera ECAT EXACT HR+, which permitted the determination of D_2 receptor availability, not only in the striatum as a whole, but also in its functional

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subdivisions (Drevets *et al*, 2001; Mawlawi *et al*, 2001; Martinez *et al*, 2003). Following the scan, CCD subjects underwent cocaine self-administration studies in a laboratory setting. In the first set of laboratory sessions (single doses sessions), subjects rated their subjective response to smoked cocaine. In the second set of laboratory sessions (multiple choice sessions), subjects received a priming dose of cocaine and were then given the choice between smoking more doses of cocaine or receiving an alternative reinforcer (monetary reward). Thus, data from this study enabled us to asses potential relationships between D_2 receptor availability, the positive effect of cocaine, and primed drug seeking behavior (a laboratory model of relapse).

Four main hypotheses were tested on this data set. The first hypothesis was that the decreased D_2 receptor availability previously observed in CCD subjects at the level of the whole striatum (Volkow *et al*, 1990, 1993, 1997) would be replicated in this cohort. Studies with laboratory animals have implicated DA transmission in the nucleus accumbens rather than in the corpus striatum in mediating the rewarding effects of psychostimulants (for review see Wise and Romprè, 1989; Di Chiara, 1999). Based on these preclinical data, the second hypothesis was that the decrease in D_2 receptor availability associated with cocaine dependence would be more pronounced in the limbic compared to the associative or sensori-motor subdivisions of the striatum. The previous studies which reported an association between low striatal D_2 receptor availability and a pleasurable experience following psychostimulant administration were performed in healthy human subjects (Volkow *et al*, 1999, 2002). However, to our knowledge, this association has not been reported in CCD subjects. Thus, the third hypothesis was that low D_2 receptor availability would be predictive of a more pleasurable experience upon smoking cocaine in CCD subjects, and that this relationship would be more pronounced in the limbic striatum. The fourth hypothesis was that low D_2 receptor expression in the limbic striatum would be associated with cocaine-seeking behavior following a priming dose of cocaine. Thus, we predicted that low D_2 receptor expression in the limbic striatum would be predictive, not only of a positive response to smoked cocaine, but also of the choice for cocaine over the monetary alternative.

MATERIALS AND METHODS

Subjects

The study was approved by the Institutional Review Boards of the Columbia Presbyterian Medical Center and the New York State Psychiatric Institute and all subjects provided written informed consent. A federal certificate of confidentiality was issued by the National Institute of Drug Abuse (NIDA) for this study.

Study criteria for CCD subjects included: (1) males or females between 21 and 45 years old; (2) fulfilling DSM-IV criteria for cocaine abuse or cocaine dependence; (3) weekly use of cocaine in excess of the doses used in this study over the last 6 months; (4) positive urine screen for cocaine; (5) not currently seeking treatment; (6) absence of DSM-IV Axis I disorder other than cocaine abuse or dependence, including abuse or dependence to other drugs and alcohol (nicotine dependence was acceptable); (7) no current (6 months) use of opiates, sedative-hypnotics, and/or cannabis more than twice a week; (8) no current (6 months) use of psychotropic medication such as antipsychotics or antidepressants; (9) no pregnancy; (10) absence of a significant medical condition, including chronic active Hepatitis B or C; (11) no metal implants or paramagnetic objects within the body which may interfere with the MRI scan; (12) no exposure to radiation in the last year; (13) subjects not on parole or probation; (14) no history of violence. Study criteria for control subjects included (1) males or females between 21 and 45 years old; (2) absence of DSM-IV Axis I disorder (nicotine dependence was acceptable); and criteria 7–14 as above.

Screening

CCD and HC subjects were recruited by local newspaper advertisements from the New York City metropolitan area. Following an initial telephone interview, potential participants provided written informed consent and underwent a full screening, which included a psychiatric assessment, physical exam, 12-lead electrocardiogram, and laboratory tests, including urine toxicology and pregnancy test. The psychiatric assessment included: interview with a research psychologist and study psychiatrist, SCID (First *et al*, 1994, 1995), Drug History Questionnaire, General Health Questionnaire, and Beck Depression Inventory (Beck *et al*, 1996). The pregnancy test was repeated on the scan day.

Monitored Abstinence Period

After completing of the screening procedures, CCD subjects were admitted to the Irving Center for Clinical Research at the New York Presbyterian Hospital for the duration of the study (19–21 days). Subjects were not permitted to leave the unit unescorted, nor were visitors allowed. During this period, participants were randomly tested to confirm drug abstinence while hospitalized. Subjects were allowed to smoke cigarettes during their admission, except on scanning days. Subjects underwent PET scanning with [^{11}C]raclopride after 2 weeks of monitored abstinence. One to 3 days following the scans, the CCD subjects underwent the first cocaine self-administration sessions (single-sample sessions). On the next 2 days, CCD subjects underwent the multiple choice sessions. While subjects were not seeking treatment as per inclusion criteria, they were offered counseling during the study and referral at the end of the study. Healthy control subjects participated as outpatients and abstained from tobacco smoking on PET scan days. HC subjects did not participate in the cocaine self-administration sessions.

PET Scan Acquisition

[^{11}C]Raclopride was prepared as previously described (Mawlawi *et al*, 2001). The PET studies were acquired using a bolus plus constant infusion method for delivery of [^{11}C]raclopride, which provides a steady-state concentration of the unmetabolized radiotracer in the plasma and in the brain throughout the time of data acquisition (Mawlawi *et al*, 2001). This method allows for a direct determination

of the equilibrium distribution volume. [^{11}C]Raclopride was delivered in a 60 cc syringe, and a bolus dose of 31 cc was delivered over 3 min using an IMED pump (Gemini PC-1, San Diego, CA). Following the bolus, the pump was reset to deliver the remaining dose at 0.28 cc/min for 80 min. Thus, [^{11}C]raclopride was administered using a bolus to infusion ratio of 105 min (ie 53% of the dose is given in the bolus). We previously demonstrated that, under this administration protocol, activities reach equilibrium at about 40 min, and that an acquisition from 40 to 80 min is adequate and sufficient for reliable determination of activity concentrations in striatal subregions (Mawlawi *et al*, 2001).

PET imaging was performed with the ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN), which has 63 slices covering an axial field of view of 15.5 cm, an axial sampling of 2.46 mm, and in plane and axial resolution of 4.4 and 4.1 mm full width half-maximum at the center of the field of view in 3D mode. Emission data were collected in the 3D mode as eight frames of 5 min duration obtained from 40 to 80 min. Images were reconstructed with attenuation correction using the data from a 10 min transmission scan and a Shepp 0.5 filter.

Four venous samples (collected at 40, 50, 60, and 70 min) were obtained and analyzed to obtain the plasma concentration of [^{11}C]raclopride as previously described (Mawlawi *et al*, 2001). Briefly, a 200 μl aliquot of plasma was collected and activity measured in a gamma counter (Wallac 1480 Wizard 3 M Automatic Gamma Counter). The samples were further processed by high-pressure liquid chromatography (HPLC) to measure the fraction of plasma activity representing the parent compound (unmetabolized [^{11}C]raclopride). Plasma-free fraction (f_1) was measured in triplicate as previously described (Gandelman *et al*, 1994).

An MRI was acquired on a GE 1.5 T Signa Horizon system. A sagittal scout was initially performed to identify the plane of the anterior and posterior commissures. A transaxial T1 weighted sequence with a 1.5 mm slice thickness was then acquired in a coronal plane orthogonal to the plane of the anterior and posterior commissures. The following parameters were used: three-dimensional SPGR (Spoiled Gradient Recalled Acquisition in the Steady State); TR of 34 ms; TE of 5 ms; flip angle of 45°; slice thickness 1.5 mm and zero gap; 124 slices; FOV 22 × 16 cm; with 256 × 192 matrix, reformatted to 256 × 256, yielding a voxel size of 1.5 mm × 0.9 mm × 0.9 mm.

PET Scan Analysis

Three sets of analysis were performed and are presented. The first analysis was based on a priori defined regions of interest (ROIs). The second analysis was also ROI based, and included partial voluming correction. The third analysis was performed at a voxel-wise level.

Spatial registration. Image analysis was performed in MEDx (Sensor Systems, Inc., Sterling, Virginia) as described previously (Mawlawi *et al*, 2001). For derivation of registration parameters, PET frames were denoised with a level 2, order 5 Battle–Lemarie wavelet transform (Battle, 1987; Lemarie, 1988; Mallat, 1989). The detail images were then set to zero using a hard threshold, and the resulting image was transformed back into the spatial domain using an inverse wavelet. The first denoised frame of the data set (acquired at 40–45 min) was chosen *a priori* as the frame of reference and was registered to the MRI using between modality AIR (Woods *et al*, 1993). Each of the following denoised PET frames were then registered to this frame using within modality AIR (Woods *et al*, 1992). In seven out of 34 studies, the frame of reference (40–45 min) provided a less than ideal registration to the MRI and the following frame (45–50 min) was successfully registered to the MRI. The transformation matrices determined from the denoised PET frames were then applied to the original (not denoised) PET frames.

Anatomical analysis. The striatum was divided into five anatomical ROIs and three functional subdivisions (Figure 1), using previously published criteria (Martinez *et al*, 2003). The ROIs included the ventral striatum (VST), the dorsal caudate rostral to the anterior commissure (precommissural dorsal caudate, preDCA), the dorsal putamen rostral to the anterior commissure (precommissural dorsal putamen, preDPU), the caudate caudal to the anterior commissure (postcommissural caudate, postCA), and the putamen caudal to the anterior commissure (postcommissural putamen, postPU). Activities from left and right regions were averaged. ROIs were classified as belonging to the limbic striatum (LST), associative striatum (AST), or sensorimotor striatum (SMST), based on cortical connectivity (for reviews see Haber and Fudge, 1997; Joel and Weiner, 2000). The LST corresponded to the VST, the AST activity was derived as the spatially weighted average of the activities in the preDCA, preDPU and postCA, and the

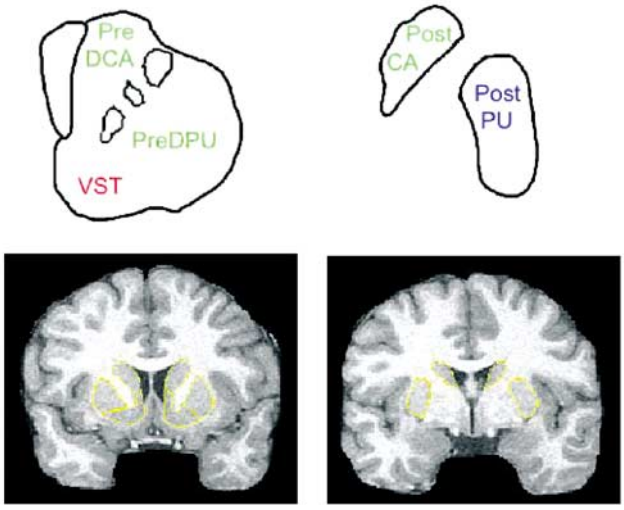

Figure 1 Striatal subregions. The top row is a schematic representation of striatal subregions in the coronal plane. The striatum anterior to the plane of the anterior commissure (AC) is on the left, and includes the VST (ventral striatum), the pre-DCA (precommissural dorsal caudate) and pre-DPU (precommissural dorsal putamen). On the right, the striatum posterior to the AC is shown, which includes the post-CA (postcommissural caudate) and post-PU (postcommissural putamen). Colors indicate functional subdivisions into limbic (red, VST), associative (green, pre-DCA, pre-DPU, and post-CA) and sensorimotor (blue, post-PU) subdivisions. The bottom row illustrates a coronal MRI image anterior (left) and posterior (right) to the AC, with the boundaries of the regions of interest (in yellow). The criteria used to delineate boundaries of VST, pre-DCA, and pre-DPU at the precommissural level are provided in Mawlawi *et al* (2001).

SMST corresponded to the postPU. See Martinez *et al* (2003) for discussion of rationale and limitations of this classification scheme. The activity in the striatum as a whole (STR) was derived as the spatially weighted average of the five ROIs. The cerebellum (CER) was used as the reference region. Regions were drawn on the MRI, and applied to the coregistered PET images for activity concentration measurement.

Derivation of outcome measures. D_2 receptor availability was estimated using two outcome measures: [^{11}C]raclopride binding potential (BP) and [^{11}C]raclopride specific to nonspecific equilibrium partition coefficient (V_3''). [^{11}C]Raclopride has a similar affinity for D_2 and D_3 receptor (Sokoloff *et al*, 1990), and the term D_2 receptors is used to denote both D_2 and D_3 receptors. Both outcome measures were obtained using equilibrium analysis applied to the PET frames obtained from 40 to 80 min. The regional tissue distribution volume (V_T, ml g^{-1}) was defined as the ratio of the ligand concentration in a region (C_T, μCi g^{-1}) to the concentration of unmetabolized ligand in venous plasma (C_P, μCi ml^{-1}) at equilibrium,

$$V_T = \frac{C_T}{C_P} \quad (1)$$

The concentration of D_2 receptors is negligible in the cerebellum (Hall *et al*, 1994). Therefore, only free and nonspecifically bound radiotracer were considered to contribute to V_T in the cerebellum ($V_{T\,CER}$), and $V_{T\,CER}$ was assumed to be equal to the nondisplaceable distribution volume (V_2). In the ROIs, V_T ($V_{T\,ROI}$) included V_2 and the specific binding distribution volume, or BP. Assuming that V_2 in the ROI was equal to $V_{T\,CER}$, BP was derived as the difference between $V_{T\,ROI}$ and $V_{T\,CER}$. BP is related to receptor parameters by

$$V_{T\,ROI} - V_{T\,CER} = BP = f_1 * \frac{B_{MAX}}{K_D'} \quad (2)$$

where f_1 is the plasma-free fraction, B_{max} is the concentration of D_2 receptors (nM per g of tissue), and K_D' is the *in vivo* equilibrium dissociation constant of the radiotracer (nM per ml of brain water) in the presence of the competitor DA. K_D' related to K_D by $K_D' = K_D\,(1 + F_{DA}/K_I)$, where F_{DA} is the free concentration of endogenous DA in the vicinity of the receptors, and K_I is the inhibition constant of DA for the binding of [^{11}C]raclopride (Laruelle *et al*, 1997). Studies in healthy subjects suggest that about 10% of D_2 receptor are occupied by DA in the baseline state in healthy subjects (Abi-Dargham *et al*, 2000). The proportion of D_2 receptors occupied by DA in CCD subjects is unknown.

V_3'' was calculated as the ratio of BP to $V_{T\,CER}$. V_3'' is related to receptor parameters by

$$\frac{V_{T\,STR} - V_{T\,CER}}{V_{T\,CER}} = V_3'' = f_2 * = \frac{B_{MAX}}{K_D'} \quad (3)$$

where f_2 is the free fraction in the nonspecific distribution volume of the brain ($f_2 = f_1/V_2$) (Laruelle *et al*, 1994). The use of BP for the between group comparison assumes that f_1 is not significantly different between groups, whereas the use of V_3'' assumes that f_2 is not significantly different between groups. In this study, both f_1 and f_2 were measured to assess the validity of these assumptions.

Partial volume error (PVE) analysis. The measurement of activity in the striatal subregions is affected by the error induced by partial volume effects (PVE). Owing to limitations in resolution, the activity emitted from a given ROI is not fully recovered within that ROI, and activities from adjacent regions contaminate the signal from the ROI. In a previous study in healthy controls, we determined that activity measured in the VST was significantly contaminated by counts spilling over from the adjacent preDCA and preDPU: $70 \pm 5\%$ of the specific binding measured in the VST originated from D_2 receptors located in the VST, while 12 ± 3 and $18 \pm 3\%$ were contributed by D_2 receptors in the preDCA and preDPU (Mawlawi *et al*, 2001). Owing to the importance of the VST measurement in this study, data analysis was repeated after PVE correction, which was performed as previously described (Rousset *et al*, 1998; Mawlawi *et al*, 2001). Briefly, the geometric transfer matrix (GTM) was formed by generating binary image sets of the ROI from the MRI, in which the voxels contained within each ROI are set to 1 and all other voxels are set to 0. The regions included the 10 ROIs, and a background region, which included the rest of the brain. The binary images were then realigned to the location of the original PET images in the camera field-of-view, and smoothed using a mathematical model of the point spread function of the PET camera at that location. The true activity in each ROI was calculated from the measured activity and the GTM. PVE correction was performed using a FWHM of 5.1 mm at the center of the field of view. This effective resolution takes into account the resolution of the PET camera, the reconstruction filter, and estimated subject movement (Mawlawi *et al*, 2001).

Voxel-wise analysis: V_3'' maps were created for each subject. First, $V_3''(t)$ images were made by dividing the activity in each MR coregistered frame between 40 and 80 min by the mean cerebellar activity of that frame and subtracting 1. The V_3'' map was then computed as the mean over frames of $V_3''(t)$. Each subject's structural MRI image was normalized to the T1 template image in SPM2 (Friston *et al*, 1995). The same transformation was then applied to the MR coregistered V_3'' image. Data were smoothed with a 12 mm Gaussian kernel. For SPM analyses, an absolute threshold mask of 0.1 was applied, that is, analysis was restricted to voxels at which all subjects' V_3'' exceeded a value of 0.1.

Laboratory Sessions

Following the scan, CCD subjects underwent cocaine self-administration laboratory sessions with doses of 0, 6, and 12 mg smoked cocaine over 3 days. The cocaine base was prepared by the Presbyterian Hospital Manufacturing Pharmacy from cocaine hydrochloride obtained from the National Institute of Drug Abuse (NIDA) as described previously (Foltin *et al*, 1990). During all sessions, subjects were under continuous EKG and frequent (every 2 min) vital sign monitoring. Subjects were monitored through a

one-way mirror and could communicate via an intercom. Participants were presented with cocaine base in a glass stem pipe and a research nurse held a lighter while the subjects inhaled the contents. Subjects were blind to the dose of cocaine. During each session, subjects were asked about their subjective experience of cocaine using the subjective-effects battery described below.

Single-sample sessions. On the first day, subjects had three single-sample sessions, separated in time by at least 2 h. Each session consisted of a single dose of 0, 6, or 12 mg of cocaine, administered in counterbalanced order. During these sessions, the subjective-effects battery was presented to the subjects at baseline, 4, 14, 30, and 60 min following the dose. The computerized subjective effects battery consisted of 26 visual analog scales (VAS) labeled 'not at all' at 0 mm and 'extremely' at 100 mm. Subjects were asked to indicate with a mark along the 100 mm line (on a computer screen) their response to the following questions: (1) 18 of the VAS start with 'I feel …' followed by 'stimulated', 'anxious', 'depressed', 'sedated', 'high', 'hungry', 'focused', 'calm', 'able to concentrate', 'alert', 'tired', 'talkative', 'self-confident', 'social', 'irritable', 'confused', 'a good drug effect', and 'a bad drug effect' (2) Four VAS were used to operationalize drug craving and were labeled 'I want …' followed by 'cocaine', 'heroin', 'alcohol', 'tobacco' (3). Four VAS were used to rate the dose, three were labeled 'I liked the choice' and 'the choice was …' followed by 'high quality' and 'potent' and one scale asked participants to indicate how much they would pay for the dose of cocaine across a range of \$0 to \$25.

A previous cluster analysis of these VAS demonstrated five clusters: positive effects (consisting of 'good drug effect', 'high', and 'stimulated'), as well as 'drug quality ratings', 'bad drug effect', 'mood states', and 'on edge/miserable' (Evans *et al*, 2002). The positive effects cluster was chosen *a priori* for correlation with D_2 receptor availability, with a *post hoc* analysis of measures of craving. For each VAS, the area under the curve (AUC) was used as outcome measure for comparison with PET data. The positive effects score was then derived as an average of the AUC for the three VAS within this cluster. Similarly, an average of the AUC was calculated for the drug quality ratings. The VAS for cocaine craving was calculated as the AUC for this scale.

During the single sample sessions blood samples for cocaine were drawn through an intravenous catheter at baseline, 4, 14, 30, 60 min. Plasma cocaine levels were centrifuged and frozen until analyzed. Cocaine plasma concentration was determined using capillary gas chromatograph–mass spectrometry as previously described (Foltin *et al*, 2003). Cocaine levels (ng/ml) obtained for each dose session were averaged.

Multiple choice sessions. On the second and third laboratory days, subjects underwent three multiple choice sessions, with each the 0, 6, and 12 mg doses, in counterbalanced order, as described previously (Foltin *et al*, 2003). In these sessions, subjects took an initial response independent or 'priming' dose of 0, 6, or 12 mg at $t=0$. Following this dose, subjects were given the choice between this same dose of cocaine or a \$5.00 merchandise voucher redeemable at local stores and paid upon discharge. Subjects were presented with this choice 5 times, spaced 14 min apart, and indicated their choice on the computer screen. A progressive ratio was used, such that participants were required to press a space bar on the computer keyboard 200, 600, 1000, 1400, and 1600 times in order to receive their choice. The outcome measure for the choice sessions was the number of times a given dose of cocaine was chosen over voucher (1–5).

Statistical Analysis

Group comparisons were performed with unpaired *t*-test or χ^2. Outcomes related to D_2 receptor availability ([^{11}C]raclopride BP and V_3''), which were analyzed by repeated measures ANOVA, with region or functional subdivisions as repeated factor and groups as cofactor. The effects of cocaine were analyzed with repeated measure ANOVA with dose as repeated factor. Voxel-wise analysis was performed with SPM2 (Friston *et al*, 1995). Relationships between continuous variables were analyzed with the Pearson product moment correlation coefficient. A two-tailed probability value of $p<0.05$ was chosen as the level of significance.

RESULTS

Group Composition

In total, 19 HC subjects and 20 CCD subjects were enrolled in this study. Two HC subjects were excluded after enrollment: one subject was unable to complete the MRI and another developed an axis I diagnosis after the study. Three CCD subjects were excluded after enrollment: two left the hospital prior to the PET scans for personal reasons and the third was removed by the study physician due to medical illness. Therefore, the final samples included 17 HC and 17 CCD subjects who completed the study. Groups were matched for age, gender, ethnicity, and cigarette smoking (Table 1). Both groups were acquired in parallel, over a 31-month period. CCD subjects reported smoking crack cocaine an average of 4.3 ± 1.7 days per week. They had been using cocaine for 15.5 ± 4.9 years and were spending \$$264\pm111$ \$US weekly over the last 6 months.

Table 1 Group Demographic Compositions

Parameter	HC	CCD	*p*
n	17	17	—
Age (mean ± SD, years)	38.5 ± 5.4	38.7 ± 3.8	0.94[a]
Gender (male/female)	13M/4F	13M/4F	—
Ethnicity (African-American/Hispanic/Caucasian not Hispanic)	11AA/1H/5C	13AA/2H/2C	0.49[b]
Smoking status (yes/ex/no)	14Y/3E/0N	13Y/3E/1N	0.59[b]
Mean ± cigarettes per day in smokers	10 ± 6	11 ± 4	0.75[a]

Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects.
[a]Unpaired *t*-test.
[b]χ^2.

Imaging Results

Injected doses. The average decay corrected injected dose was 13.3 ± 3.8 mCi for HC subjects and 12.4 ± 4.3 mCi for CCD subjects ($p = 0.5$). The average specific activity was 1473 ± 735 Ci/mmol with an injected mass of 3.6 ± 1.2 μg for HC subjects and 1673 ± 1067 Ci/mmol with an injected mass of 3.1 ± 1.1 μg for CCD subjects ($p = 0.5$ for specific activity and $p = 0.2$ for mass).

Plasma analysis. The concentration of parent compound ([^{11}C]raclopride) was constant over 40–70 min. The changes in plasma parent concentration over time, during the 40–70 min interval, were calculated as the slope of the regression over time and expressed relative to the average concentration. These changes were not significantly different from zero (one sample *t*-test: HC: 0.6 ± 23%/h, $p = 0.91$; CCD: 5 ± 26%/h, $p = 0.44$), nor were they different between groups ($p = 0.61$). Plasma clearance did not differ between groups (HC: $12.7 \pm 3.9\,l\,h^{-1}$; CCD: $12.3 \pm 2.2\,l\,h^{-1}$; $p = 0.7$). Likewise, plasma free fraction (f_1) did not differ between groups (HC: 3.8 ± 0.8%; CCD: 3.4 ± 0.7%; $p = 0.13$).

Cerebellum V_2. The volume of distribution of the cerebellum (V_2) was $0.40 \pm 0.07\,ml\,g^{-1}$ in HC subjects and $0.39 \pm 0.05\,ml\,g^{-1}$ in CCD subjects ($p = 0.6$). The free fraction of the cerebellum (f_2) was 9.8 ± 2.6% in HC subjects and 8.8 ± 1.7% in CCD subjects ($p = 0.2$).

ROI volumes. ROIs volumes did not differ between the two groups (Table 2).

D_2 receptor availability: non-PVE-corrected data. Representative [^{11}C]raclopride scans in one HC subject and one CCD subject are presented in Figure 2. Regional non-PVE corrected values for BP and V_3'' are provided in Tables 3 and 4, respectively. Significant group differences in D_2 receptor availability were found with both BP and V_3'' ([^{11}C]raclopride BP: region factor: $p < 0.001$; group factor: $p = 0.014$; group by region interaction: $p = 0.004$; [^{11}C]raclopride V_3'': region factor: $p < 0.001$; group factor: $p < 0.001$; group by region interaction: $p = 0.001$). CCD subjects exhibited lower D_2 receptor availability compared to HC subjects, and the decreases were of similar magnitude for BP and V_3''. When the regions were examined individually, a significant difference was found in all regions for BP (Table 3) and V_3'' (Table 4), with the

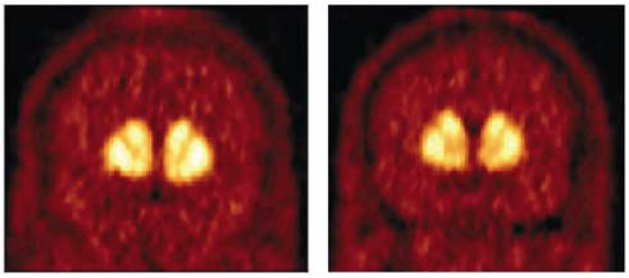

Figure 2 [^{11}C]raclopride distribution in a healthy control subject (left) and a cocaine-dependent subject (right). Both images are the mean of data acquired from 40 to 80 min and the image display was corrected for injected dose. The selected images include the striatum rostral to the anterior commissure. Cocaine-dependent subjects were found to have significantly lower D_2 receptor availability compared to healthy controls.

Table 2 Region of Interest Volumes (mm^3)

Functional subdivision	Anatomical subdivision	HC	CCD	*p**
LST	VST	2080 ± 784	1878 ± 816	0.47
AST	Pre-DPU	3946 ± 851	3745 ± 880	0.50
	Pre-DCA	5170 ± 640	4872 ± 709	0.21
	Post-CA	1724 ± 377	1646 ± 409	0.57
SMST	Post-PU	4972 ± 784	5377 ± 1370	0.30

Values are mean ± SD, $n = 17$ per groups. *Unpaired *t*-test. Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects; LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; pre-DPU, precommissural dorsal putamen; pre-DCA, precommissural dorsal caudate; post-CA, postcommissural caudate; post-PU, postcommisural putamen.

Table 3 [^{11}C]Raclopride Binding Potential (BP, $ml\,g^{-1}$)

Functional subdivision	Anatomical subdivision	HC	CCD	Difference (%)	*p**
LST	VST	0.84 ± 0.20	0.71 ± 0.15	−15.2	0.04
AST		1.03 ± 0.22	0.87 ± 0.13	−15.0	0.02
	Pre-DCA	0.98 ± 0.21	0.84 ± 0.13	−13.7	0.03
	Pre-DPU	1.22 ± 0.25	1.01 ± 0.17	−17.2	<0.01
	Post-CA	0.72 ± 0.18	0.64 ± 0.11	−11.2	0.12
SMST	Post-PU	1.22 ± 0.24	1.01 ± 0.17	−17.1	<0.01
STR		1.06 ± 0.22	0.90 ± 0.13	−15.2	0.02

Values are mean ± SD, $n = 17$ per groups. *Unpaired *t*-test. Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects; LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; pre-DPU, precommissural dorsal putamen; pre-DCA, precommissural dorsal caudate; post-CA, postcommissural caudate; postPU, post-commisural putamen; STR, striatum as a whole.

Table 4 [^{11}C]Raclopride Specific to Nonspecific Partition Coefficient (V_3'', Unitless)

Functional subdivision	Anatomical subdivision	HC	CCD	Difference (%)	*p**
LST	VST	2.12 ± 0.34	1.84 ± 0.28	−13.1	0.01
AST		2.57 ± 0.25	2.24 ± 0.18	−12.5	<0.001
	Pre-DCA	2.45 ± 0.27	2.18 ± 0.20	−11.2	0.002
	Pre-DPU	3.05 ± 0.31	2.59 ± 0.24	−15.1	<0.001
	Post-CA	1.81 ± 0.30	1.66 ± 0.26	−8.5	0.12
SMST	Post-PU	3.07 ± 0.32	2.61 ± 0.28	−15.0	<0.001
STR		2.65 ± 0.26	2.31 ± 0.19	−12.9	<0.001

Values are mean ± SD, $n = 17$ per groups. *Unpaired *t*-test. Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects; LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; pre-DPU, precommissural dorsal putamen; pre-DCA, precommissural dorsal caudate; post-CA, postcommissural caudate; post-PU, postcommisural putamen; STR, striatum as a whole.

exception of the postCA, with this region being the source of the significant region by group interaction.

This analysis was also performed at the level of the subdivisions. Significant group differences in D_2 receptor availability were found with both BP and V_3'' ([^{11}C]raclopride BP: subdivision factor: $p<0.001$; group factor: $p=0.013$; group by region interaction: $p=0.042$; [^{11}C]raclopride V_3'': subdivision factor: $p<0.001$; group factor: $p<0.003$; group by region interaction: $p=0.045$). When the subdivisions were examined individually, a significant difference was found in all subdivisions for BP (Table 3) and V_3'' (Table 4). The significance level of the group difference in the SMST was higher than in the AST and LST, a difference being the source of the significant interaction.

D_2 receptor availability: PVE-corrected data. PVE corrected values for BP and V_3'' are provided in Tables 5 and 6 not found. PVE correction resulted in a significant increase in the measured values of BP and V_3'' for each ROI (RM ANOVA, $p<0.05$ for all regions). Significant group differences in regional D_2 receptor availability were found with both PVE corrected BP and V_3'' (PVE corrected [^{11}C]raclopride BP: region factor: $p<0.001$; group factor: $p=0.010$; group by region interaction: $p=0.06$; PVE corrected [^{11}C]raclopride V_3'': region factor: $p<0.001$; group factor: $p=0.002$; group by region interaction: $p=0.06$). Thus, even after PVE correction, CCD subjects still exhibited lower D_2 receptor availability compared to HC subjects. When ROIs were examined individually, a significant difference was found in all ROIs and subdivisions for PVE corrected BP (Table 5) and V_3'' (Table 6), except in the postCA. Figure 3 displays the individual values of PVE corrected V_3'' in LST, AST and SMST in HC and CCD subjects.

This analysis was also performed at the level of the subdivisions. Significant group differences in PVE-corrected D_2 receptor availability were found with both BP and V_3'' (PVE corrected [^{11}C]raclopride BP: subdivision factor: $p<0.001$; group factor: $p=0.009$; group by region interaction: $p=0.084$; PVE corrected [^{11}C]raclopride V_3'': subdivision factor: $p<0.001$; group factor: $p=0.002$; group by region interaction: $p=0.14$). When the subdivisions were examined individually, a significant difference was found in all subdivisions for BP (Table 5) and V_3'' (Table 6). Thus, the main difference between PVE and non-PVE corrected analysis of the subregions was that the interaction term became nonsignificant after PVE correction.

Table 5 [^{11}C]Raclopride Binding Potential (BP, ml g^{-1}), Following Partial Volume Effect Correction

Functional subdivision	Anatomical subdivision	HC	CCD	Difference (%)	p*
LST	VST	1.38±0.35	1.16±0.29	−16.5	<0.05
AST		1.59±0.33	1.35±0.19	−14.7	<0.05
	Pre-DCA	1.49±0.30	1.29±0.19	−13.2	<0.05
	Pre-DPU	1.77±0.35	1.45±0.25	−17.9	<0.001
	Post-CA	1.49±0.40	1.32±0.24	−11.3	0.15
SMST	Post-PU	2.14±0.45	1.74±0.32	−18.4	<0.01
STR		1.71±0.34	1.45±0.40	−15.4	<0.01

Values are mean±SD, $n=17$ per groups. *Unpaired *t*-test. Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects; LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; pre-DPU, precommissural dorsal putamen; pre-DCA, precommissural dorsal caudate; post-CA, postcommissural caudate; post-PU, postcommisural putamen; STR, striatum as a whole.

Table 6 [^{11}C]Raclopride Specific to Nonspecific Partition Coefficient (V_3'', Unitless), Following Partial Volume Effect Correction

Functional subdivision	Anatomical subdivision	HC	CCD	Difference (%)	p*
LST	VST	3.37±0.82	2.85±0.59	−15.3	<0.05
AST		3.82±0.43	3.35±0.32	−12.4	<0.001
	Pre-DCA	3.60±0.44	3.20±0.33	−11.0	<0.01
	Pre-DPU	4.27±0.50	3.58±0.43	−16.0	<0.001
	Post-CA	3.57±0.65	3.29±0.59	−8.1	0.19
SMST	Post-PU	5.16±0.75	4.32±0.71	−16.2	<0.01
STR		4.13±0.49	3.58±0.40	−13.2	<0.001

Values are mean±SD, $n=17$ per groups. *Unpaired *t*-test. Abbreviations: HC, healthy control subjects; CCD, chronic cocaine-dependent subjects; LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; pre-DPU, precommissural dorsal putamen; pre-DCA, precommissural dorsal caudate; post-CA, postcommissural caudate; post-PU, postcommisural putamen; STR, striatum as a whole.

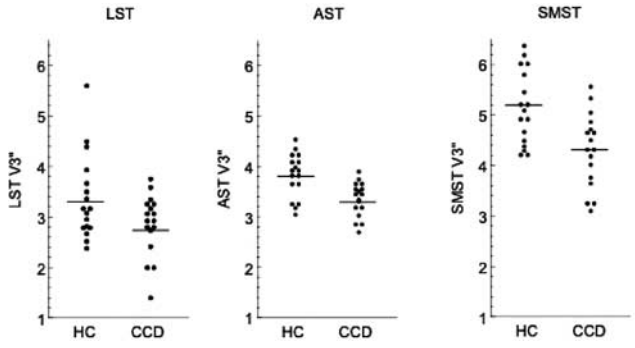

Figure 3 Partial voluming corrected [^{11}C]raclopride V_3'' in healthy subjects (HC, $n=17$) and cocaine-dependent subjects (CCD, $n=17$) in limbic striatum (LST), associative striatum (AST) and sensorimotor striatum (SMST). In all regions, [^{11}C]raclopride V_3'' was significantly lower in CCD subjects compared to controls (unpaired *t*-test, $p<0.05$).

D_2 receptor availability: voxel-wise analysis. V_3'' maps for controls and CCD are presented in Figure 4. Results of the voxel-wise group comparison are presented in Figure 5. Two significant clusters appeared corresponding to the left and right sides of the striatum in the contrast for control V_3'' greater than cocaine user V_3''. These were significant at the $p=0.004$ and 0.015 levels, respectively, when using the random field family-wise error multiple comparisons correction. The significant regions primarily overlapped putamen (pre- and postcommissural). These were connected to small portions of the precommissural caudate, which, while exceeding the threshold for display, did not reach significance. The display threshold on the image

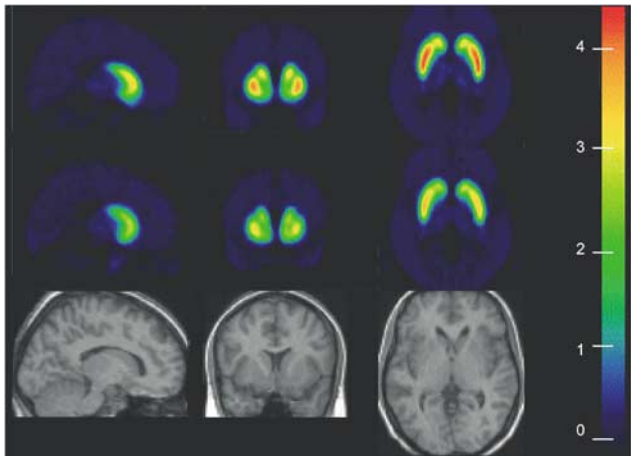

Figure 4 Spatially normalized mean V_3'' parametric map in healthy controls ($n=17$, top row) and cocaine-dependent subject ($n=17$, middle row). V_3'' parametric maps were created for each subjects by applying Eq. 3) on each voxel. V_3'' maps were then spatially normalized to a MRI template. The color scale was calibrated in V_3'' units, and is identical for both groups. Comparison of the maps illustrates the decreased [^{11}C]raclopride V_3'' in cocaine-dependent subject compared to controls.

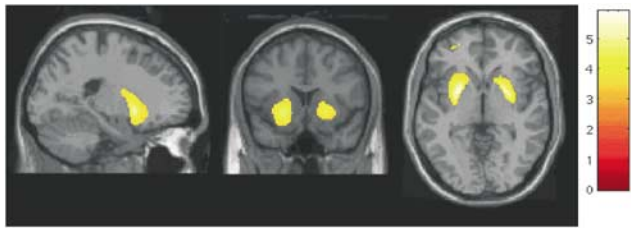

Figure 5 Results of SPM analysis, showing the brain areas were [^{11}C]raclopride V_3'' was significantly lower in cocaine-dependent subjects compared to controls (display threshold = 3.37, the *T*-value associated with uncorrected $p=0.001$).

corresponds to an uncorrected *p*-value of 0.001 ($T=3.37$, $n=34$, df = 32). A small cluster in the frontal cortex exceeded the display threshold, but did not survive the multiple comparisons procedures ($p=0.325$). No voxels were significant at any uncorrected *p* level in the contrast for cocaine user V_3'' greater than control V_3''.

Laboratory Session Results

Single-sample sessions. The mean ± SD AUC for each VAS of the positive effect cluster and for the positive effects cluster itself are shown in Figure 6 for each dose of cocaine. Ratings of the positive effects of the 6 mg dose did not differ from the 0 mg dose ($p=0.73$), whereas ratings of the 12 mg dose differed significantly from both the 0 and 6 mg doses ($p<0.001$ for both comparisons). A similar pattern was seen for each of the individual VAS (stimulated, high, and good drug effect): a significant difference was seen between the 12 and 0 mg doses ($p\leqslant 0.005$ for each VAS) and the 12 and 6 mg doses ($p\leqslant 0.02$ for each VAS), with no difference between the scores for the 0 mg and 6 mg doses. Ratings of drug quality followed the same pattern as the positive effects score. The 12 mg dose (378 ± 761) differed from both the 0 mg dose (170 ± 381, $p=0.01$) and the 6 mg dose

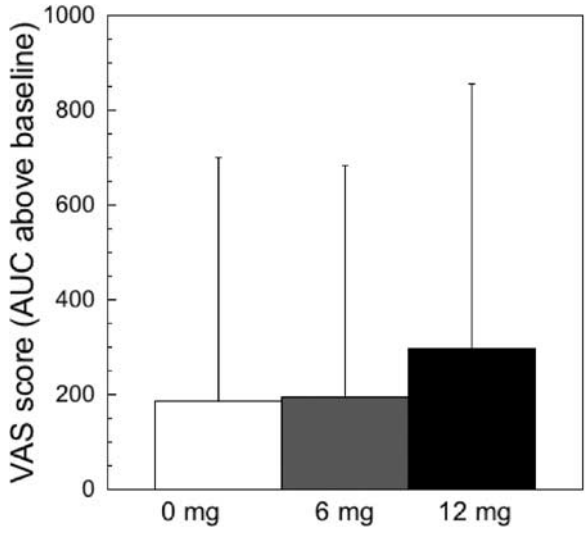

Figure 6 Positive effects of cocaine following 0, 6, and 12 mg of smoked cocaine. The visual analog scales (VAS) that make up the positive effects cluster include ratings of 'high', 'stimulated', and 'good drug effect'. For each VAS the area under the curve (AUC) was calculated. The average of these three ratings was used to derive the AUC for positive effects. No difference in any of these measures was seen between the 0 and 6 mg doses. However, ratings of the 12 mg dose were significantly higher than the 0 or 6 mg doses.

(219 ± 625, $p=0.05$), whereas the 0 and 6 mg doses did not differ from each other ($p=0.5$). Ratings of craving for cocaine did not differ significantly between the doses: the 0 mg dose was 1609 ± 2271 compared to 1283 ± 2028 for the 6 mg dose and 1526 ± 2016 for the 12 mg dose. Since only the 12 mg dose elicited positive subjective effects different from placebo, the effects of the 12 mg dose were selected for comparison with the scan data.

The averaged cocaine plasma levels for the different doses were as follows: 1.26 ± 3.06 ng ml^{-1} for the 0 mg dose, 16.63 ± 18.61 ng ml^{-1} for the 6 mg dose, and 32.53 ± 32.35 ng ml^{-1} for the 12 mg dose. The difference between the levels obtained for each dose was significant for each comparison (0 *vs* 6 *vs* 12 mg). A minimal detectable cocaine level was seen for the 0 mg dose, which most likely resulted from the fact that the dose order was counterbalanced, such that some subjects had received a 6 or 12 mg dose prior to the 0 mg dose. However, the cocaine levels were low for the 0 mg does and were unlikely to affect the VAS scales obtained for this dose. No correlation was seen between the plasma levels of cocaine drawn at 4 min following the dose and the positive effects of cocaine (0 mg dose: $r=0.2$, $p=0.51$: 6 mg dose: $r=0.04$, $p=0.90$, and 12 mg dose: $r=0.32$, $p=0.27$).

Multiple choices sessions. One subject did not undergo choice sessions due to a scheduling problem. Thus, 16 of the cocaine-dependent subjects completed the choice sessions. The results of the choice sessions are shown in Figure 7. Out of five possible choices, the 0 mg dose was chosen 0.50 ± 1.26 times, the 6 mg dose was chosen 1.75 ± 1.81 times, and the 12 mg dose was chosen 3.69 ± 1.49 times. There was a significant difference between each of the three doses: the 12 mg dose was chosen more frequently than both

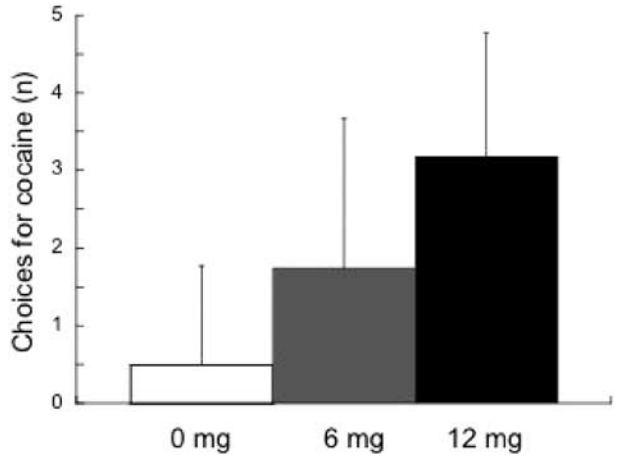

Figure 7 Choices for cocaine over monetary reward following a priming dose of cocaine. Subjects were presented this choice five times, and the number of doses of cocaine chosen is on the *y*-axis (range is 0–5). Subjects chose both the 6 and 12 mg doses more frequently than the 0 mg dose ($p = 0.01$ and $p < 0.0001$, respectively). There was also a significant difference in the choice for the 12 mg dose *vs* 6 mg ($p = 0.0002$).

the 0 mg ($p < 0.0001$) and the 6 mg dose ($p = 0.0002$). The 6 mg dose was also chosen more frequently than the 0 mg dose ($p = 0.01$). No correlation was seen between the positive effects reported by each individual subject during the single-dose session and their choice for either the 6 mg ($r = 0.02$, $p = 0.94$) or the 12 mg dose ($r = 0.32$, $p = 0.23$).

The rationale for using low doses of cocaine in the self-administration sessions was to ensure enough variability between subjects to allow comparison with the [^{11}C]raclopride data. The highest variance was seen for the 6 mg dose, (3.27) compared to the 0 mg (1.60) and 12 mg (2.23) doses. Therefore, the 6 mg was chosen for comparison with the PET data.

Relationships between Scan, Behavioral, and Clinical Data

No association was seen between LST [^{11}C]raclopride V_3'' and the positive effects of 12 mg cocaine ($r = 0.26$, $p = 0.31$), craving for cocaine ($r = 0.49$, $p = 0.85$), or with cocaine-taking behavior (choice frequency for the 6 mg dose of cocaine over money, $r = 0.18$, $p = 0.51$). No relationship was seen between LST [^{11}C]raclopride V_3'' and years of cocaine exposure (Table 7), which was also true when age was entered into the model (age factor, $p = 0.42$, years of abuse factor, $p = 0.99$). Similarly, no relationships were observed between [^{11}C]raclopride V_3'' in other regions and each of these behavioral variables (positive effects of cocaine, primed cocaine-seeking behavior, and years of exposure, Table 7).

DISCUSSION

The results of this study replicate the observation that striatal D_2 receptor availability is decreased in recently detoxified chronic cocaine abusers (Volkow *et al*, 1990, 1993, 1997). This decrease was of a modest magnitude, and affected to the same extent the limbic, associative, and sensorimotor regions of the striatum. In CCD subjects, low D_2 receptor availability in the limbic striatum (or in the other regions of the striatum) was not predictive of the positive effects of smoked cocaine, cocaine-induced cocaine-taking behavior, nor of the duration of cocaine abuse. Thus, while this study replicated the previous observations of low striatal D_2 receptors in cocaine abuse, it failed to detect an anatomical selectivity of this alteration within the striatum, and failed to detect the behavioral significance of this abnormality.

D_2 Receptor Availability and Cocaine Dependence

In this data set, cocaine dependence was associated with a reduction in both BP and V_3''. No between-group difference was seen in nonspecific binding (V_2), free fraction of the plasma (f_1), or free fraction of the cerebellum (f_2). Under these conditions, results derived with BP and V_3'' should be in accordance (which was the case here). Furthermore, the decrease in binding parameters was not an artifact due to lower striatal volume in CCD subjects and partial volume effects. First, CCD subjects did not show differences in striatal volume compared to controls (a finding that contrasts with previous observation of increased striatal volume in CCD, Jacobsen *et al*, 2001). Second, partial volume effect correction produced results that enhanced the difference between the two groups. Thus, the decrease in binding parameters BP and V_3'' can be attributed with confidence to a decrease in the D_2 receptor Bmax/K_D' ratio. Since this study was performed only with tracer doses [^{11}C]raclopride, it is not possible to separate changes in B_{max} from changes in K_D'. In theory, a reduction in the number of D_2 receptors available to bind to [^{11}C]raclopride could be due to elevated synaptic DA levels (which would translate into higher K_D' under a competitive model, lower

Table 7 Relationship Between [^{11}C]Raclopride V_3'' and Cocaine Use Parameters in Chronic Cocaine-Dependent Subjects

	Positive effects of cocaine		Choice for cocaine over money		Years of cocaine abuse	
Functional subdivision	***R***	***p***	***r***	***p***	***r***	***p***
LST	0.26	0.31	0.18	0.51	0.12	0.65
AST	0.06	0.82	0.32	0.22	0.04	0.88
SMST	0.15	0.56	0.22	0.23	0.08	0.76
STR	0.06	0.82	0.34	0.19	0.03	0.92

$n = 16$. Abbreviations: LST, limbic striatum; AST, associative striatum; SMST, sensori-motor striatum; VST, ventral striatum; STR, striatum as a whole.

B_{max} under a noncompetitive model, or both under a mixed model). However, previous studies have demonstrated that cocaine abuse is associated with a reduction in [^{18}F]6-FDOPA uptake (Wu *et al*, 1997) as well as a blunted DA response following a psychostimulant challenge (Volkow *et al*, 1997). Based on these findings, it is expected that DA synaptic concentration, if altered, would be lower in CCD. In this case, the reduction in D_2 receptor availability observed here would actually represent an underestimation of the true effect.

Previous PET studies have shown a decrease in D_2 receptor availability of a similar magnitude in the striatum. Volkow *et al* previously reported a decrease of 11% in striatal [^{11}C]raclopride binding (Volkow *et al*, 1997) and decreases of 38% (Volkow *et al*, 1990), and 14% (Volkow *et al*, 1993) in [^{18}F]*N*-methylspiroperidol striatal binding in CCD subjects. Whether this decreased D_2 receptor expression represents a vulnerability factor or a consequence of long-term cocaine exposure cannot be determined from these studies. Rodent studies investigating the long-term effects of cocaine exposure on D_2 receptor density have yielded inconsistent findings: studies have reported unchanged (Dwoskin *et al*, 1988; Alburges *et al*, 1993; Neisewander *et al*, 1994; Claye *et al*, 1995), increased (Taylor *et al*, 1979; Trulson and Ulissey, 1987; Zeigler *et al*, 1991) and decreased (Goeders and Kuhar, 1987; Kleven *et al*, 1990) D_2 receptor densities in the striatum. Studies in nonhuman primates are less numerous, but more consistent. D_2 receptor density is unaffected by short-term administration of cocaine (Farfel *et al*, 1992; Nader *et al*, 2002), but is decreased following prolonged exposure (Moore *et al*, 1998; Nader *et al*, 2002). Thus, the hypothesis that the decrease in D_2 receptor availability observed in CCD subjects is a consequence of prolonged exposure to cocaine is supported by nonhuman primate data and cannot be ruled out.

Yet, the alternate hypothesis (low D_2 receptor availability is a risk factor for the development of cocaine addiction) is supported by several indirect lines of evidence. First, decreases in D_2 receptor availability of a similar magnitude have been shown in PET and SPECT studies of other addictive behaviors, including heroin addiction (Wang *et al*, 1997), alcohol dependence (Hietala *et al*, 1994; Volkow *et al*, 1996), methamphetamine abuse (Volkow *et al*, 2001), and obesity (Wang *et al*, 2001). Together, these studies suggest that low D_2 receptor availability might be a general risk factor for addiction. Low D_2 receptor availability might be associated with low sensitivity to naturally occurring reinforcers, and a propensity to depend on pharmacological stimulation or excessive consumption to experience reward. Low striatal D_2 receptor availability is also found in other conditions, such as social phobia (Schneier *et al*, 2000) and social detachment in healthy control subjects (Farde *et al*, 1997; Breier *et al*, 1998), conditions which might be conceptualized as resulting from a low reinforcing effect of social interactions. An additional line of evidence supporting a role for low D_2 receptor availability as a risk factor for addiction includes studies in healthy controls, which showed that low D_2 receptor availability is associated with a more pleasurable experience following the administration of methylphenidate (Volkow *et al*, 1999, 2002). However, these results were not observed with amphetamine: in healthy subjects, D_2 receptor availability measured with [^{11}C]raclopride or [^{123}I]IBZM were not predictive of the pleasurable effects reported following amphetamine administration (Abi-Dargham *et al*, 2003; Martinez *et al*, 2003). Finally, low D_2 receptor availability is associated with a propensity to self-administer cocaine in nonhuman primates, an observation that also supports the hypothesis that low D_2 receptor availability might constitute a risk factor for the development of addiction (Morgan *et al*, 2002). In conclusion, the literature provide data consistent with both hypotheses (toxic effect or vulnerability factor), and this issue cannot currently be settled.

D_2 Receptor Availability in Functional Subdivisions of the Striatum

In the present study, the use of a high-resolution PET camera (ECAT EXACT HR+) allowed measurement of D_2 receptor availability in the limbic, associative, and sensorimotor subdivisions of the striatum. Given the number of preclinical studies that have shown the connection between reinforcement and DA transmission in the nucleus accumbens (Nestler *et al*, 1990; Terwilliger *et al*, 1991; Striplin and Kalivas, 1993; Porrino *et al*, 2002), we formulated the hypothesis that, if low D_2 receptor availability is associated with a vulnerability to develop addiction, this alteration might be more pronounced in the limbic compared to other subdivisions of the striatum of human cocaine abusers. The method used here to measure [^{11}C]raclopride activity in the functional subdivisions of the striatum has been shown to have good test/retest reproducibility (Mawlawi *et al*, 2001), and to reliably detect between region differences of the effects of amphetamine on [^{11}C]raclopride binding (Drevets *et al*, 2001; Martinez *et al*, 2003). In addition, the present data were analyzed with PVE correction, to remove cross-regional contamination of the signals. The relative regional distribution of D_2 receptors measured in this study in HC subjects was similar to that previously reported in other control groups (Mawlawi *et al*, 2001; Martinez *et al*, 2003). The reduction in [^{11}C]raclopride binding measured in the LST of CCD subjects was similar to that measured in the AST and SMST. Thus, these data do not support a selective decrease in D_2 receptor availability within the striatal subregions. The only region in which this decrease failed to reach significance was the postCA. The lack of significance in the postCA might be due to the noise involved in measuring this small structure. However, the fact that the coefficient of variation in the post-CA was not increased compared to that of other regions, suggest a possible preservation of D_2 receptors in this brain region.

D_2 Receptor Availability and the Effects of Psychostimulants

In the present study, no correlation was observed between D_2 receptor availability and the positive subjective effects of cocaine in CCD subjects. This result was consistent with the observation that D_2 receptor availability is not associated with the pleasurable effects of amphetamine in HC (Abi-Dargham *et al*, 2003; Martinez *et al*, 2003), although it might be associated with the pleasurable effects of methylphenidate in HC (Volkow *et al*, 1999, 2002). The difference

between results observed with methylphenidate and amphetamine in HC might be related to differences in the mode of action of methylphenidate, an uptake blocker, and amphetamine, an uptake blocker and DA releaser. The difference between results obtained in HC with methylphenidate and in CCD with cocaine (both drugs being uptake blockers) is more likely to be due to differences in patient populations. Thus, low D_2 receptor availability might be related to a positive psychostimulant experience in HC subjects, but not in CCD subjects. In this scenario, low D_2 receptor availability might play a role in the initial development of the addictive behavior, but once addiction is established, it might not affect the maintenance of drug-seeking behavior.

D_2 receptor availability and cocaine-taking behavior. The most difficult aspect of treating cocaine abusers is their propensity to relapse after a period of abstinence. In fact, about 75% of 'detoxified' cocaine abusers relapse within a year of withdrawal (Carroll *et al*, 1994; Whiters *et al*, 1995). Cocaine abusers often describe their relapse as being precipitated by cocaine craving, which might be triggered by environmental stimuli associated with cocaine use, or by a 'priming' dose of cocaine itself (Childress *et al*, 1993). Thus, the identification of neurobiological factors that would confer vulnerability to relapse might provide important avenues for treatment. The cocaine-primed drug-taking behavior in the presence of an alternative reinforcer, as measured in the laboratory, provides a behavioral measure that, combined with brain imaging, might help to identify the neurobiological factors associated with the vulnerability to relapse.

The results from the cocaine self-administration study revealed the difference between drug liking and drug-taking behavior. Subjects reported no differences in the positive effects of a 6 mg dose of smoked cocaine and that of placebo. However, when asked to choose between this 6 mg dose and a $5 voucher (an amount worth more than the dose of drug), they chose the doses of cocaine more often than when given the choice between money and placebo. Furthermore, no correlation was seen between the positive effects reported by each subject from the sample dose and their subsequent choice for that dose in the multiple dose session.

These findings are in line with other behavioral studies of substance abuse which show that the reinforcing effects of drugs of abuse are more complex than simply the pleasurable or euphorigenic effects they produce (Fischman *et al*, 1990; Robinson and Berridge, 1993; Foltin and Fischman, 1996). Fischman (1989), have previously shown that the reinforcing effects of cocaine can be separated from the subjective effects in the laboratory. In a study of chronic cocaine abusers, subjects presented with a dose of cocaine that was too low to produce subjective effects, still chose cocaine over placebo (Fischman, 1989). In a similar study, Lamb *et al* (1991) demonstrated that opiate-dependent subjects would work to self-administer morphine, despite the fact that the dose was too low to be distinguished from placebo. Previous studies have also shown that medications that decrease the positive subjective effects of cocaine do not necessarily decrease its consumption (Fischman *et al*, 1990; Haney *et al*, 1999; Evans *et al*, 2001). Overall, these studies demonstrate that the reinforcing effects of cocaine involve neural pathways beyond those mediating drug-induced euphoria.

In this study, D_2 receptor availability in the LST was not predictive of the drug-taking behavior following a priming dose of cocaine. To the extent that this laboratory paradigm adequately models subject's behavior in the natural environment, this result indicate that this neurobiological parameter does not significantly affect the risk of relapse following initial exposure to cocaine in CCD subjects.

CONCLUSION

The data from this study, by replicating the results of previous studies (Volkow *et al*, 1990, 1993, 1997), add to a growing body of evidence that low D_2 receptor availability is associated with chronic cocaine abuse in human subjects. This study expanded on previous studies by demonstrating that D_2 receptor availability is decreased in each functional subdivision of the striatum. Whether this decreased density is a consequence of chronic cocaine exposure or represents a vulnerability to develop this addiction remains to be firmly established. In addition, this study did not detect a relationship between D_2 receptor availability and the positive subjective effects of cocaine or drug-taking behavior following a priming dose of cocaine within the CCD group. Thus, D_2 receptor availability per se might not play a significant role in the maintenance of the addictive behavior. Additional studies are warranted to unravel neurobiological factors that might affect the risk of relapse.

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