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Dopamine D1 Receptors in Cocaine Dependence Measured with PET and the Choice to Self-Administer Cocaine

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The goal of this study was to determine D_1 receptor availability in human cocaine-dependent (CD) subjects and matched healthy controls (HCs). In addition, the CD subjects performed cocaine self-administration sessions in order to explore the association between D_1 receptor availability and cocaine-seeking behavior. Twenty-five CD subjects (40 ± 4 years, 19M/6 F) and 23 matched HCs (38 ± 4 years, 19M/4F) were scanned with PET and the radiotracer [^{11}C]NNC 112. During the cocaine self-administration sessions, CD volunteers were given the choice to self-administer cocaine (0, 6, and 12 mg) or to receive a monetary voucher worth $5. D_1 receptor availability was measured in the limbic, associative, and sensori-motor striatum in addition to cortical brain regions. No difference in D_1 receptor availability was seen between the two groups. A negative association was seen between D_1 receptor BP_{ND} in the limbic striatum and the choice for the 6 mg dose of cocaine ($r = -0.47$, $p = 0.02$, corrected for age). These results do not support the hypothesis that cocaine dependence is associated with a reduction in D_1 receptor availability in the striatum. However, within the CD subjects, low D_1 receptor availability in the ventral striatum was associated with the choice to self-administer cocaine, suggesting that low D_1 receptor availability may be associated with an increased risk of relapse in cocaine dependence.
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INTRODUCTION

Recent studies investigating the role of the D_1 receptor in animal models of cocaine dependence suggest that increased signaling, at this receptor, may provide a novel treatment approach for this disorder (Self *et al*, 1996a, 2000). In animal models of cocaine dependence, the administration of a D_1 agonist attenuates cocaine-seeking behavior elicited by a priming dose of cocaine in rodents and non-human primates (De Vries *et al*, 1999; Dias *et al*, 2004; Khroyan *et al*, 2000; Self *et al*, 1996a). Similar results have shown that a D_1 agonist also reduces cue-induced cocaine-seeking behavior (Alleweireldt *et al*, 2002). In a related study, rats with higher preferred levels of cocaine self-administration were found to be less sensitive to D_1-mediated inhibition of cocaine-seeking behavior, compared with rats having lower levels of cocaine intake (Edwards *et al*, 2007). Alternatively, D_1 antagonists administered directly into the nucleus accumbens have been shown to increase cocaine self-administration in rodents (Caine *et al*, 1995; Maldonado *et al*, 1993). Taken together, these data suggest that excessive cocaine self-administration may be associated with a loss of signaling at the D_1 receptor, and that D_1 receptor blockade in the nucleus accumbens may increase the risk of relapse.

In line with this theory, it might be expected that cocaine dependence is associated with a decrease in D_1 receptor availability. However, earlier studies in rodents and non-human primates have shown both a decrease (Farfel *et al*, 1992; Kleven *et al*, 1990; Moore *et al*, 1998), as well as an increase (Lim *et al*, 1990; Nader *et al*, 2002; Unterwald *et al*, 1994) in striatal D_1 receptors after chronic exposure to cocaine. In humans, a post-mortem study showed that striatal D_1 receptor mRNA was unchanged in chronic cocaine abusers, although D_1 receptor density was not measured (Meador-Woodruff *et al*, 1993). Only one earlier study has used PET imaging to measure changes in D_1 receptor binding associated with cocaine exposure, and this study showed a significant decrease in rodents exposed to cocaine for at least 7 days (Tsukada *et al*, 1996).

In order to investigate the effects of cocaine dependence on D_1 receptor availability, we used PET and the radiotracer [^{11}C]NNC 112 in a group of human cocaine-dependent (CD)

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subjects and matched healthy controls (HCs). Following the PET scans, the CD subjects underwent cocaine self-administration sessions in order to explore the association between D_1 receptor availability and cocaine-seeking behavior. Animal studies have shown that a priming dose of cocaine reinstates cocaine self-administration (Khroyan *et al*, 2000; Self *et al*, 1996a; Shaham *et al*, 2003), and a similar laboratory model has been developed for human subjects (Foltin *et al*, 2003; Martinez *et al*, 2004). In this model, non-treatment seeking, recently detoxified CD volunteers were given the choice to self-administer cocaine over an alternative reinforcer (money) after a response-independent ('priming') dose of cocaine. The self-administration sessions provide a measure of each subject's vulnerability to the reinforcing effects of cocaine, which can then be correlated with D_1 receptor availability. Our hypotheses were: (1) cocaine dependence would be associated with a decrease in D_1 receptor availability in the ventral striatum (VST), and (2) the CD subjects with the lowest D_1 receptor availability in the VST would be more likely to choose cocaine over an alternative reinforcer, in the self-administration sessions.

MATERIALS AND METHODS

Human Subjects

The study was approved by the Institutional Review Board of the New York State Psychiatric Institute. All subjects provided written informed consent. The CD volunteers were medically healthy, and fulfilled the DSM-IV criteria for cocaine dependence, with no other current axis I diagnosis. The CD participants had weekly cocaine use greater than the amount of cocaine used in this study, and tested positive for cocaine (urine toxicology) at screening. They were not seeking treatment, but were informed that a referral for treatment was available. CD subjects were required to use alcohol or cannabis less than twice a week and no use of prescription medications or other illicit drugs was permitted in the 6 months prior to study entry. Seventeen of the CD subjects had been scanned with another radiotracer in an earlier reported study (Martinez *et al*, 2004). HC subjects were between the ages of 21 and 45 and had no current or past DSM-IV Axis I disorder. Nicotine dependence was acceptable for both groups.

The CD subjects were admitted to the Irving Center for Clinical Research at the New York Presbyterian Hospital and underwent random urine tests to confirm abstinence. The PET scans were performed after 14 days of abstinence, and the cocaine self-administration sessions were performed 2–3 days after the PET scans.

PET Scan Acquisition

[^{11}C]NNC 112 was synthesized as described previously (Halldin *et al*, 1998), and injected intravenously over 45 s after a transmission scan. Emission data were acquired using the ECAT EXACT HR+ camera in 3D mode for 90 min, as described previously (Abi-Dargham *et al*, 2000). The arterial input was obtained by collecting arterial samples every 10 s with an automated sampling system (for the first 2 min) followed by manual samples at longer intervals, for a total of 30 samples. Six samples were collected (at 2, 8, 16, 30, 50, and 70 min) and further processed by high-pressure liquid chromatography to measure the percent of plasma activity representing unmetabolized (parent) [^{11}C]NNC 112. The measured input function values (C_a(t), μCi/ml) were analyzed as described previously and used for the kinetic analysis of the regional brain uptake (Abi-Dargham *et al*, 2000). The clearance of the parent compound (C_L, l/h) was calculated as the ratio of the injected dose to the area under the curve of the input function. The plasma-free fraction (f_P), was calculated as the ratio of the ultrafiltrate to the total activity concentration as described previously (Abi-Dargham *et al*, 2000).

PET Image Analysis

Image analysis was performed in MEDx (Sensor Systems, Inc., Sterling, VA) using a region of interest (ROI) analysis as described previously (Abi-Dargham *et al*, 2000). Correction for head movement and co-registration of the PET data to the MR were performed using the automated image registration (Woods *et al*, 1992, 1993). The ROIs were identified on each individual subject's MRI, acquired on the GE 1.5 T Signa Advantage system. The ROIs included both cortical and subcortical regions. The subcortical regions included the striatum (STR), amygdala, and hippocampus. The STR was divided into the caudate, putamen, and VST. The caudate and putamen were further subdivided along their rostral-caudal axis using the anterior commissure to derive the following ROIs: (1) preDCA (pre-commissural dorsal caudate), (2) preDPU (pre-commissural dorsal putamen), (3) the postCA (post-commissural caudate), and (4) the postPU (post-commissural putamen). The striatal ROIs were classified as belonging to the limbic striatum (LST), associative striatum, or sensori-motor striatum, based on cortical connectivity (for reviews, see Haber and Fudge, 1997; Joel and Weiner, 2000). The LST corresponded to the VST, the associative striatum activity was derived as the spatially weighted average of the activities in the preDCA, preDPU, and postCA, and the sensori-motor striatum corresponded to the postPU. Details of the anatomical criteria and functional classification of the STR have been described previously (Martinez *et al*, 2003). The cortical regions included the dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex, parietal cortex, temporal cortex, occipital cortex, and anterior cingulate cortex as described previously (Abi-Dargham *et al*, 2000). A segmentation procedure was implemented for the cortical regions so that only the voxels classified as gray matter were used to measure the activity distribution (Abi-Dargham *et al*, 2000). For all bilateral regions, right and left values were averaged.

PET Outcome Measures

The regional distribution volumes (V_T, milliliter of plasma per gram of tissue) were derived with a kinetic analysis using the arterial input function as described previously (Abi-Dargham *et al*, 2000). A one-tissue compartment was used in the cerebellum (CER), and a two-tissue compartment in other regions. D_1 receptor availability was calculated with two outcome measures: [^{11}C]NNC 112

binding potential (BP_P, ml/g) and the specific to non-specific partition coefficient (BP_{ND}, unitless) (Innis *et al*, 2007; Slifstein and Laruelle, 2001).

BP_P and BP_{ND} are defined as:

$$BP_p = V_{T\,ROI} - V_{T\,CER} = f_p * \frac{B_{MAX}}{K_{D'}}$$

$$BP_{ND} = \frac{V_{T\,ROI-}\,V_{T\,CER}}{V_{T\,CER}} = f_{ND} * \frac{B_{MAX}}{K_{D'}}$$

V_T ($ml\,g^{-1}$) is the regional tissue distribution volume for the ROIs and CER, fND is the free fraction in the non-specific distribution volume of the brain, f_P is the free fraction in the plasma, *B*max is the concentration of D_1 receptors (nmol/g of tissue), and $K_{D'}$ is the *in vivo* equilibrium dissociation constant of the radiotracer in the presence of dopamine (Slifstein and Laruelle, 2001). V_TCER was measured for each subject in order to ensure that there was no difference in non-specific binding between the two groups. The contribution of total plasma activity to the regional time activity data was calculated assuming a fixed 5% blood volume in the ROIs(Mintun *et al*, 1984). It should be noted that [^{11}C]NNC 112 labels both the D_1 and D_5 receptors, and the term D_1 is used to denote both receptors.

Self-Administration Sessions

The CD subjects underwent two types of cocaine self-administration sessions: sample sessions and choice sessions. In the sample sessions, the subjects self-administered a single dose of smoked cocaine (0, 6, or 12 mg of cocaine, one session of each dose per subject). The subjects were asked to rate the subjective effects at baseline, and at 4, 14, 30, and 60 min after the dose. The computerized subjective effects battery consisted of visual analog scales labeled 'not at all' at 0 mm and 'extremely' at 100 mm, as described previously (Foltin *et al*, 1990). A previous cluster analysis showed that the visual analog scale 'good drug effect', 'high', and 'stimulated' can be grouped into the positive effects cluster (Evans *et al*, 2002). The positive effects cluster was chosen *a priori* for correlation with D_1 receptor availability. For each visual analog scale, the area under the curve was calculated relative to the baseline score and the positive effects score was derived as the average area under the curve for the visual analog scale within this cluster.

In the choice sessions, the CD subjects underwent three cocaine self-administration sessions with 0, 6, and 12 mg doses of smoked cocaine presented in counterbalanced order, as described previously (Foltin *et al*, 2003; Martinez *et al*, 2004). Each session began with a response-independent or 'priming' dose of cocaine (0, 6, or 12 mg). After this dose, subjects were given the choice between the same dose of cocaine or a $5 merchandize voucher redeemable at local stores and paid upon discharge. The subjects were presented with this choice five times, spaced 14 min apart. Participants were required to press a space bar in order to receive their choice using a progressive ratio (200, 600, 1000, 1400, and 1600 responses required). The outcome measure for the choice sessions was the number of times a given dose of cocaine was chosen over voucher (range 0–5).

Statistical Analysis

Group demographic comparisons were performed with unpaired *t*-tests. Differences in [^{11}C]NNC 112 BP_P and BP_{ND} between the CD and HC were analyzed by multivariate analysis of variance. The vector of regional BP_P and BP_{ND} measurements was the multivariate statistic. *Post hoc* tests, when indicated, were performed by region, controlling the false discovery rate at the $\alpha = 0.05$ level. Regional volumes were also compared across groups by multivariate analysis of variance. Unpaired *t*-tests were used to compare differences in scan parameters, V_{TCER} and f_1 between the two groups.

The correlation of D_1 receptor availability and cocaine-seeking behavior was analyzed by linear regression between BP_P and BP_{ND} and the choice for cocaine. For this analysis, the VST was chosen *a priori* for correlation with the choice for a 6 mg dose of cocaine. Exploratory analysis was performed to examine the correlation between receptor availability and the positive effects of cocaine. A two-tailed probability value of $p < 0.05$ was chosen as the level of significance for these analyses.

RESULTS

Group Comparison

Twenty-five CD subjects and 23 HC subjects were enrolled in this study. The group demographics are shown in Table 1. Here, of the 25 CD subjects, one completed the PET scans and the self-administration sample session, but not the choice session because of a scheduling conflict. The CD subjects had been smoking crack cocaine for an average of 16.4 ± 4.5 years and had spent an average of $\$264 \pm \$118$/week over the last 6 months.

Table 1 Group demographics

Parameter	HC	CD	*p*
n	23	25	—
Age (mean ± SD, years)	38 ± 4	40 ± 4	0.33
Gender (Male/Female)	19M/6F	19M/4F	—
Ethnicity (Afro-American/Hispanic/Caucasian not Hispanic)	16AA/4H/5C	12AA/5H/6C	0.61
Smoking status (Yes/Ex/No)	16Y/3E/4N	19Y/3E/3N	0.53
Mean ± cigarettes per day in smokers	11 ± 8	11 ± 4	0.82

CD, cocaine dependent; HC, healthy control.

PET Scan Parameters

There was no significant difference between the two groups with respect to injected dose (HC: 14.3 ± 3.4 mCi, CD: 13.1 ± 4.2 mCi; $p = 0.38$) or specific activity (HC: 1007 ± 456 Ci/mmol, CD: 969 ± 454 Ci/mmol; $p = 0.77$). Plasma clearance did not differ between groups (HC: 83.6 ± 31.2 l/h, CD: 93.0 ± 27.4 l/h; $p = 0.28$) nor did the plasma free fraction (f_1) (HC: 0.88 ± 0.41%, CD: 0.86 ± 0.36%; $p = 0.89$). The volume of distribution of the cerebellum (V_{TCER}) was 2.17 ± 0.49 ml/g in HC subjects and 2.32 ± 0.46 ml/gin CD subjects ($p = 0.28$).

The volumes of the ROI for each group were analyzed with a multivariate analysis of variance, which did not show a significant volume difference between groups (Hotelling's trace, $p = 0.102$). Two regions did have low p values when unpaired t-tests were applied on individual regions (orbitofrontal cortex, $p = 0.013$ and temporal cortex, $p = 0.015$), but these did not survive multiple comparison correction by the false discovery rate criterion.

D_1 Receptor Availability

Representative PET scans are shown in Figure 1. There was no significant difference between groups for BP_P and BP_{ND} (multivariate analysis of variance, $p = 0.35$ for BP_P and $p = 0.219$ for BP_{ND}). The values are provided in Table 2. Unpaired t-tests on individual regions did not reach significance after correction for multiple comparisons according to the false discovery rate criterion. Although a decrease in BP_P and BP_{ND} was seen in the VST in the CD subjects compared with HCs, this difference did not reach significance.

Cocaine Self-Administration Session Results

In the sample sessions, the positive effects of cocaine varied with the dose. The area under the curve of the positive effects cluster of the 12 mg dose (314 ± 622) was higher than that of the 0 mg (135 ± 441) and 6 mg doses (151 ± 419) ($p < 0.05$ for both comparisons). No significant difference was seen between the positive effects of the 0 and 6 mg doses ($p = 0.30$). As 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 PET scan data.

In the choice sessions, subjects could choose cocaine 0–5 times. The 0 mg dose was chosen on an average of 0.33 ± 1.05 times, the 6 mg dose was chosen 1.58 ± 1.67 times, and the 12 mg dose was chosen 3.21 ± 1.61 times. The 12 mg dose was chosen more frequently than both the 0 and 6 mg dose ($p < 0.001$ for both cases), and the 6 mg dose was also chosen more frequently than the 0 mg dose ($p = 0.002$). 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 PET data. The coefficient of variation was higher for the 6 mg dose (1.05) compared with the 12 mg (0.50). Therefore, the 6 mg was chosen *a priori* for comparison with the PET data.

Relationship Between Pet Data and Cocaine Self-Administration

As shown in Figure 2, there was a significant negative correlation between D_1 receptor BP_{ND} in the VST and the choice for cocaine ($r = -0.47$, $p = 0.02$, corrected for age), such that the CD subjects with the lowest values for BP_{ND} were more likely to choose a 6 mg dose of smoked cocaine. Exploratory analysis with the other striatal ROIs failed to show significant association between choice and BP_{ND} (preDCA: $r = 0.27$, $p = 0.21$; preDPU: $r = 0.19$, $p = 0.37$; postCA: $r = 0.12$, $p = 0.60$; postPU: $r = 0.05$, $p = 0.83$; STR: $r = 0.23$, $p = 0.30$). No correlation was seen between BP_P in the VST, or any other ROI, and the choice to self-administer 6 mg cocaine. No correlation was seen between BP_P or BP_{ND} in any brain region and the choice to self-administer the 12 mg dose of cocaine. No correlation was seen between BP_P or BP_{ND} and the positive effects of the 12 mg dose of cocaine.

A significant negative correlation was also seen between BP_{ND} in the VST and years of cocaine use ($r = -0.59$,

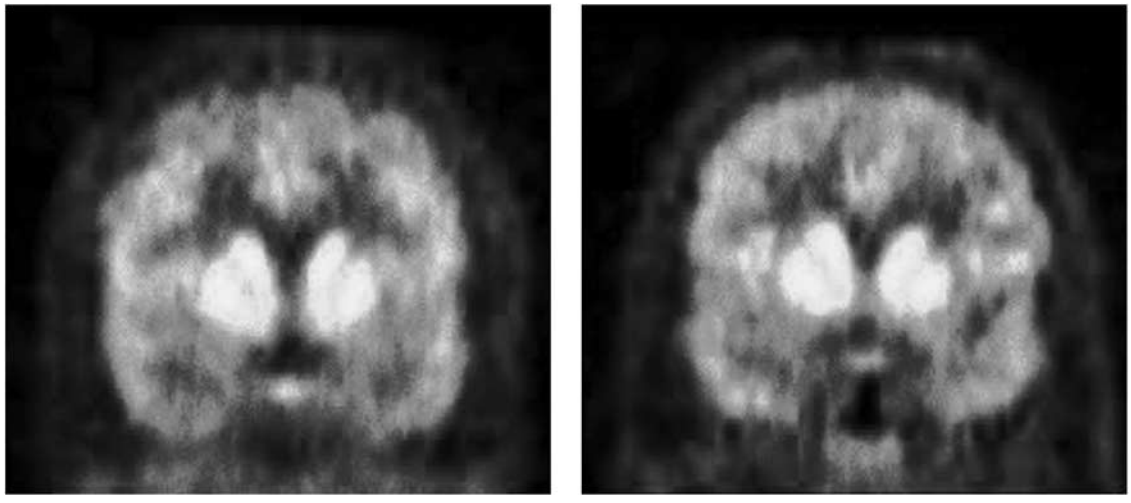

Figure 1 [^{11}C]NNC 112 distribution in a healthy control subject (left) and a cocaine-dependent subject (right). Both images are the mean of data acquired from 0–90 min and the image display was corrected for injected dose. The selected images include the striatum rostral to the anterior commissure. No significant difference in D_1 receptor availability was seen between the two groups.

Table 2 [^{11}C]NNC 112 binding potential (BP_P, ml/g) and specific to non-specific partition coefficient (BP_{ND}, unitless)

	BP_P		BP_{ND}	
Region of interest	**HC**	**CD**	**HC**	**CD**
Striatum				
Ventral striatum	5.03 ± 1.61	4.89 ± 1.11	2.32 ± 0.51	2.13 ± 0.43
Pre-commissural dorsal caudate	6.02 ± 1.57	6.19 ± 1.32	2.78 ± 0.43	2.67 ± 0.33
Post-commissural dorsal caudate	4.38 ± 1.38	4.81 ± 1.36	2.06 ± 0.37	2.02 ± 0.46
Pre-commissural dorsal putamen	6.69 ± 1.76	6.70 ± 1.28	3.08 ± 0.43	2.91 ± 0.33
Post-commissural dorsal putamen	6.15 ± 1.81	6.45 ± 1.26	2.82 ± 0.46	2.80 ± 0.32
Subcortical				
Amygdala	1.08 ± 026	1.18 ± 0.34	0.51 ± 0.11	0.51 ± 0.12
Hippocampus	0.66 ± 0.26	0.63 ± 0.20	0.31 ± 0.11	0.27 ± 0.07
Cortical				
Dorsolateral prefrontal cortex	1.18 ± 0.37	1.10 ± 0.30	0.55 ± 0.12	0.47 ± 0.09
Medial prefrontal cortex	1.41 ± 0.40	1.35 ± 0.27	0.65 ± 0.13	0.59 ± 0.08
Orbitofrontal cortex	1.00 ± 0.35	0.97 ± 0.37	0.47 ± 0.15	0.42 ± 0.13
Anterior cingulate	1.54 ± 0.43	1.57 ± 0.38	0.71 ± 0.13	0.68 ± 0.12
Temporal cortex	1.25 ± 0.33	1.27 ± 0.30	0.58 ± 0.10	0.55 ± 0.09
Parietal cortex	1.24 ± 0.38	1.14 ± 0.29	0.57 ± 0.13	0.49 ± 0.08
Occipital cortex	1.24 ± 0.39	1.22 ± 0.28	0.58 ± 0.13	0.53 ± 0.08

CD, cocaine dependent; HC, healthy control.
Values are Mean ± SD. No significant differences were seen between the two groups.

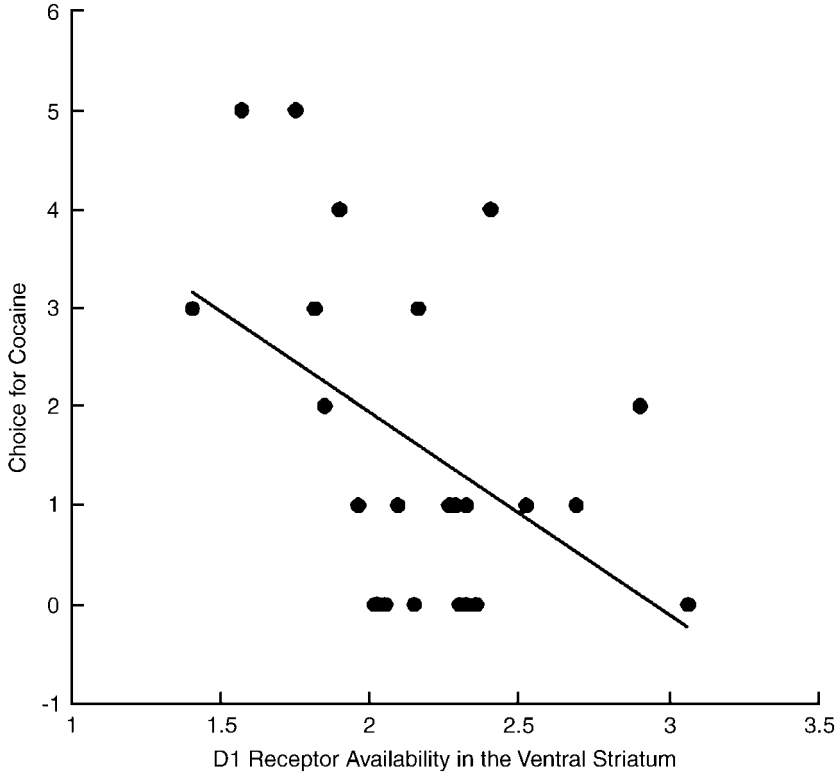

Figure 2 Correlation between [^{11}C]NNC 112 BP_{ND} in the VST (*x* axis) and the choice to self-administer 6 mg doses of cocaine (*y* axis, range 0–5). A significant correlation was found between D_1 receptor availability and the choice to self-administer cocaine over an alternative reinforcer (voucher worth $5) ($r = -0.47$, $p = 0.02$, corrected for age).

$p = 0.01$, corrected for age). Exploratory analysis failed to detect significant correlation between years of use and BP_{ND} or BP_P in any other striatal region.

DISCUSSION

The results of this study do not support the hypothesis that D_1 receptor availability, measured with PET and the radiotracer [^{11}C]NNC 112, is reduced in the VST of CD subjects compared with HCs. However, within the CD subjects, low D_1 receptor availability in the VST may be associated with the choice to self-administer cocaine. In this study, an association was seen between [^{11}C]NNC 112 BP_{ND} (although not BP_P) in the VST and the choice to self-administer the 6 mg dose of smoked cocaine.

D_1 Receptor Availability and Cocaine Dependence

In this dataset, we found no significant difference in [^{11}C]NNC 112 BP_P or BP_{ND} in each of the investigated ROIs. Although this finding is in agreement with a human post-mortem study reporting that striatal D_1 receptor mRNA is unchanged after chronic cocaine exposure (Meador-Woodruff *et al*, 1993), pre-clinical studies investigating this effect have not been consistent. Earlier studies in rodents have reported both an increase and a decrease in striatal D_1 receptors after cocaine exposure (Kleven *et al*, 1990; Lim *et al*, 1990; Unterwald *et al*, 1994). To our knowledge, only one earlier study has used PET imaging and the radiotracer [^{11}C]SCH23390 to measure changes D_1 receptor binding, and this study showed a significant decrease in BP_{ND} in rodents after at least 7 days of cocaine administration (Tsukada *et al*, 1996).

Studies in non-human primates have also shown conflicting results. Two studies in rhesus monkeys have reported a decrease in D_1 receptor binding after cocaine exposure. Farfel *et al* reported that 14 days of experimenter-administered cocaine followed by 14 days withdrawal resulted in a decrease in D_1 receptor density in the caudate, with no change in the nucleus accumbens (Farfel *et al*, 1992). A subsequent study used [^{3}H]SCH23390 to label the D_1 receptor, and reported decreased binding in the nucleus accumbens in rhesus monkeys who self-administered cocaine for 18–22 months (Moore *et al*, 1998). However, two other studies in rhesus monkeys have used [^{3}H]SCH23390 to label the D_1 receptor and shown increases in receptor binding after cocaine self-administration. The study by Nader *et al* (Nader *et al*, 2002) showed that 100 days of cocaine self-administration increased D_1 receptor binding in the dorsolateral and ventromedial caudate and putamen in addition to the shell of the nucleus accumbens. More recently, Beveridge *et al* (Beveridge *et al*, 2008) used the same paradigm and showed similar results, but also showed that D_1 receptor binding returned to baseline after 90 days of abstinence. Overall, these data in animals suggest that D_1 receptor availability may vary with respect to the duration of cocaine exposure and abstinence, and a recent study in rodents also showed that D_1 receptor binding varies with the time of withdrawal (Ben-Shahar *et al*, 2007). In this study, the CD participants had a long history of cocaine exposure, such that the design of this study is more in line with that of Moore *et al* (Moore *et al*, 1998). Although we saw a decrease in striatal D_1 receptor availability, it was not significant. However, it is possible that D_1 receptor BP might have been lower had we performed the PET scans after a shorter duration of abstinence. In other words, it is possible that the cocaine subjects had lower D_1 receptor BP prior to the 14 days of abstinence, and in this study, they were scanned as D_1 receptor density was returning to baseline.

Another potential issue that must be considered in this study is that of cigarette smoking. An earlier PET study using the radiotracer [^{11}C]NNC 112 reported a decrease in D_1 receptor availability in the VST of cigarette smokers compared with non-smokers (Dagher *et al*, 2001). In this study, subjects were matched for smoking, so it is unlikely that smoking status was a source of artifact. Nevertheless, we performed a two-way ANOVA with group (HC and CD) and smoking status (non-smokers and ex-smokers pooled) as treatments. In fact VST BP_{ND} was higher among smokers than non-smokers at trend level (smokers $= 2.30 \pm 0.46$, non-smokers $= 2.04 \pm 0.46$, $p = 0.078$), though the group by smoker interaction was not significant ($p = 0.613$).

It is also possible that this study lacked the power to detect a between group difference. If the variance observed in this study is taken as an estimate of population variance, then the between group difference in BP_{ND} required to reach significance would be about 17% (for $\alpha = 0.05$ critical level and $1-\beta = 0.8$ power). However, we saw only a non-significant decrease of 8% in BP_{ND} in the VST, and less of a difference in the other striatal regions.

D_1 Receptor Transmission and Cocaine Dependence

Earlier pre-clinical studies have shown conflicting results with respect to the effects of D_1 agonist and antagonist administration on the behavioral effects of cocaine administration. Earlier studies have shown that D_1 agonists reduce cocaine-seeking behavior (De Vries *et al*, 1999; Milivojevic *et al*, 2004; Self *et al*, 1996b), decrease cocaine self-administration (Barrett *et al*, 2004; Caine *et al*, 1999), and increased the latency for cue-induced cocaine-seeking behavior (Alleweireldt *et al*, 2002). In addition, a recent study in D_1 knockout mice showed that the D_1 receptor is crucial for mediating the reinforcing effects of cocaine (Caine *et al*, 2007). Similar results have been reported in non-human primates (Katz and Witkin, 1992; Khroyan *et al*, 2000; Mutschler and Bergman, 2002; Platt *et al*, 2001). However, the opposite effect has also been shown, in which D_1 antagonist administration attenuates priming- and cue-induced cocaine-seeking behavior (Alleweireldt *et al*, 2002; Barrett *et al*, 2004; Khroyan *et al*, 2000, 2003; Kleven and Woolverton, 1990), blocks cocaine-induced conditioned place preference (Baker *et al*, 1998; Nazarian *et al*, 2004), and blocks the reinstatement of cocaine self-administration (Bachtell *et al*, 2005; Schmidt and Pierce, 2006). In short, some studies show that D_1 receptor activation may inhibit cocaine-seeking behavior, whereas other studies suggest that D_1 receptor blockade may have a more beneficial effect.

Studies in humans, although limited, suggest that stimulation of D_1 receptors in humans may reduce the reinforcing effects of cocaine, whereas blockade of the D_1 receptor enhances the reinforcing effects. In a study of CD

participants, the D_1 antagonist SCH 39166 has been shown to increase both cocaine self-administration in addition to the subjective measures of 'High,' 'Stimulated,' and 'Good Drug Effect' (Haney *et al*, 2001). Alternatively, the administration of ABT-431, a full agonist at the D_1 receptor, to CD subjects significantly decreased the positive subjective effects of cocaine (Haney *et al*, 1999). ABT-431 did not significantly affect cocaine self-administration, although its dosage is limited in humans because of its side effects.

D_1 Receptor Availability and the Addictive Phenotype

In this study, low D_1 receptor availability correlated with both the choice to self-administer low-dose cocaine and years of cocaine use. This finding suggests that low D_1 receptor binding potential may be indicative of a particular phenotype. CD subjects with low D_1 receptor binding may have a more severe addiction, such that they are more vulnerable to the effects of a priming dose of cocaine and self-administer more cocaine. This is in agreement with the recent study investigating the 'addictive phenotype' in rodents (Edwards *et al*, 2007). In this study, rodents trained to self-administer cocaine were characterized as having higher *vs* lower preferred levels of cocaine intake. The rodents with higher levels of cocaine intake were found to be less sensitive to the effects of D_1 receptor agonist in reducing cocaine-induced reinstatement of cocaine-seeking behavior (Edwards *et al*, 2007). Notably, chronic cocaine exposure produces a persistent upregulation of cAMP-PKA pathways in the nucleus accumbens, which then weakens further D_1 receptor signaling and down-regulates D_1 receptor expression (Self, 2004; Ventura and Sibley, 2000). Thus, we had hypothesized that cocaine dependence would be associated with a decrease in D_1 receptor binding compared with HCs. Although we did see a decrease in [^{11}C]NNC 112 BP_{ND} in the LST, it was not significant (BP_{ND} was 2.32 in HC *vs* 2.13 in CD, $p = 0.17$, two group *t*-test, not corrected for multiple observations). However, the possibility remains that CD subjects who chose to self-administer higher doses of cocaine may represent a phenotype in which D_1 receptor binding is decreased in the LST. In order to test this hypothesis, we performed a *post hoc* analysis, in which the CD subjects were divided into two groups: those who self-administered 0 or 1 dose of cocaine and those who self-administered 2–5 doses of cocaine. This analysis showed that the low (0–1) self-administration group had a higher D_1 receptor BP_{ND} compared with those who self-administered 2–5 doses of cocaine (BP_{ND} was 2.32 in low self-administration group *vs* 2.13 in the high self-administration group, $p = 0.04$). This finding is consistent with the hypothesis that a phenotype of CD subjects with low D_1 receptor binding in the VST may represent a group with greater vulnerability to the reinforcing effects of cocaine.

Study Limitations

The limitations of this study include the lack of a significant correlation between BP_P and the choice to self-administer cocaine, the lack of a correlation between the choice to administer the 12 mg dose of cocaine and BP_{ND}, and the lack of selectivity of [^{11}C]NNC 112 for D_1 *vs* serotonin type 2A receptor (5-HT2A) receptors (Slifstein *et al*, 2007). Although there was evidence of a negative correlation between [^{11}C]NNC 112 BP_P and the choice to self-administer the 6 mg dose of cocaine, this was not significant ($r = -0.30$, $p = 0.19$). Thus, it is possible that this study lacked the power to detect a correlation with BP_P, given that this outcome measure has a higher variability than BP_{ND}. The lack of a correlation between the 12 mg dose of cocaine and [^{11}C]NNC 112 binding (both BP_P and BP_{ND}) may be because of the lower coefficient of variation seen with the 12 mg self-administration sessions. The majority of subjects (17 of 24) self-administered 3 or more doses of the 12 mg dose in the cocaine self-administration sessions, so that there may have been insufficient variability to detect a correlation. Lastly, although $\sim$30% of the binding of [^{11}C]NNC 112 can be attributed to the 5-HT2A receptor in the cortex, there does not appear to be any significant binding to the 5-HT2A receptor in the STR (Slifstein *et al*, 2007). The same is also true for [^{11}C]SCH23390, so that the difference seen between this study and that of Tsukada *et al* (Tsukada *et al*, 1996) cannot be attributed to this issue.

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The authors report no conflicts of interest associated with the content of this paper.
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