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Imaging dopamine transmission in cocaine dependence: response to treatment linked to neurochemistry

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Abstract

Previous research has shown that dopamine signaling in the limbic striatum is crucial for selecting adaptive, motivated behavior, and that disrupted dopamine transmission is associated with impulsive and maladaptive behavior. In humans, Positron Emission Tomography (PET) imaging studies have shown that cocaine dependence is associated with the dysregulation of striatal dopamine signaling, which is associated with cocaine seeking behavior. The goal of the present study was to investigate whether this association applies to the treatment setting. Our hypothesis was that dopamine signaling in the limbic striatum would be associated with response to a behavioral treatment that uses positive reinforcement to replace impulsive cocaine use with constructive personal goals. Prior to treatment, cocaine dependent subjects underwent two PET scans using [^{11}C]raclopride, before and after the administration of a stimulant (methylphenidate), to measure striatal $D_{2/3}$ receptor binding and pre-synaptic dopamine release. The results showed that both of these outcome measures were reduced in the volunteers who failed to respond to treatment compared to those who experienced a positive treatment response. These findings provide insight into the neurochemistry of treatment response and show that low dopamine transmission is associated with treatment failure. In addition, these data suggest that the combination of behavioral treatment with methods that increase striatal dopamine signaling might serve as a therapeutic strategy for cocaine dependence.

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Introduction

Cocaine dependence, for many patients, is a chronic, refractory disorder with a high relapse rate. However, a subpopulation of cocaine dependent patients respond well to treatment and recover from addiction. Previous studies have sought predictors of this positive response (1, 2), but neurochemistry has been a missing component. Thus, the goal of the present study was to investigate whether neurochemistry, specifically striatal dopamine signaling in the limbic striatum, is associated with success or failure to respond to a well-established behavioral treatment for cocaine dependence.

The role of dopamine in the striatum is among the most studied phenomena of the brain. For almost a half-century, it has been shown that striatal dopamine is a crucial component of reward, reward-based learning, and addiction (3, 4). The nucleus accumbens, which is contained within the limbic striatum in humans, serves as a hub of the brain's reward pathways, and dopamine transmission in this brain region plays a central role in selecting adaptive, motivated behavior (5). Positron Emission Tomography (PET) imaging with the radioligand [^{11}C]raclopride is frequently used to provide quantitative information about striatal dopamine type 2/3 ($D_{2/3}$) receptors. In addition to measuring $D_{2/3}$ receptors, this radiotracer is sensitive to fluctuations in endogenous dopamine (6, 7). The administration of a psychostimulant, such as methylphenidate, blocks the dopamine transporter and prevents dopamine re-uptake from the synapse, which then increases extra-cellular dopamine. In the setting of increased dopamine levels, imaging with [^{11}C]raclopride results in lower radioligand binding, since fewer $D_{2/3}$ receptors are available to bind to the radiotracer (6, 8).

Using these methods, previous studies have shown that both baseline $D_{2/3}$ receptor binding and stimulant-induced dopamine release are reduced in cocaine dependent subjects compared to healthy controls (9, 10). Our group previously investigated the relationship between dopamine release and a laboratory model of cocaine-seeking behavior (10). In that study, PET scans were performed on non-treatment seeking human cocaine dependent volunteers followed by cocaine self-administration sessions. In these sessions, participants choose between low dose smoked cocaine and an alternative positive reinforcer (money). The results showed that cocaine abusers with low stimulant-induced dopamine release (measured as the change in [^{11}C]raclopride binding potential) in the limbic striatum were more likely to choose cocaine over money, and suggest that low dopamine release is associated with compulsive cocaine use (10).

The goal of the present study was to investigate whether this finding from the laboratory applies to the "real world" treatment clinic. Treatment-seeking cocaine dependent subjects underwent PET scans using [^{11}C]raclopride to image two parameters associated with dopamine transmission: 1) baseline dopamine $D_{2/3}$ receptor binding (measured as binding potential or $BP_{ND} = f_{ND}(B_{MAX}/K_D)$, please see methods for full definition) and; 2) stimulant-induced pre-synaptic dopamine release (measured as the stimulant-induced change in BP_{ND} orΔ BP_{ND}). Following the scans, the subjects were enrolled in treatment using contingency management combined with the community reinforcement approach developed by Higgins et al (11, 12). This treatment uses positive reinforcement (monetary vouchers) to induce abstinence from cocaine, which is similar to the choice presented in the laboratory in our previous study (10). Since the results of our previous study showed that the subjects who chose to self-administer cocaine over a money had low pre-synaptic dopamine release (ΔBP_{ND}) in the limbic striatum, we hypothesized that treatment-seeking subjects who failed to respond to a treatment that uses a monetary reward to reduce cocaine use would also have low dopamine release (ΔBP_{ND}) in the limbic striatum. In addition, since previous studies in animals have shown that low $D_{2/3}$ receptor binding potential (BP_{ND}) is associated with greater cocaine self-administration (13, 14) we hypothesized that subjects who failed to

respond to treatment would also have low dopamine receptor binding potential in the limbic striatum.

A group of control subjects was also included in order to show that this cohort of cocaine dependent subjects had the same changes in neurochemistry reported in previous studies (9, 10, 15, 16). In addition, the cocaine dependent subjects were asked to return for follow up PET scans at the end of treatment (12 weeks) in order to asses the effect of treatment on dopamine transmission. Our hypothesis was that subjects who responded to treatment would show normalization (i.e., increases) in both baseline $D_{2/3}$ receptor binding potential (BP_{ND}) and pre-synaptic dopamine release (ΔBP_{ND}) compared to their pre-treatment scans.

Methods

The study was approved by the New York State Psychiatric Institute Institutional Review Board and all participants gave written informed consent. The cocaine dependent subjects (22M/3F) were medically healthy individuals with cocaine dependence and no other psychiatric diagnosis. A group of healthy matched control subjects (21M/3F) with no DSM-IV Axis I disorder was included. The cocaine dependent subjects underwent the following procedures: 1) screening; 2) 14 days of abstinence; 3) first PET imaging session; 4) twelve weeks of behavioral treatment; 5) second PET session); 6) an additional twelve weeks of treatment. Please see the supplemental information for the full description of these procedures.

For all subjects, [^{11}C]raclopride 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 [^{11}C]raclopride: baseline and following oral methylphenidate (60 mg) administration, using methods previously described (17). A plasma sample for analysis of methylphenidate level was obtained just prior to the second scan. The PET data was analyzed using the Simplified Tissue Reference Modeling (18) using the cerebellum as a reference region to estimate non-specific binding. The PET outcome measure was binding potential (BP_{ND}) defined as:

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

where ND is the non-displaceable binding, f_{ND} is the free fraction in the non-displaceable distribution volume of the brain, B_{max} is the concentration of $D_{2/3}$ receptors(nmoles per g of tissue), and K_D is the inverse of the affinity of the radiotracer for the receptor (19). The percent change in [^{11}C]raclopride binding following methylphenidate administration was calculated as ΔBP_{ND} and defined as ($BP_{ND\ baseline} - BP_{ND\ methylphenidate}$)/$BP_{ND\ baseline}$) (9, 10). This methodology has been used extensively in PET imaging (20) to provide an estimate of stimulant-induced changes in extracellular dopamine in the striatum.

In addition to the PET scans, each participant also underwent a magnetic resonance (MR) scan (GE Signa EXCITE 3T/94 cm scanner, GE Medical Systems, Milwaukee, WI) for identification of the regions of interest. Based on our previous study showing that dopamine release in the limbic striatum correlated with the choice to self-administer cocaine, the primary region of interest in this study was the limbic striatum (10). The caudate and putamen were also included, and were subdivided at the anterior commissure into their rostral and caudal portions, as previously described (21, 22). Activity from the right and left regions were averaged together. The identification of the regions of interest, motion

correction, and PET to MRI registration was performed with MEDx (Sensor Systems, Inc., Sterling, Virginia) as previously described (22).

Following the PET scans, the cocaine dependent subjects were enrolled in treatment using Contingency Management with the Community Reinforcement Approach, carried out in accordance with the NIDA manual (23). All therapy sessions were conducted twice weekly by a trained therapist, who was supervised by one of the investigators (KC). The voucher incentive component of the program followed procedures previously outlined by Higgins et al. (11, 12). Briefly, participants received voucher points for each urine sample that tested negative for cocaine metabolite (i.e. benzoylecgonine). The vouchers points ($0.25) were acquired on an escalating schedule which started at 10 points for first cocaine-free sample, and each subsequent cocaine-free sample increased the voucher value by 5 points. Participants also received a bonus of 40 points ($10.00) for every three consecutive cocaine free urine samples (equivalent to a week of abstinence). Participants could earn a maximum of $997.50 in vouchers for submitting cocaine free urines on 100% of the scheduled treatment visits (36 over the course of 12 weeks). Please see supporting data for further description of the treatment.

The cocaine dependent subjects were given the option of returning for PET scans using the same methods (two scans with [^{11}C]raclopride before and after 60 mg methylphenidate) at the end of the 12 weeks of treatment, in order to investigate the effect of treatment on these parameters of dopamine transmission.

Statistical Analysis

Group demographic comparisons and group differences in the PET scan parameters were performed with unpaired t tests. Differences between cocaine abusers and healthy controls in [^{11}C]raclopride BP_{ND} and ΔBP_{ND} were analyzed with a repeated measures ANOVA, with the region of interest as the repeated measure and diagnostic group as the co-factor. Based on the animal literature showing that the nucleus accumbens plays a critical role in reward based behaviors (3, 5) and our previous study showing that ΔBP_{ND} specifically in the limbic striatum correlated with cocaine self-administration (10), the limbic striatum was our primary region of interest for the comparison between the treatment responders and non-responders. Thus, the primary analysis was performed on this brain region using an unpaired t test to compare BP_{ND} and ΔBP_{ND} between the treatment responders and non-responders. After this analysis, an exploratory analysis of the remaining regions was performed with unpaired t tests with correction for multiple observations. The comparison of BP_{ND} and ΔBP_{ND} in cocaine dependent subjects scanned before and after the 12 weeks of treatment was also performed with unpaired t tests.

Results

Twenty five cocaine dependent volunteers (22M/3F, 37 ± 7 years) completed this study. One subject underwent only the PET scan measuring pre-methylphenidate BP_{ND}, thus the comparisons with ΔBP_{ND} included only 24 of the cocaine dependent subjects. A group of 24 medically healthy control subjects (21M/3F) was included, matched for cigarette smoking, gender, and ethnicity. Please see the supplemental data for demographic comparisons between the cocaine abusers and healthy controls.

Comparison of Healthy Controls and Cocaine Dependent Subjects

Compared to the control subjects, cocaine dependence was associated with both lower $D_{2/3}$ receptor BP_{ND} (Repeated Measures ANOVA, sphericity-corrected, effect of diagnosis $F(1, 47) = 5.794$, $p = 0.02$, effect of region $F(3,141) = 399.28$, $p < 0.001$; diagnosis by region

interaction $F(3,141) = 2.42$, $p = 0.07$) and ΔBP_{ND} (Repeated Measures ANOVA, sphericity-corrected, effect of diagnosis $F(1,46) = 11.678$, $p = 0.001$, effect of region $F(2.9,133) = 3.61$, $p = 0.016$; diagnosis by region interaction $F(4,184) = 1.52$, $p = 0.213$). The values for both $D_{2/3}$ receptor BP_{ND} (pre-methylphenidate) ΔBP_{ND} for each region are provided in table 1.

Response to Treatment

Response to treatment among the cocaine dependent subjects was measured as the amount of voucher money earned, since this outcome measure is dependent on continuous cocaine-free urine samples and reflects the degree of abstinence obtained. As shown in figure 1, the response to treatment among the cocaine dependent subjects was bimodal, which is a frequent finding in studies using this treatment modality (24, 25). Thus, the analysis regarding the response to treatment was performed comparing the group of cocaine abusers who clustered on the left portion of the graph (non-responders, n=15) to those who on the right (treatment responders, n=10). Of the ten treatment responders, nine experienced continued recovery at six months past the start of treatment (the remaining subject provided 100% cocaine-negative urines until week 11, then moved and was not available for follow up in person, although by phone reported continued abstinence). Of the 14 non-responders, none achieved sustained abstinence. No differences in age, tobacco smoking, or amount of cocaine use prior to study entry was seen between the responders and non-responders (all $p > 0.2$, see supplemental data). However, the non-responders had been using cocaine longer compared to the treatment responders (17 ± 8 years vs 11 ± 8 years, $p = 0.03$).

Comparison of PET data between Treatment Responders and Non-responders

Figure 2 shows the average BP_{ND} (calculated per voxel) in the baseline condition and following methylphenidate in the treatment responders and non-responders. The primary analysis for this study was with the limbic striatum, and both BP_{ND} and ΔBP_{ND} were higher in responders compared to the non-responders (1.94 ± 0.27 vs 1.75 ± 0.17, $p = 0.05$ for BP_{ND}; and $-12.1 \pm 6.9\%$ in responders compared to $-1.3 \pm 6.7\%$ in non-responders for ΔBP_{ND}, $p < 0.001$, two-tailed t-tests). As shown in figure 2, this effect was more pronounced for ΔBP_{ND} than that of BP_{ND}.

An exploratory analysis was performed to compare BP_{ND} and ΔBP_{ND} in the remaining regions (table 2). While the values for BP_{ND} and ΔBP_{ND} in some of the remaining regions are lower in the non-responders compared to the treatment responders, these results do not survive correction for multiple observations.

Comparison of PET data before and after 12 weeks treatment

Of the 25 cocaine dependent subjects, 15 returned for PET scans after 12 weeks of treatment, and 9 of these were treatment responders. The data comparing BP_{ND} and ΔBP_{ND} before and after treatment in the treatment responders (table 3) shows no significant differences. Comparisons of BP_{ND} and ΔBP_{ND} for the 6 non-responders showed no significant differences in the before and after conditions (all $p > 0.5$, data not shown). Notably, a post-hoc analysis of the treatment responders and controls showed that there was no difference in BP_{ND} or ΔBP_{ND} (all $p > 0.1$) between these two groups.

Discussion

The results of this study show that response to a behavioral treatment for cocaine dependence is related to dopamine signaling in the limbic striatum, measured with PET as dopamine $D_{2/3}$ receptor binding (BP_{ND}) and pre-synaptic dopamine release (ΔBP_{ND}). The cocaine dependent subjects who responded to a behavioral treatment that uses positive

reinforcement and psychotherapy had higher $D_{2/3}$ receptor binding and dopamine release (ΔBP_{ND}) compared to subjects who experienced relapse in this treatment setting.

Animal studies have previously shown that deficits in dopamine signaling in the nucleus accumbens impair operant conditioning, response inhibition, and behavioral flexibility with respect to reinforced behavior (26). Lesioning the nucleus accumbens in rodents results in a profound deficit in the animals' ability to choose appropriately between two reinforcers: they impulsively and consistently chose a lesser reward over a delayed reinforcer of greater value (27). These findings suggest that dopamine signaling in the limbic striatum is critical for making the shift between competing reinforcers, such that in the setting of low dopamine transmission a habitual behavior is emitted, even in the presence of an alternative reward of greater value. We have demonstrated a similar finding in human cocaine abusers. In two cohorts of cocaine dependent volunteers, non-treatment seeking (10) and treatment seeking (reported here), low dopamine release in the limbic striatum was associated with the choice to consume cocaine over alternative reinforcers. In each case, subjects with the low dopamine transmission made the non-adaptive choice between competing rewards. Our previous study in the laboratory gave subjects the choice between a low dose of cocaine (6mg) and $5, and the choices were weighted toward the money, since the street value of this dose of cocaine was less than $5. In the present study, subjects presented to the clinic in search of treatment, and could earn money for pursuing their goal. Therefore, in both the non-treatment and the treatment studies, the more adaptive response is to choose money and abstinence over cocaine, yet in both studies there were a number of subjects who reliably chose cocaine. The failure of the cocaine dependent subjects with low dopamine release to alter their behavior can be viewed as a perseverative error in the setting of competing rewards, or as a blunted brain reward system that is unable to respond to alternative sources of reward.

Ultimately the question is whether PET radioligand imaging in human cocaine abusers can be used to guide the development of better treatment. Imaging studies have consistently shown that dopamine transmission is blunted in cocaine dependent subjects compared to controls, measured as four different parameters: 1) reduced baseline $D_{2/3}$ receptor binding (BP_{ND}) of the post-synaptic neurons (9, 10, 15, 16); 2) decreased pre-synaptic dopamine release (ΔBP_{ND}) (9, 10); 3) reduction in pre-synaptic neuronal stores of dopamine (28); and 4) reduced baseline levels of endogenous dopamine (29). The present study investigated the association between dopamine transmission and response to treatment, and these results show that a positive response is associated with higher $D_{2/3}$ receptors and greater methylphenidate-induced dopamine release compared to those who failed treatment. These findings suggest that increasing striatal dopamine transmission would be the most appropriate strategy for converting treatment non-responders to responders, either by increasing $D_{2/3}$ receptors or increasing pre-synaptic dopamine. Previous studies in rodents have shown that using a viral vector to increase striatal D_2 receptors reduces the animals' preference for drugs of abuse (14, 30). Combined with the data from the present study, it can be surmised that increasing $D_{2/3}$ would improve treatment response, but this technology is unlikely to translate into human use in the near future.

Another approach is to increase pre-synaptic dopamine release. A number of previous clinical trials have investigated medications that increase striatal dopamine transmission, and while some report success, others do not (31). One reason for this inconsistency may be that medications that are known to increase dopamine transmission in the non-addicted brain may have a minimal effect in the addicted brain, as shown by this study. Notably, a recent study by Schmitz et al (32) reported that treatment of cocaine abusers with contingency management and levodopa/carbidopa, which would be expected to improve dopamine transmission by increasing pre-synaptic stores in the striatum, resulted in a greater response

to treatment compared to placebo. Another approach may be to increase dopamine transmission by targeting other receptor systems, such as the kappa or acetylcholine receptors (for review see (33, 34) or others. Together, these findings strongly suggest that the combination of pharmacology to address the deficit in dopamine transmission combined with a behavioral treatment that presents tangible alternatives to cocaine use, may provide the best approach for the treatment of cocaine addiction.

This study also examined the effect of treatment on dopamine receptor binding and pre-synaptic dopamine release. No effect of treatment was seen in the nine treatment responders who were scanned before and after treatment, contrary to our hypothesis. However, it is interesting that the treatment responders did not differ from the control subjects prior to treatment, suggesting that pre-synaptic dopamine was largely intact in the responders to begin with. Among the non-responders, only six returned for scans after 3 months, and there was also no change in dopamine receptor binding or dopamine release, which is expected since these subjects had continued their cocaine use.

Study limitations

Previous studies using fMRI have investigated the correlation between brain activation and treatment response (35, 36). Kosten et al (35) showed that low treatment effectiveness correlated with greater cue-induced activation of sensory, motor, and limbic cortical areas while Moeller et al (36) used a working memory task to show that cocaine dependent subjects with low thalamic activation had a poor treatment response. A limitation of PET imaging with [^{11}C]raclopride is that our investigations are limited to the striatum and other brain regions are also likely to play a critical role in the human condition (for review see (37)). However, imaging with [^{11}C]raclopride allows a more direct investigation of the aberration in chemistry that occurs with drug addiction, which may provide more guidance in the selection of candidate medications.

Based on previous studies in both animals and humans showing that the limbic striatum is most directly involved in reward related behaviors, we limited our initial analysis to the limbic striatum. With this constraint, both BP_{ND} and ΔBP_{ND} were significantly lower in the non-responders. However, had we used correction for multiple observations (which would have been necessary had out hypothesis included all regions) only the finding with ΔBP_{ND} would have reached significance. Interestingly, in our previous study (10) we saw no correlation between the choice to self-administer cocaine and BP_{ND}, which suggests that the BP_{ND} effect is less than that of ΔBP_{ND}. Another limitation of this study is that the left and right regions were averaged and not analyzed individually, such that there could have been an effect of laterality that we did not see. In addition, while the stimulant-induced decrease in [^{11}C]raclopride binding correlates with pre-synaptic dopamine release (6), recent studies have shown that receptor internalization or dimerization play a key role (7, 38, 39).

Conclusion

In conclusion, the findings from this study are as follows: 1) compared to controls, striatal dopamine signaling is blunted in cocaine dependent subjects, 2) within the cocaine dependent subjects, a positive response to treatment was associated with greater dopamine signaling; 3) treatment itself did not change dopamine transmission. These findings, combined with data from previous studies, strongly suggest that improving dopamine transmission may be the most appropriate treatment strategy for cocaine dependent subjects who seek treatment, but relapse nonetheless.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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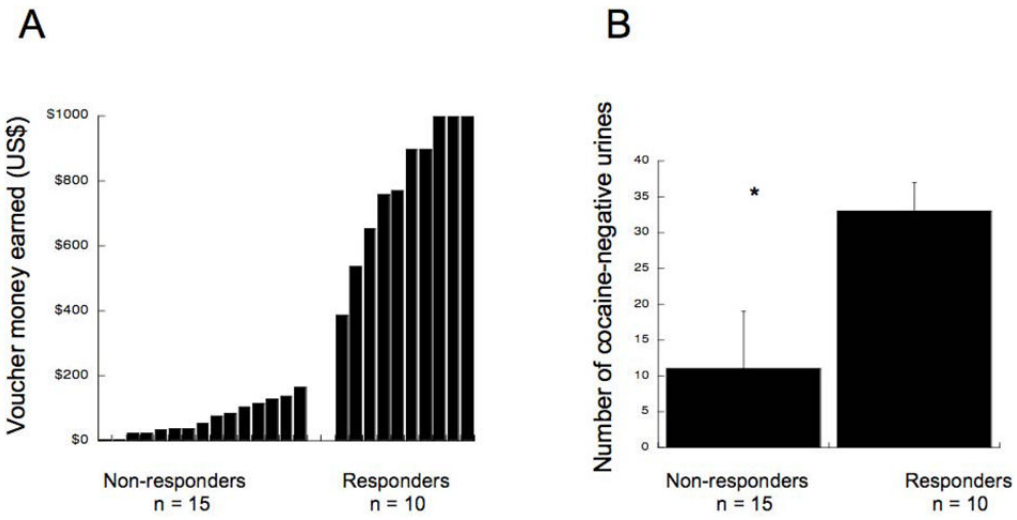

Figure 1.

A) Plot of all cocaine dependent subjects (n = 25) showing the amount of voucher money earned for cocaine-negative urine samples (range $0 – $977.50). The subjects' response to treatment shows a bimodal distribution, which was used to classify subjects as responders or non-responders. B) Comparison of the average number of cocaine-negative urines provided over 12 weeks in the non-responders and responders (range 0–36). The values are the average and standard deviation for each group.

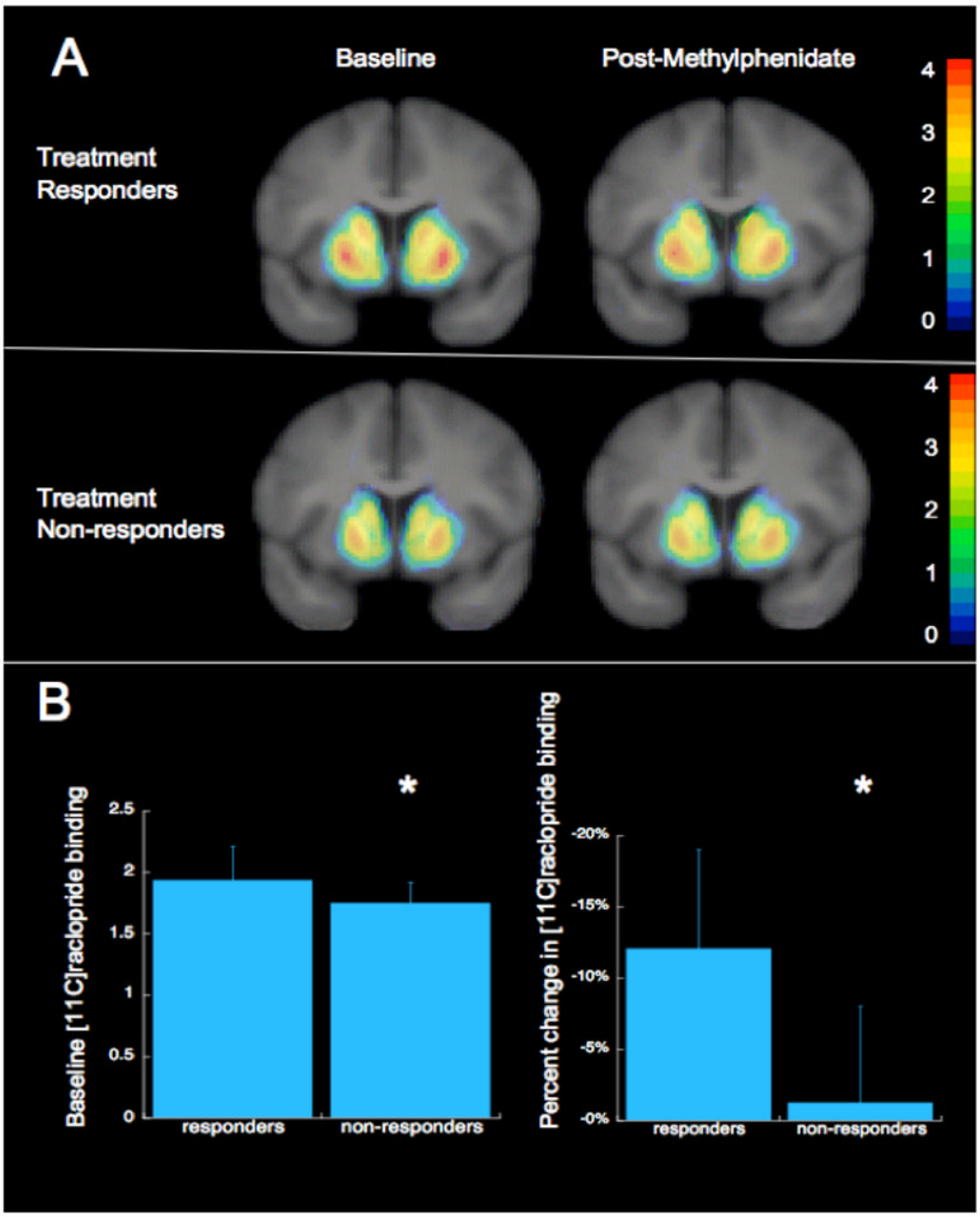

Figure 2.

A) Average [^{11}C]raclopride $D_{2/3}$ receptor binding (BP_{ND}) in the treatment responders (top) and non-responders (bottom). The scans shown are before (left) and after (right) 60 mg PO methylphenidate administration, which increases extracellular dopamine so that fewer $D_{2/3}$ receptors are available to bind to [^{11}C]raclopride. The color bar shows the values for BP_{ND}. B) Bar graphs showing the differences between the treatment responders and non-responders in the limbic striatum for (left) BP_{ND} (pre-methylphenidate $D_{2/3}$ receptor binding) and (right) ΔBP_{ND}, the percent decrease in methylphenidate-induced [^{11}C]raclopride binding. These data show that treatment responders had higher dopamine $D_{2/3}$ receptor binding and greater pre-synaptic dopamine release compared to non-responders in the limbic striatum.

Table 1

Comparison of the PET scan data between the healthy control and cocaine dependent subjects: (top) baseline (pre-methylphenidate) [^{11}C]raclopride BP_{ND}; and (bottom) percent change in [^{11}C]raclopride binding (ΔBP_{ND}) in response to methylphenidate administration (60 mg PO). The values presented are mean and standard deviation and the p values were obtained with a two-tailed unpaired t test.

BP_{ND}					
Region of Interest	**Healthy Control**		**Cocaine Dependent**		
	mean	**sd**	**mean**	**sd**	**p**
Limbic Striatum	2.00	0.26	1.83	0.23	0.02
Anterior Caudate	2.14	0.29	2.02	0.24	0.10
Posterior Caudate	1.37	0.24	1.35	0.22	0.80
Anterior Putamen	2.56	0.23	2.36	0.29	0.01
Posterior Putamen	2.66	0.24	2.47	0.30	0.02
ΔBP_{ND}					
Region of Interest	Healthy Control		Cocaine Dependent		
	mean	sd	mean	sd	p
Limbic Striatum	−13.7%	8.7 %	−5.8 %	8.6 %	0.003
Anterior Caudate	−6.3%	10.4 %	−6.1 %	10.6 %	0.9
Posterior Caudate	−11.6%	11.1 %	−5.6 %	10.6 %	0.06
Anterior Putamen	−10.3%	7.9 %	−4.2 %	8.7 %	0.01
Posterior Putamen	−16.2 %	9.4 %	−8.5 %	7.0 %	0.002

Table 2

Comparison of the PET scan data between the treatment responders and non-responders: (top) baseline (pre-methylphenidate) [^{11}C]raclopride BP_{ND}; and (bottom) percent change in [^{11}C]raclopride binding (ΔBP_{ND}) in response to methylphenidate administration (60 mg PO). The values presented are mean and standard deviation and the p values were obtained with a two-tailed unpaired t test.

BP_{ND}					
Region of Interest	**Responders**		**Non-responders**		
	mean	**sd**	**mean**	**sd**	**p**
Limbic Striatum	1.94	0.27	1.75	0.17	0.05
Anterior Caudate	2.11	0.31	1.96	0.17	0.12
Posterior Caudate	1.40	0.26	1.32	0.19	0.40
Anterior Putamen	2.51	0.34	2.26	0.20	0.03
Posterior Putamen	2.59	0.39	2.39	0.20	0.09
ΔBP_{ND}					
Region of Interest	Responders		Non-responders		
	mean	sd	mean	sd	p
Limbic Striatum	−12.1%	6.8 %	−1.3 %	6.7 %	<0.001
Anterior Caudate	−8.5%	10.7 %	−2.6 %	9.9 %	0.18
Posterior Caudate	−9.4%	10.9 %	−0.3 %	7.8 %	0.04
Anterior Putamen	−7.4%	11.2 %	−1.9 %	6.0 %	0.13
Posterior Putamen	−11.0%	7.9 %	−6.7 %	5.8 %	0.15

Table 3

[^{11}C]raclopride BP_{ND} and ΔBP_{ND} in treatment responders (n = 9) before and after treatment. The values presented are the mean and standard deviation. No significant changes were seen in either outcome measure.

BP_{ND}					
	Pre-treatment		**Post-treatment**		
Region of Interest	**mean**	**sd**	**mean**	**sd**	**p**
Limbic Striatum	1.95	0.28	2.02	0.36	0.70
Anterior Caudate	2.11	0.33	2.34	0.31	0.17
Posterior Caudate	1.42	0.27	1.50	0.31	0.28
Anterior Putamen	2.52	0.36	2.77	0.33	0.15
Posterior Putamen	2.61	0.40	2.90	0.41	0.20
ΔBP_{ND}					
	Pre-treatment		Post-treatment		
Region of Interest	mean	sd	mean	sd	p
Limbic Striatum	−11.8%	7.2 %	−10.6 %	11.5 %	0.80
Anterior Caudate	−8.0%	11.4 %	−4.5 %	12.7 %	0.60
Posterior Caudate	−9.4%	10.9 %	−9.9 %	14.9 %	0.65
Anterior Putamen	−6.3%	11.3 %	−4.3 %	10.1 %	0.70
Posterior Putamen	−9.5 %	6.9%	−11.1 %	9.5 %	0.73