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Deficits in dopamine D2 receptors and pre-synaptic dopamine in heroin dependence: commonalities and differences with other types of addiction

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Abstract

Background—Positron Emission tomography (PET) imaging studies have shown that addiction to a number of substances of abuse is associated with a decrease in dopamine D_{2/3} receptor binding and decreased pre-synaptic dopamine release in the striatum. Some studies have also shown that these reductions are associated with the severity of addiction. For example, in cocaine dependence, low dopamine release is associated with the choice to self-administer cocaine. The goal of the present study was to investigate these parameters of striatal dopamine transmission in heroin dependence and their association with drug seeking behavior.

Methods—Heroin dependent and healthy control subjects were scanned with [¹¹C]raclopride before and after stimulant administration (methylphenidate) to measure striatal D_{2/3} receptor binding and pre-synaptic dopamine release. Following the PET scans, the heroin dependent subjects performed heroin self-administration sessions.

Results—Both striatal D_{2/3} receptor binding and dopamine release were reduced in the heroin dependent subjects compared to healthy controls. However, neither PET measure of dopamine transmission predicted the choice to self-administer heroin.

Conclusions—These findings show that heroin addiction, like addiction to other drugs of abuse, is associated with low D_{2/3} receptor binding and low pre-synaptic dopamine. However, neither of these outcome measures were associated with the choice to self-administer heroin.

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Keywords

PET imaging; dopamine; dopamine receptors; addiction; heroin dependence; drug self-administration

Introduction

Drug addiction is associated with changes in brain neurotransmission, which can be imaged with Positron Emission Tomography (PET). In humans, PET imaging studies show that striatal dopamine transmission is impaired in drug and alcohol addiction (for review see (1, 2)). Most of these studies have been performed with the PET radiotracer [^{11}C]raclopride, which labels the $\text{D}_{2/3}$ receptor and can also be used to measure changes in endogenous dopamine (3, 4). Changes in endogenous dopamine can be measured with the administration of a stimulant, such as methylphenidate, which blocks dopamine uptake and increases extracellular dopamine. In the setting of increased dopamine, fewer $\text{D}_{2/3}$ receptors are available to bind to [^{11}C]raclopride, and the percent decrease in binding provides an estimate of the stimulant-induced increase in extracellular dopamine (3, 5). Thus, PET imaging with [^{11}C]raclopride before and after a stimulant challenge provides two outcome measures that are indicative of striatal dopamine transmission: 1) the availability of the dopamine $\text{D}_{2/3}$ receptors in the striatum at baseline (pre-stimulant administration); and 2) the effect of stimulant administration on endogenous dopamine released from the pre-synaptic dopamine neurons, measured as the percent decrease in [^{11}C]raclopride binding to the $\text{D}_{2/3}$ receptors (3, 5).

Using these methods, previous PET imaging studies have investigated these two outcome measures and shown that baseline dopamine $\text{D}_{2/3}$ receptor availability is reduced in cocaine, alcohol, tobacco, opiate and methamphetamine dependent subjects compared to healthy control subjects (6–14). Pre-synaptic dopamine release has been measured less frequently, but has consistently been shown to be blunted in cocaine and alcohol dependence (2, 15–17).

Previous imaging studies have also investigated the behavioral relevance of this alteration in brain dopamine transmission. In non-addicted human subjects, low baseline $\text{D}_{2/3}$ receptor binding is associated with increased sensitivity to the positive effects of drugs of abuse (18, 19). In animals, low $\text{D}_{2/3}$ receptor binding predicts the choice to self-administer alcohol and cocaine (20–22). A previous study in human cocaine abusers by our group showed that low pre-synaptic dopamine release in the limbic striatum was associated with increased cocaine self-administration, suggesting that low pre-synaptic dopamine release is predictive of greater cocaine use (17). Taken together, these studies suggest that low $\text{D}_{2/3}$ receptor binding and low pre-synaptic dopamine release are associated with greater positive effects of drug of abuse and an increased likelihood of drug self-administration.

The goal of the present study was to investigate striatal dopamine transmission in heroin dependence and its association with drug taking behavior. Heroin dependent subjects were scanned with [^{11}C]raclopride before and after methylphenidate administration in order to measure both baseline $\text{D}_{2/3}$ receptor binding and pre-synaptic dopamine release. Following the PET scans, the heroin dependent subjects performed self-administration sessions in order to investigate the correlation between dopamine transmission and 1) the positive effects of heroin; and 2) the choice to self-administer heroin. A group of healthy control subjects underwent the PET imaging scans only. Our hypotheses were: 1) heroin dependence would be associated with both a decrease in $\text{D}_{2/3}$ receptor binding and pre-synaptic dopamine release compared to control subjects; and, 2) within the heroin dependent subjects, low $\text{D}_{2/3}$

receptor binding and low pre-synaptic dopamine release in the limbic striatum would correlate with the choice to self-administer heroin.

Method

This study was approved by the Institutional Review Board of the New York State Psychiatric Institute and all participants provided written informed consent. The heroin dependent volunteers were medically healthy individuals who fulfilled DSM-IV criteria for heroin dependence, with no other current axis I diagnosis, including current cocaine or alcohol abuse or dependence. The heroin dependent volunteers who participated in this study were not seeking treatment, but were informed that treatment for heroin dependence was available at any time. All heroin dependent subjects were required to demonstrate opiate withdrawal in response to naloxone, using methods described previously (23). The control subjects were medically healthy volunteers who had no current or past major DSM-IV Axis I disorder.

The heroin dependent subjects were admitted to the research unit of the New York State Psychiatric Institute for the entire study. Upon admission, the heroin dependent subjects underwent detoxification from opiates with buprenorphine (4 mg PO Q 12 hours, administered for 3 days) and clonazepam (1 mg PO Q12 hours, administered for 5 days). Random urine testing for drugs was performed twice weekly following detoxification to further ensure abstinence. The PET scans were performed 14 days after the last dose of buprenorphine and 12 days after the last dose of clonazepam. Additional medications available for detoxification included trimethabenzamide and zolpidem, which were discontinued 7 days before the PET scans.

PET scans

[¹¹C]Raclopride (7.2 – 14.0 mCi) was administered as a bolus and the PET scans were acquired on the ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN) in 3D mode over 60 minutes. All participants underwent two scans with [¹¹C]raclopride: before and 60 minutes after oral methylphenidate administration (60 mg PO), as previously described (24, 25). A venous methylphenidate level was obtained just prior to the second injection of [¹¹C]raclopride.

Simplified tissue reference modeling (SRTM) (26) using the cerebellum as a reference region was used to measure [¹¹C]raclopride binding potential (BP_{ND}) (27) defined as:

$$BP_{ND} = f_{ND} * \frac{B_{MAX}}{K_D}$$

In this equation, f_{ND} is the free fraction of the radiotracer in the nonspecific distribution volume (cerebellum), B_{max} is the concentration of D_{2/3} receptors (nmoles per cm⁻³), and K_D is the inverse of the affinity of the radiotracer for the receptor (28).

The change in [¹¹C]raclopride binding due to the dose of methylphenidate was calculated as the percent change in BP (ΔBP_{ND}), where:

$$\% \Delta BP_{ND} = 100 * \frac{BP_{NDbaseline} - BP_{NDmethylphenidate}}{BP_{NDbaseline}}$$

A magnetic resonance image (MRI) was acquired on each subject on the GE Signa EXCITE 3T/94 cm scanner (GE Medical Systems, Milwaukee, WI) to identify each region of interest (ROI). The striatum was subdivided using previously reported anatomical criteria (29, 30). The regions included the following: 1) the ventral, or limbic, striatum which includes the nucleus accumbens, ventral caudate, and ventral putamen; 2) the anterior caudate (caudate anterior to the anterior commissure); 3) the anterior putamen (putamen anterior to the anterior commissure); 4) the posterior caudate (caudate posterior to the anterior commissure); and 5) the posterior putamen (putamen posterior to the anterior commissure). These subdivisions reflect the functional input to the striatum, as follows: 1) the ventral striatum receives input from the limbic brain regions; 2) the caudate (both anterior and posterior) and anterior putamen largely receive input from the associative cortex; and, 3) the posterior putamen is largely involved in sensori-motor processing (for details of the anatomic criteria and rationale for the subdivisions see (29, 30)). Activity from the right and left regions were averaged together. The identification of each ROI, motion correction, and PET to MRI registration was performed with MEDx (Sensor Systems, Inc., Sterling, Virginia) as previously described (29, 30).

Laboratory sessions

Following the PET scans, the heroin dependent participants completed laboratory sessions during which they were given the opportunity to self administer doses of 0, 6.25, and 12.5 mg of intranasal heroin, using methods described previously (31, 32). During all sessions, subjects were under continuous EKG and frequent vital sign monitoring. Two types of sessions were performed for each dose: 1) a sample session, in which the volunteer received a single dose of heroin, and 2) choice sessions, in which the participant chose between heroin and an alternative reinforcer (money). The laboratory sessions occurred on 3 days (one dose each day), with the sample session in the morning and the choice session in the afternoon. Subjects were aware that the dose was the same as that provided in the sample session. The sample and choice sessions were separated by a minimum of 3 hours, in order to avoid carry-over effects from one session to the next. During the sessions, a research nurse monitored vital signs continuously and all drugs were insufflated in the presence of a physician.

In the sample sessions, participants received either heroin or placebo and \$20. During the choice session, participants were allowed to choose between the dose of drug they received in the sample session, another \$20, or any combination of the two in increments of 10% using a modified progressive ratio paradigm. The participants were informed that they could work for all or part of the dose of heroin or amount of money by pressing the computer mouse a designated number of times, and that the number of presses increased with each choice. Heroin and money were available under independent progressive ratio schedules (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, 2800 presses) and there were 10 opportunities to choose between these two options, as previously described (31, 32). Thus, each choice consisted of 10% of the heroin dose (total 0 mg, 6.25 mg, or 12.5 mg) or the money (total \$20) available to them for that session. In order to receive all of the drug or money available in each session, participants were required to emit a total of 11550 responses, whereas fewer total responses were required if their choices were distributed between the two options. Participants were able to keep track of the amount of heroin or money they earned on the computer screen and the portion of the heroin dose chosen and/or money was provided at the end of the session. The principal outcome measure was the breakpoint (highest ratio completed) for the dose of heroin, and a secondary outcome was the number of doses of heroin chosen over money.

During the sample sessions, the participants were asked to complete a computerized subjective-effects battery at baseline and 5, 15, 45, 60, 90, and 120 minutes following the

dose. This consisted of 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) the subjective effects of the dose by indicating their response to the questions such as: “I feel high”, “I feel a good drug effect”, “I liked the choice”, “the choice was of good quality”, “the choice was potent”, and one scale asked participants to indicate how much they would pay for the dose of cocaine across a range of \$0 to \$20. The peak rating (change from baseline) was used as the outcome measure for the VAS.

Statistical Analysis

Group demographic comparisons were performed with unpaired t tests and chi squared tests, where appropriate. The comparisons of [^{11}C]raclopride BP_{ND} and $\Delta\text{BP}_{\text{ND}}$ between the control and heroin dependent subjects were analyzed by linear mixed modeling (LMM), with regions of interest as repeated measure and diagnostic group as fixed factor (SPSS statistics, Chicago, Illinois). Within the heroin dependent subjects, the correlations between [^{11}C]raclopride BP_{ND} and $\Delta\text{BP}_{\text{ND}}$ and the choice to self-administer heroin were analyzed by Pearson product moment correlation coefficient. A two tailed probability value of $p < 0.05$ was chosen as significant for all analyses.

Results

Sixteen heroin dependent subjects (14M/2F, 39 ± 5 years) and sixteen control subjects (14M/2F, 38 ± 6 years, $p = 0.3$) completed this study. The heroin dependent subjects had been using heroin an average of 12 ± 7 years and were currently using an average of 6 ± 3 bags/day of heroin (13 were predominantly intranasal users and 3 used both intravenous and intranasal heroin). Of the 16 subjects, 6 had a history of cocaine abuse (none met criteria for cocaine abuse in at least 7 years) and 2 met criteria for past alcohol abuse (both more than 15 years ago). All but 2 subjects had been detoxified for opiates previously (range 1–10 times). The demographics of heroin dependent and control groups are shown in table 1. One subject performed the PET scans, but declined to perform the self-administration sessions, so that 15 heroin dependent subjects were included in the correlation of the self-administration sessions and the PET data.

No differences between the two groups were seen with respect to the size of the regions of interest (two tailed unpaired ttest all $p > 0.1$, data not shown) or the PET scan parameters (injected dose, specific activity, and methylphenidate level; all $p > 0.2$, data not shown).

As shown in table 2, heroin dependence was associated with significantly lower [^{11}C]raclopride BP_{ND} in the baseline (pre-methylphenidate condition) compared to the healthy control subjects (LMM, effect of diagnosis, $F(1,30) = 19.6$, $p < 0.001$; effect of region, $F(4,120) = 246.6$, $p < 0.001$; region by diagnosis interaction, $F(4,120) = 2.8$, $p = 0.03$). Tests of between group differences in each ROI based on estimated marginal means were significant at the $\alpha = 0.05$ level in all five striatal subregions. All comparisons except in the limbic striatum survive Bonferroni correction and all five subregions remain significant following false discovery rate correction. Similarly, the percent decrease in methylphenidate-induced [^{11}C]raclopride BP_{ND} ($\Delta\text{BP}_{\text{ND}}$) was lower in the heroin dependent subjects compared to the control subjects (LMM, effect of diagnosis, $F(1,30) = 27.4$, $p < 0.001$; effect of region, $F(4,120) = 4.5$, $p = 0.002$; region by diagnosis interaction, NS), as shown in table 3. Tests of between group differences in each ROI based on estimated marginal means were significant at the $\alpha = 0.05$ level in all five striatal subregions. All comparisons except in the limbic striatum and posterior caudate survive Bonferroni correction and all five subregions remain significant following false discovery rate correction. Figure 2 illustrates the between-group differences in BP_{ND} and $\Delta\text{BP}_{\text{ND}}$.

Heroin self-administration sessions

In the self-administration sample sessions, both the 6.25 mg and 12.5 mg doses were rated as having greater positive effects compared to the placebo dose for five of the six VAS (shown in table 4). Only the VAS labeled “I feel high” did not differ significantly between the placebo dose and the 6.25 mg dose ($p=0.09$), although there was a difference between placebo and the 12.5 mg dose. Notably, the 6.25 mg and 12.5 mg doses were not rated as being significantly different from each other on any of the VAS, with the exception of the VAS “I would pay”, which did show a greater effect for the 12.5 mg dose ($p = 0.01$).

In the choice sessions, the break point for the placebo was 216.67 ± 364.33 presses compared to 867.13 ± 1067.75 presses for the 6.25 mg dose and 1446.67 ± 1013.39 presses for the 12.5 mg dose. The breakpoints for both 6.25 mg and 12.5 mg were significantly different from placebo ($p = 0.02$ and $p = 0.002$). Out of a possible total of 10 choices for each dose, placebo was chosen 1.4 ± 2.3 times, compared to 4.3 ± 4.5 times for the 6.25 mg dose and 6.0 ± 3.8 times for the 12.5 mg dose. The number of choices for both 6.25 mg and 12.5 mg were significantly different from placebo ($p = 0.006$ and $p = 0.003$), as shown in figure 1.

Correlations between PET data and choice to self-administer heroin

The correlation with the PET data was performed a priori using the data for the ventral striatum. No significant correlation was seen between BP_{ND} in the ventral striatum and the break point for the 6.25 mg dose of heroin ($r = 0.043$, $p = 0.9$), or the 12.5 mg dose ($r = 0.311$, $p = 0.3$). Similarly, no correlation was seen between ΔBP_{ND} and the breakpoint for 6.25 mg dose of heroin ($r = 0.025$, $p = 0.9$), or for the 12.5mg dose ($r = 0.14$, $p = 0.6$). No correlation was seen with either BP_{ND} or ΔBP_{ND} the ventral striatum and the number of choices for the 6.25 or 12.5 mg doses (all $p > 0.3$). A post-hoc analysis of the remaining regions of interest also showed no correlation between either BP_{ND} or ΔBP_{ND} and the breakpoint or number of doses chosen in both the 6.25 mg and 12.5 mg choices session (all $p > 0.1$).

The correlations between the subjective effects VAS of the 6 and 12 mg doses of heroin and the PET measures (BP_{ND} and ΔBP_{ND}) in the ventral striatum were also investigated. No correlation was seen between BP_{ND} and the subjective effects (all $p > 0.2$). However, as shown in table 5, some of the subjective effects both doses showed a negative correlation with ΔBP_{ND} in the ventral striatum. This correlation is present for some, but not all, of the VAS and these would not survive correction for multiple observations. Yet, the pattern suggests that subjects with higher methylphenidate-induced dopamine release (measured as a greater decrease in ΔBP_{ND}) report less positive effects from the doses of heroin.

Discussion

The main findings from this study are as follows: 1) heroin dependence in humans, measured with PET imaging, is associated with both a decrease in $D_{2/3}$ receptor availability (BP_{ND}) and a decrease in pre-synaptic dopamine release (ΔBP_{ND}); and 2) neither of these parameters of striatal dopamine transmission correlate with the choice to self-administer heroin.

Two previous imaging studies in opiate (heroin/methadone) dependent human volunteers have shown that striatal $D_{2/3}$ receptor binding BP_{ND} is reduced compared to control subjects (8, 13), and the results of the current study are in agreement with these previous results. Notably, studies in rodents have also shown that opiate exposure is associated with a decrease in $D_{2/3}$ receptor binding in the striatum (33, 34). In addition to low $D_{2/3}$ receptor binding, the results of the present study show that heroin dependence is associated with a

decrease in pre-synaptic dopamine release (ΔBP_{ND}). While this finding has not been reported previously in humans, this result is in agreement with studies in rodents showing that chronic exposure and withdrawal from morphine results in a profound and long lasting decrease in dopamine transmission (35).

Previous studies have shown that the spontaneous neuronal activity, including both firing rate and burst firing, of the dopamine neurons are reduced by morphine withdrawal in rats (36, 37) as well as their morphology and size (38). Chronic morphine exposure has been shown to increase GABA signaling in the ventral tegmental area (39, 40) and to reduce excitatory post-synaptic currents (41), both of which would be expected to reduce dopamine transmission (35). In animals, these changes have been shown to extend the period of acute withdrawal, and it has been suggested that the hypodopaminergic state contributes to the motivation to maintain drug use and relapse (35, 42).

Previous imaging studies in humans have shown that addiction, including cocaine, alcohol, methamphetamine, tobacco, and opiate dependence, is associated with a decrease in $D_{2/3}$ receptor availability (BP_{ND}) in the striatum (6–14). Fewer imaging studies have investigated pre-synaptic dopamine release (ΔBP_{ND}) in addiction, yet these consistently show that cocaine, alcohol, and now heroin dependence, are associated with reduction in this parameter of dopamine transmission (2, 15–17). In addition to investigating the changes in brain chemistry that occur in addiction, it is important to understand the behavioral significance of these changes. Our group previously performed a study in cocaine abusers using PET to image pre-synaptic dopamine release and correlated the PET findings with cocaine self-administration (17). The results of this previous study showed that low pre-synaptic dopamine release in the ventral striatum predicted the choice to self-administer cocaine over an alternative reinforcer (also money) in the laboratory. More recently, we showed that low dopamine release (measured with a methylphenidate challenge) was also associated with increased cocaine use in the treatment setting (25). Therefore, we had hypothesized that low dopamine release would correlate with the choice to self-administer heroin. However, the current study did not show a similar finding in heroin dependent subjects, and no association was seen between $D_{2/3}$ receptor ΔBP_{ND} in any of the striatal subdivisions and the choice to self-administer heroin. The reason for this is not immediately clear. The results of heroin self-administration sessions were similar to that reported previously by our group (32, 43). The session data showed that the subjective effects of the two active doses of heroin were greater than that seen with placebo, and the two active doses of heroin were self-administered with more frequency compared to placebo. The choice procedure was used to model street heroin use, in which individuals must choose among reinforcers like heroin and money, and we have previously shown that progressive-ratio break point allows a comparison of heroin's reinforcing strength compared to the alternate reinforcer (32, 43). Additionally, the heroin dependent subjects showed a range of choices for heroin, suggesting that the self-administration session provided variability needed to correlate with the PET data (i.e., had all subjects chosen to self-administer all doses of heroin, there would be insufficient data to correlate with the PET data). Thus, it seems unlikely that the design of the self-administration sessions themselves was a factor. Furthermore, the PET results in the current study are consistent with previous imaging studies, suggesting that there was no confound within the PET data. Although our previous laboratory study in cocaine abusers was performed using amphetamine to displace [^{11}C]raclopride, we recently showed that a 60mg dose of oral methylphenidate produced a similar decrease in ΔBP_{ND} in treatment-seeking cocaine abusers (25), suggesting that the stimulant challenge was not a factor. Thus, taken in the context of previous studies, these results suggest that, in humans, dysregulation in dopamine transmission is similar across different addictions, but that the correlation between neurochemistry and drug seeking behavior appears to vary with the particular drug of abuse.

Our data did suggest that there may be a correlation between dopamine release and the subjective effects of heroin, such that subjects with greater release report less of a positive effect. This correlation, if replicated, suggests that low dopamine release may be associated with greater susceptibility, in that subjects who experience a positive effect to low dose heroin following a period of abstinence may be at greater risk for relapse. Alternatively, a study by Zijlstra et al (13) showed that pre-synaptic dopamine release elicited with drug-related cues in opiate dependent subjects correlated with craving measured prior to the cue, but not with the increase in craving produced by the cue itself. While these two studies appear to show the opposite finding with respect to dopamine release (this study suggests that dopamine release in response to a stimulant may be protective, while the study of Zijlstra reports that dopamine release in response to a cue may be associated with greater craving for drug) there are too many differences in methodology (such as the method used to elicit dopamine release, radiotracers used, and length of abstinence) between the two studies to make a direct comparison. In addition, this particular finding in our study did not survive correction for multiple observations, and thus must be considered as only a suggestion.

Limitations

In heroin dependent subjects, both BP_{ND} and ΔBP_{ND} were significantly lower compared to controls. However, it should be noted that differences in baseline BP_{ND} can be affected by differences in receptor concentration, receptor affinity for the radiotracer, or levels of endogenous dopamine. Thus, there could be differences in baseline levels of endogenous dopamine that affect the results presented in this study. In addition, while previous studies have shown that the stimulant-induced decrease in [^{11}C]raclopride binding correlate with pre-synaptic dopamine release (3), this correlation is associated with a significant loss of sensitivity (4). In addition, recent studies have shown that receptor internalization play a crucial role in the stimulant-induced decrease in radiotracer binding (44). Thus, unknown differences in baseline levels of endogenous dopamine, internalization or receptor affinity could play a role, and future studies would be required to clarify this. In this study, the right and left brain regions were averaged together, such that differences in laterality that may have been present would not have been detected. In addition, although the heroin-dependent subjects were required to demonstrate opiate dependence, testing for drugs other than heroin over an extended period of time and hair analysis was not done, and it cannot be ruled out with certainty that no other drugs were being used sporadically by this group.

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Figure 1. Breakpoint (left panel) and number of choices (right panel) for the three doses of heroin (0mg, 6.25 mg, and 12.5 mg).

Figure 2.

BP_{ND} maps averaged across all subjects, coregistered to a common template. Left Column: Representative MRI from one subject showing the level of the coronal PET slices (bottom). The black line in the sagittal view (top) shows the level of the coronal slices. Center and Right Columns: Healthy control subjects (top) and heroin dependent subjects (bottom) at baseline (center) and following MP (right).

Table 1

Group demographics comparing the healthy control and heroin dependent subjects

	Healthy Control	Heroin Dependent	p
Age (mean $\pm$ SD, in years)	38 $\pm$ 6	39 $\pm$ 5	0.3 ^a
Gender (Male/Female)	14M/2F	14M/2F	-
Ethnicity (African-American/Hispanic/Caucasian not Hispanic)	7AA/4H/5C	7AA/6H/3C	0.90 ^b
Smoking status (Yes/Ex/No)	13Y/3N	14Y/2N	0.63 ^b
Mean $\pm$ cigarettes per day in smokers	11 $\pm$ 7	11 $\pm$ 6	0.8 ^a

Abbreviations:

^a unpaired t test;^b chi-squares.

Table 2

PET scan data between the healthy control (n=16) and heroin dependent (n=16) subjects baseline (pre-methylphenidate) [^{11}C]raclopride BP_{ND} . The values presented are mean and standard deviation and the p values were obtained with a two-tailed unpaired t test.

Region of Interest	Healthy Control	Heroin Dependent	p
Limbic Striatum	1.93 $\pm$ 0.28	1.74 $\pm$ 0.18	0.03
Anterior Caudate	2.06 $\pm$ 0.24	1.74 $\pm$ 0.28	0.002
Posterior Caudate	1.31 $\pm$ 0.22	1.08 $\pm$ 0.23	0.004
Anterior Putamen	2.47 $\pm$ 0.29	2.09 $\pm$ 0.26	0.001
Posterior Putamen	2.60 $\pm$ 0.23	2.16 $\pm$ 0.26	0.0001

Table 3

Values for BP_{ND} following methylphenidate administration (60 mg PO) and percent change in [¹¹C]raclopride binding (Δ BP_{ND}) in response to methylphenidate in healthy control (n=16) and heroin dependent subjects (n=16). The values presented are mean and standard deviation and the p values (for Δ BP_{ND}) were obtained with a two-tailed unpaired t test. The differences for BP_{ND} following methylphenidate are not significant.

Region of Interest	BP _{ND} following methylphenidate		Percent change in BP _{ND} (Δ BP _{ND})		p
	Healthy Control	Heroin Dependent	Healthy Control	Heroin Dependent	
Limbic Striatum	1.69 ±0.22	1.68 ±0.26	-12.1 ±10.6 %	-3.6 ±10.5 %	0.03
Anterior Caudate	1.88 ±0.24	1.80 ±0.25	-8.5 ±6.9 %	4.4 ±11.3 %	0.0007
Posterior Caudate	1.19 ±0.26	1.11 ±0.21	-8.5 ±13.6 %	4.7 ±12.6 %	0.02
Anterior Putamen	2.22 ±0.27	2.11 ±0.27	-9.6 ±8.4 %	-0.9 ±8.1 %	0.001
Posterior Putamen	2.18 ±0.33	2.06 ±0.30	-16.0 ±9.7 %	-4.7 ±9.2 %	0.002

Visual analog scale ratings of the doses of heroin (0mg, 6mg, and 12mg doses). Participants were asked to indicate their subjective experience to each dose along the 100 mm line (on a computer screen) for each dose.

Table 4

Visual Analog scale (VAS)	Placebo	6 mg	p (0mg vs 6.25mg)	12.5 mg	p(12.5mg vs 0mg)
"I feel high"	7.1 ±17.1	22.1 ±26.4	0.09	34.6 ±25.7	0.003
"I feel a good drug effect"	4.0 ±13.5	29.2 ±29.3	0.007	37.2 ±26.1	<0.001
"I liked the choice"	4.7 ±13.7	28.4 ±29.6	0.01	44.1 ±30.1	<.001
"The choice was of good quality"	5.5 ±12.4	25.1 ±27.1	0.02	39.3 ±28.1	<0.001
"The choice was potent"	5.4 ±14.5	25.1 ±27.4	0.02	37.2 ±30.9	0.001
"I would pay for the choice"	0.4 ±1.1	4.1 ± 5.8	0.02	10.4 ±6.1	<0.001

Table 5

Correlations between the VAS and the [¹¹C]raclopride displacement (measured as ΔBP_{ND}) for both the 6.25 mg and 12.5 mg doses of heroin. The columns show the correlation coefficient (r) and p value for the correlation for each VAS for each dose and ΔBP_{ND} .

Visual Analog scale (VAS)	6.25 mg dose (IN) of heroin		12.5 mg dose (IN) of heroin	
	r	p	r	p
"I feel high"	0.44	0.12	0.65	0.01
"I feel a good drug effect"	0.42	0.14	0.63	0.02
"I liked the choice"	0.48	0.08	0.32	0.27
"The choice was of good quality"	0.52	0.06	0.44	0.12
"The choice was potent"	0.48	0.08	0.43	0.13
"I would pay for the choice"	0.58	0.03	0.31	0.29