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Dopamine D₁ receptors in cocaine dependence measured with PET and the choice to self-administer cocaine

Diana Martinez, MD¹, Mark Slifstein, PhD¹, Rajesh Narendran, MD¹, Richard W Foltin, PhD¹, Allegra Broft, MD¹, Dah-Ren Hwang, PhD¹, Audrey Perez, RN¹, Anissa Abi-Dargham, MD¹, Marian W Fischman, PhD¹, Herbert D Kleber, MD¹, and Marc Laruelle, MD^{1,2}

¹Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY

²Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY

Abstract

Objective—The goal of this study was to determine D₁ receptor availability in human cocaine dependent (CD) subjects and matched healthy controls (HC). In addition, the cocaine dependent subjects performed cocaine self-administration sessions in order to explore the association between D₁ receptor availability and cocaine seeking behavior.

Methods—25 cocaine dependent subjects (40 ± 4 yrs, 19M/6 F) and 23 matched healthy controls (38 ± 4 yrs, 19M/4F) were scanned with PET and the radiotracer [¹¹C]NNC 112. During the cocaine self-administration sessions, cocaine dependent volunteers were given the choice to self-administer cocaine (0, 6, and 12 mg) or to receive a monetary voucher worth \$5. D₁ receptor availability was measured in the limbic, associative and sensori-motor striatum in addition to cortical brain regions.

Results—No difference in D₁ receptor availability was seen between the two groups. A negative association was seen between D₁ 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).

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Correspondence to: Diana Martinez.

Corresponding Author Diana Martinez, M.D. New York State Psychiatric Institute 1051 Riverside Drive, Box #31 New York, NY 10032 Telephone: (212) 543-6628 Fax: (212) 568-6171.

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Conclusions—These results do not support the hypothesis that cocaine dependence is associated with a reduction in D₁ receptor availability in the striatum. However, within the cocaine-dependent subjects, low D₁ receptor availability in the ventral striatum was associated with the choice to self-administer cocaine, suggesting that low D₁ receptor availability may be associated with an increased risk of relapse in cocaine dependence.

Keywords

PET; D₁ receptor; cocaine; cocaine-seeking behavior; striatum; limbic striatum

Introduction

Recent studies investigating the role of the D₁ 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; Self et al., 2000). In animal models of cocaine dependence, the administration of a D₁ 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 D₁ 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 D₁ mediated inhibition of cocaine-seeking behavior compared to rats with lower levels of cocaine intake (Edwards et al., 2007). Alternatively, D₁ 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). Together, these data suggest that excessive cocaine self-administration may be associated with a loss of signaling at the D₁ receptor, and that D₁ 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 D₁ receptor availability. However, previous studies in rodents and non-human primates have demonstrated 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 D₁ receptors following chronic exposure to cocaine. In humans, a post-mortem study showed that striatal D₁ receptor mRNA was unchanged in chronic cocaine abusers, although D₁ receptor density was not measured (Meador-Woodruff et al., 1993). Only one previous study has used PET imaging to measure changes in D₁ receptor binding associated with cocaine exposure, and this study showed a significant decrease in rodents exposed to cocaine for at least seven days (Tsukada et al., 1996).

In order to investigate the effects of cocaine dependence on D₁ receptor availability, we used PET and the radiotracer [¹¹C]NNC 112 in a group of human cocaine dependent (CD) subjects and matched healthy controls (HC). Following the PET scans, the cocaine dependent subjects underwent cocaine self-administration sessions in order to explore the association between D₁ 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 cocaine dependent volunteers were given the choice to self-administer cocaine over an alternative reinforcer (money) following 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 D₁ receptor availability. Our hypotheses were: 1) cocaine dependence would be associated with a decrease in D₁ receptor availability in the ventral striatum, and; 2) the cocaine dependent subjects with the lowest D₁ receptor availability in the ventral striatum 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 cocaine dependent volunteers (CD) were medically healthy, and fulfilled 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 six months prior to study entry. Seventeen of the CD subjects had been scanned with another radiotracer in a previously reported study (Martinez et al., 2004). Healthy control subjects (HC) 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 following 14 days of abstinence, and the cocaine self-administration sessions were performed 2 to 3 days after the PET scans.

PET scan acquisition

[¹¹C]NNC 112 was synthesized as previously described (Halldin et al., 1998), and injected intravenously over 45 seconds following a transmission scan. Emission data were acquired using the ECAT EXACT HR+ camera in 3D mode for 90 minutes, as previously described (Abi-Dargham et al., 2000). The arterial input was obtained by collecting arterial samples every 10 seconds with an automated sampling system (for the first 2 minutes) 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 minutes) and further processed by high pressure liquid chromatography (HPLC) to measure the percent of plasma activity representing unmetabolized (parent) [¹¹C]NNC 112. The measured input function values ($C_a(t)$, $\mu\text{Ci/mL}$) were analyzed as previously described 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 previously described (Abi-Dargham et al., 2000).

PET image analysis

Image analysis was performed in MEDx (Sensor Systems, Inc., Sterling, Virginia) using a region of interest analysis as described previously (Abi-Dargham et al., 2000). Correction for head movement and coregistration of the PET data to the MR were performed using automated image registration (AIR) (Woods et al., 1992; Woods et al., 1993). The regions of interest (ROIs) were identified on each individual subject's MRI, acquired on the GE 1.5 T Signa Advantage system. The ROI's included both cortical and subcortical regions. The subcortical regions included the striatum (STR), amygdala (AMY), and hippocampus (HIP). The striatum was divided into the caudate, putamen, and ventral striatum (VST). The caudate and putamen were further subdivided along their rostral-caudal axis using the anterior commissure (AC) to derive the following ROIs: 1) pre-commissural dorsal caudate (preDCA), 2) pre-commissural dorsal putamen (preDPU), 3) the post-commissural caudate (postCA) and 4) the post-commissural putamen (postPU). The striatal 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 SMST corresponded to the postPU. Details of the anatomical criteria and functional classification of the striatum have been described previously (Martinez et al., 2003). The cortical regions included the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), and anterior cingulate cortex (ACC) 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 , mL of plasma / g of tissue) were derived with a kinetic analysis using the arterial input function as previously described (Abi-Dargham et al., 2000). A one tissue compartment was used in the cerebellum, 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 nonspecific partition coefficient (BP_{ND} , unitless) (Innis et al., 2007; Slifstein and Laruelle, 2001).

BP_p and BP_{ND} are defined as:

$$BP_p = V_{T\text{ ROI}} - V_{T\text{ CER}} = f_p * \frac{B_{MAX}}{K_D'} \quad BP_{ND} = \frac{V_{T\text{ ROI}} - V_{T\text{ CER}}}{V_{T\text{ CER}}} = f_{ND} * \frac{B_{MAX}}{K_D'}$$

V_T (mL g^{-1}) is the regional tissue distribution volume for the ROIs and cerebellum (CER), f_{ND} is the free fraction in the nonspecific distribution volume of the brain, f_p is the free

fraction in the plasma, B_{\max} is the concentration of D_1 receptors (nmoles per 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). $V_{\text{T CER}}$ 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 regions of interest (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 cocaine dependent 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, 1 session of each dose per subject). The subjects were asked to rate the subjective effects at baseline, and at 4, 14, 30, and 60 minutes following the dose. The computerized subjective effects battery consisted of visual analog scales (VAS) labeled “not at all” at 0 mm and “extremely” at 100 mm, as previously described (Foltin et al., 1990). A previous cluster analysis demonstrated that the VAS “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 VAS, the area under the curve (AUC) was calculated relative to the baseline score and the positive effects score was derived as the average AUC for the VAS within this cluster.

In the choice sessions, the CD subjects underwent three cocaine self-administration sessions with 0 mg, 6 mg, and 12 mg doses of smoked cocaine presented in counterbalanced order, as previously described (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). Following this dose, subjects were given the choice between the 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 minutes 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 (MANOVA). 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 (FDR) at the $\alpha = 0.05$ level. Regional volumes were also compared across groups by MANOVA. Unpaired t-tests were used to compare differences in scan parameters, $V_{\text{T CER}}$ 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 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 twenty-three HC subjects were enrolled in this study. The group demographics are shown in table 1. Of the 25 CD subjects, one completed the PET scans and the self-administration sample session but not the choice session due to a scheduling conflict. The CD subjects had been smoking crack cocaine an average of 16.4 ± 4.5 years and spent an average of $\$264 \pm \$118/\text{week}$ over the last six months.

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/mmoles, CD: 969 ± 454 Ci/mmoles; $p = 0.77$). Plasma clearance did not differ between groups (HC: 83.6 ± 31.2 L h⁻¹; CD: 93.0 ± 27.4 L h⁻¹, $p = 0.28$) nor did the plasma free fraction (f_1) (HC: $0.88 \pm 0.41\%$; CD: $0.86 \pm 0.36\%$, $p = 0.89$). The volume of distribution of the cerebellum (VT_{CER}) was 2.17 ± 0.49 mL g⁻¹ in HC subjects and 2.32 ± 0.46 mL g⁻¹ in CD subjects ($p = 0.28$).

The volumes of the regions of interest for each group were analyzed with a MANOVA, 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 (OFC, $p = 0.013$ and TC, $p = 0.015$) but these did not survive multiple comparison correction by the FDR criterion.

D₁ receptor availability

Representative PET scans are shown in figure 1. There was no significant difference between groups for BP_p and BP_{ND} (MANOVA, $p = 0.35$ 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 FDR criterion. Although a decrease in BP_p and BP_{ND} was seen in the ventral striatum in the cocaine dependent subjects compared to healthy controls, 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 AUC 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 ($p = 0.30$). 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 PET scan data.

In the choice sessions, subjects could choose cocaine 0 to 5 times. The 0 mg dose was chosen 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 mg 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 (%CV) was higher for the 6 mg dose (1.05) compared to 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 ventral striatum and the choice for cocaine ($r = -0.47$, $p = 0.02$, corrected for age), such that the cocaine dependent 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 ventral striatum, 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 ($r = -0.59$, $p = 0.01$, 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 ventral striatum of cocaine dependent subjects compared to healthy controls. However, within the cocaine dependent subjects, low D_1 receptor availability in the ventral striatum 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 ventral striatum 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 regions of interest investigated. While this finding is in agreement with a human postmortem study reporting that striatal D_1 receptor mRNA is unchanged following chronic cocaine exposure (Meador-Woodruff et al., 1993), pre-clinical studies investigating this effect have not been consistent. Previous studies in rodents have reported both an increase and decrease in striatal D_1 receptors following cocaine exposure (Kleven et al., 1990; Lim et al., 1990; Unterwald et al., 1994). To our knowledge, only one previous 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 following 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 following 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 [^3H]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 [^3H]SCH23390 to label the D_1 receptor and shown increases in receptor binding following 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 following 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 the present study, the cocaine dependent 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 following 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. A previous PET study using the radiotracer [^{11}C]NNC 112 reported a decrease in D_1 receptor availability in the ventral striatum of cigarette smokers compared to non-smokers (Dagher et al., 2001). In the present study, subjects were matched for smoking, so it is unlikely that smoking status was a source of artifact. Nevertheless, we performed a 2 way ANOVA with group (HC and CD) and smoking status (nonsmokers and ex-smokers pooled) as treatments. In fact VST BP_{ND} was higher among smokers than non-smokers at trend level (smokers = 2.30 ± 0.46 , non-smokers = 2.04 ± 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 ventral striatum, and less of a difference in the other striatal regions.

D₁ receptor transmission and cocaine dependence

Previous pre-clinical studies have shown conflicting results with respect to the effects of D₁ agonist and antagonist administration on the behavioral effects of cocaine administration. Previous studies have shown that D₁ 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 D₁ knock-out mice showed that the D₁ receptor is crucial for mediating the reinforcing effects of cocaine (Caine et al., 2007). Similar results have been reported with 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 D₁ antagonist administration attenuates priming- and cue-induced cocaine-seeking behavior (Alleweireldt et al., 2002; Barrett et al., 2004; Khroyan et al., 2000; Khroyan et al., 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 D₁ receptor activation may inhibit cocaine-seeking behavior, while other studies suggest that D₁ receptor blockade may have a more beneficial effect.

Studies in humans, while limited, suggest that stimulation of D₁ receptors in humans may reduce the reinforcing effects of cocaine, whereas blockade of the D₁ receptor enhances the reinforcing effects. In a study of cocaine-dependent participants, the D₁ 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 D₁ receptor, to cocaine dependent 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 due to side effects.

D₁ receptor availability and the addictive phenotype

In the present study, low D₁ receptor availability correlated with both the choice to self-administer low dose cocaine and years of cocaine use. This finding suggests that low D₁ receptor binding potential may be indicative of a particular phenotype. Cocaine dependent subjects with low D₁ 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 D₁ 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 D₁ receptor signaling and down-regulates D₁ receptor expression (Self, 2004; Ventura and Sibley, 2000). Thus, we had hypothesized that cocaine dependence would be associated with a decrease in D₁ receptor binding compared to healthy controls. While we did see a decrease

in [^{11}C]NNC 112 BP_{ND} in the limbic striatum, 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 cocaine dependent subjects who chose to self-administer higher doses of cocaine may represent a phenotype in which D₁ receptor binding is decreased in the limbic striatum. In order to test this hypothesis, we performed a post-hoc analysis in which the cocaine dependent subjects were divided into two groups: those who self-administered 0 or 1 dose of cocaine and those who self-administered 2 to 5 doses of cocaine. This analysis showed that the low (0 to 1) self-administration group had a higher D₁ receptor BP_{ND} compared to those who self-administered 2 to 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 cocaine dependent subjects with low D₁ receptor binding in the ventral striatum 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 12mg dose of cocaine and BP_{ND}, and the lack of selectivity of [^{11}C]NNC 112 for D₁ versus serotonin type 2A receptor (5-HT_{2A}) receptors (Slifstein et al., 2007). While 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 due to 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, while approximately 30% of the binding of [^{11}C]NNC 112 can be attributed to the 5-HT_{2A} receptor in the cortex, there does not appear to be any significant binding to the 5-HT_{2A} receptor in the striatum (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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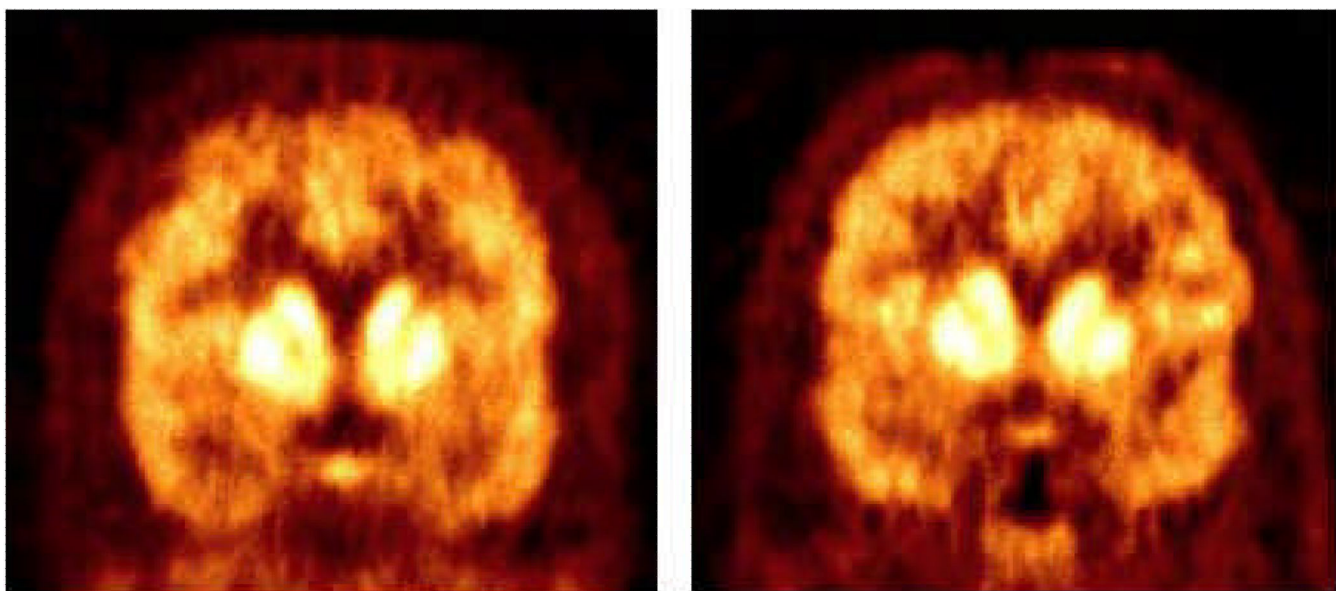


Figure 1. [^{11}C]NNC 112 distribution in a healthy control subject (left) and a cocaine dependent subject (right). Both images are the mean of data acquired from 0-90 minutes and the image display was corrected for injected dose. The selected images include the striatum rostral to the anterior commissure.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

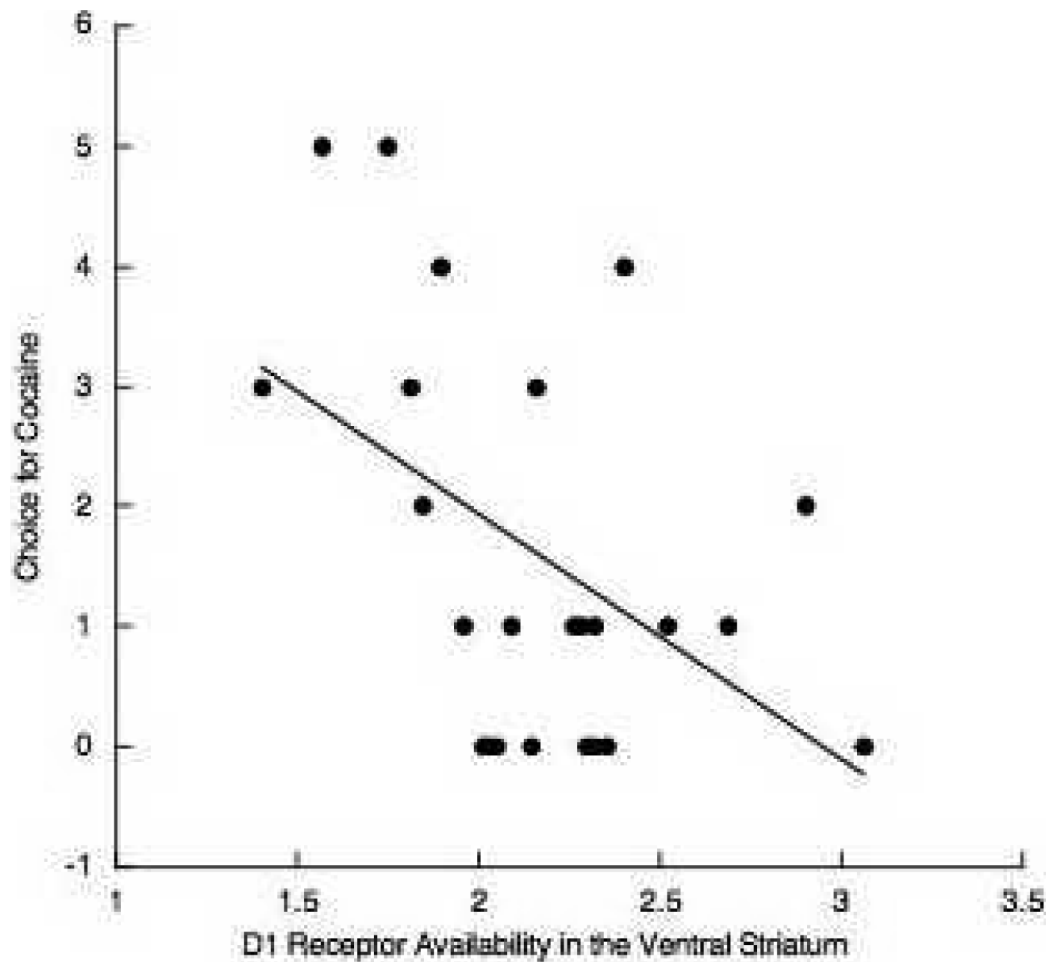


Figure 2.

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 D₁ 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).

Table 1

Group demographics

Parameter	HC	CD	p
n	23	25	-
Age (mean \pm SD, years)	38 \pm 4	40 \pm 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 \pm cigarettes per day in smokers	11 \pm 8	11 \pm 4	0.82

Abbreviations: HC: healthy control subjects; CD: cocaine dependent subjects.

¹¹C]NNC 112 binding potential (BP_P, mL·g⁻¹) and specific to nonspecific partition coefficient (BP_{ND}, unitless)

Table 2

Region of interest	BP _P		BP _{ND}	
	HC	CD	HC	CD
Striatum	5.03 ± 1.61	4.89 ± 1.11	2.32 ± 0.51	2.13 ± 0.43
	6.02 ± 1.57	6.19 ± 1.32	2.78 ± 0.43	2.67 ± 0.33
Pre-commissural dorsal caudate	4.38 ± 1.38	4.81 ± 1.36	2.06 ± 0.37	2.02 ± 0.46
	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
	1.08 ± 0.26	1.18 ± 0.34	0.51 ± 0.11	0.51 ± 0.12
Subcortical	0.66 ± 0.26	0.63 ± 0.20	0.31 ± 0.11	0.27 ± 0.07
	1.18 ± 0.37	1.10 ± 0.30	0.55 ± 0.12	0.47 ± 0.09
Dorsolateral prefrontal cortex	1.41 ± 0.40	1.35 ± 0.27	0.65 ± 0.13	0.59 ± 0.08
	1.00 ± 0.35	0.97 ± 0.37	0.47 ± 0.15	0.42 ± 0.13
Medial prefrontal cortex	1.54 ± 0.43	1.57 ± 0.38	0.71 ± 0.13	0.68 ± 0.12
	1.25 ± 0.33	1.27 ± 0.30	0.58 ± 0.10	0.55 ± 0.09
Orbitofrontal cortex	1.24 ± 0.38	1.14 ± 0.29	0.57 ± 0.13	0.49 ± 0.08
	1.24 ± 0.39	1.22 ± 0.28	0.58 ± 0.13	0.53 ± 0.08
Anterior cingulate				
Temporal cortex				
Parietal cortex				
Occipital cortex				

Values are Mean ± SD. No significant differences were seen between the two groups.