Imaging Dopamine Transmission in Cocaine Dependence: Link Between Neurochemistry and Response to Treatment

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Objective: 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 linked to cocaine-seeking behavior. The goal of the present study was to investigate whether this association applies to the treatment setting. The authors hypothesized 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.

Method: Prior to treatment, cocaine-dependent subjects underwent two PET scans using [^{11}C]raclopride, before and after the administration of a stimulant (methylphenidate), for measurement of striatal dopamine $D_{2/3}$ receptor binding and presynaptic dopamine release.

Results: Both of the outcome measures were lower in the volunteers who did not respond to treatment than in those who experienced a positive treatment response.

Conclusions: 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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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 of 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 and type 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 reuptake from the synapse, which then increases extracellular 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, investigators have shown that both baseline $D_{2/3}$ receptor binding and stimulant-induced dopamine release are lower in cocaine-dependent subjects than in healthy comparison subjects (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 of non-treatment-seeking cocaine-dependent human volunteers were followed by cocaine self-administration sessions. In these sessions, the participants chose 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 they suggest that low dopamine release is associated with compulsive cocaine use (10).

This article is discussed in an editorial by Dr. Martis (p. 572).

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 provide two parameters associated with dopamine transmission: 1) baseline dopamine $D_{2/3}$ receptor binding, measured as nondisplaceable binding potential (BP_{ND}) (described in the Method section), and 2) stimulant-induced presynaptic dopamine release, measured as the stimulant-induced change in BP_{ND}. Following the scans, the subjects were enrolled in treatment consisting of 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 cocaine use over money had low presynaptic dopamine release (change in BP_{ND}) in the limbic striatum, we hypothesized that treatment-seeking subjects who did not respond to a treatment that uses a monetary reward to reduce cocaine use would also have low dopamine release (change in BP_{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 did not respond to treatment would also have low dopamine receptor binding potential in the limbic striatum.

A group of comparison subjects was also included in order to show that this cohort of cocaine-dependent subjects had the same abnormalities 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 assess 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 presynaptic dopamine release (change in BP_{ND}) in relation to their pretreatment scans.

Method

Subjects and Procedure

The study was approved by the New York State Psychiatric Institute institutional review board, and all participants gave written informed consent. The cocaine-dependent patients were 22 men and three women (mean age=37 years, SD=7) who were medically healthy and had diagnoses of cocaine dependence but no other psychiatric diagnosis. A group of healthy matched comparison subjects (21 men, three women; mean age=36 years, SD=6) with no DSM-IV axis I disorder was included; they were matched for cigarette smoking, gender, and ethnicity. The cocaine-dependent subjects underwent the following procedures: 1) screening, 2) 14 days of abstinence, 3) first PET imaging session, 4) 12 weeks of behavioral treatment, 5) second PET session, and 6) an additional 12 weeks of treatment. The procedures are fully described in the supplement accompanying the online version of the article.

PET and MRI Scanning

For all subjects, [^{11}C]raclopride was administered as a bolus and the PET scans were acquired on the ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn.) in three-dimensional mode over 60 minutes. All participants underwent two scans with [^{11}C]raclopride: at baseline and following administration of oral methylphenidate (60 mg), according to methods previously described (17). A plasma sample for analysis of methylphenidate level was obtained just before the second scan. The PET data were analyzed by means of simplified tissue reference modeling (18), with the cerebellum used as a reference region to estimate nonspecific 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 nondisplaceable binding, f_{ND} is the free fraction in the nondisplaceable distribution volume of the brain, B_{max} is the concentration of $D_{2/3}$ receptors (nanomoles per gram 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 defined as $(BP_{NDbaseline} - BP_{NDmethylphenidate})/BP_{NDbaseline}$ (9, 10). This method has been used extensively in PET imaging (20) to provide an estimate of the stimulant-induced change in extracellular dopamine in the striatum.

In addition to the PET scans, each participant also underwent a magnetic resonance imaging (MRI) scan (GE Signa EXCITE 3T/94 cm scanner, GE Medical Systems, Milwaukee, Wis.) for identification of the regions of interest. On the basis of our previous study showing that dopamine release in the limbic striatum correlated with the choice to self-administer cocaine (10), the primary region of interest in this study was the limbic striatum. 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 measurements from the right and left regions were averaged. Identification of the regions of interest, motion correction, and PET-to-MRI registration were performed with MEDx (Sensor Systems, Sterling, Va.) as previously described (22).

Treatment

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 National Institute on Drug Abuse manual (23). The therapy sessions were conducted twice weekly by a trained therapist, who was supervised by one of the investigators (K.M.C.). The voucher incentive component of the program followed procedures previously outlined by Higgins et al. (11, 12). The participants received voucher points for each urine sample that tested negative for a cocaine metabolite (i.e., benzoylecgonine). The voucher points ($0.25) were acquired on an escalating schedule that started at 10 points for the 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 urine samples at 100% of the scheduled treatment visits (36 over the course of 12 weeks). The treatment is described further in the online supplemental data.

The cocaine-dependent subjects were given the option of returning for PET scans after 12 weeks of treatment, in order to in-

TABLE 1. PET Scan Measures of Dopamine Transmission in Healthy Comparison Subjects and Cocaine-Dependent Patients

	Healthy Comparison Subjects (N=24)		Cocaine-Dependent Patients (N=25[a])		Two-Tailed Unpaired t Test		
PET Measure and Region of Interest	Mean	SD	Mean	SD	t	df	p
Baseline nondisplaceable binding potential (BP_{ND}) of [^{11}C]raclopride							
Limbic striatum	2.00	0.26	1.83	0.23	2.43	47	0.02
Anterior caudate	2.14	0.29	2.02	0.24	1.67	47	0.10
Posterior caudate	1.37	0.24	1.35	0.22	0.26	47	0.80
Anterior putamen	2.56	0.23	2.36	0.29	2.67	47	0.01
Posterior putamen	2.66	0.24	2.47	0.30	2.51	47	0.02
Change in BP_{ND} in response to 60 mg of methylphenidate (%)							
Limbic striatum	–13.7	8.7	–5.8	8.6	3.14	46	0.003
Anterior caudate	–6.3	10.4	–6.1	10.6	0.08	46	0.90
Posterior caudate	–11.6	11.1	–5.6	10.6	1.92	46	0.06
Anterior putamen	–10.3	7.9	–4.2	8.7	2.56	46	0.01
Posterior putamen	–16.2	9.4	–8.5	7.0	3.21	46	0.002

[a] N=24 for change in BP_{ND}.

vestigate the effect of treatment on these measures of dopamine transmission. The posttreatment scans used the same methods as the initial set, i.e., two scans with [^{11}C]raclopride before and after 60 mg of methylphenidate.

Statistical Analysis

Differences between groups in demographic variables and PET scan measures were examined with unpaired t tests. Differences between the cocaine abusers and healthy comparison subjects in [^{11}C]raclopride BP_{ND} and change in BP_{ND} were analyzed with a repeated-measures analysis of variance (ANOVA), with the region of interest as the repeated measure and the diagnostic group as the cofactor. Because of the animal literature showing that the nucleus accumbens plays a critical role in reward-based behaviors (3, 5) and our previous study showing that change in BP_{ND} specifically in the limbic striatum correlated with cocaine self-administration (10), the limbic striatum was our primary region of interest for the comparison of the treatment responders and nonresponders. Thus, the primary analysis was performed on this brain region by using an unpaired t test to compare BP_{ND} and change in BP_{ND} in the responders and nonresponders. After this analysis, we conducted an exploratory analysis of the remaining regions using unpaired t tests with correction for multiple observations. BP_{ND} and change in BP_{ND} in the cocaine-dependent subjects scanned before and after the 12 weeks of treatment were compared by means of paired t tests.

Results

The study was completed by 25 cocaine-dependent volunteers. One subject underwent only the PET scan before methylphenidate administration; thus, the analyses of change in BP_{ND} included only 24 of the cocaine-dependent subjects. Comparisons of the demographic characteristics of the cocaine abusers and healthy comparison subjects are presented in the online data supplement.

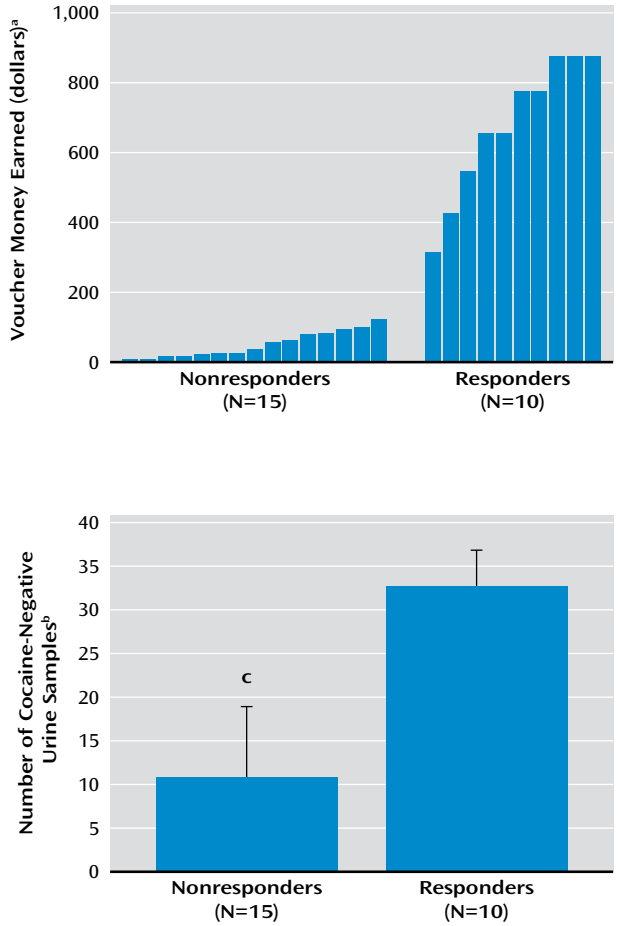
BP_{ND} and Change in BP_{ND} in Comparison and Cocaine-Dependent Subjects

In relation to the comparison subjects, cocaine dependence was associated with both lower $D_{2/3}$ receptor BP_{ND} (repeated-measures ANOVAs corrected for sphericity; effect of diagnosis: F=5.79, df=1, 47, p=0.02; effect of region: F=399.28, df=3, 141, p<0.001; diagnosis-by-region interaction: F=2.42, df=3, 141, p=0.07) and less change in BP_{ND} (repeated-measures ANOVAs corrected for sphericity; effect of diagnosis: F=11.68, df=1, 46, p=0.001; effect of region: F=3.61, df=2.9, 133, p=0.02; diagnosis-by-region interaction: F=1.52, df=4, 184, p=0.22). The values for both $D_{2/3}$ receptor BP_{ND} (premethylphenidate) and change in BP_{ND} for each region are provided in Table 1.

Response to Treatment

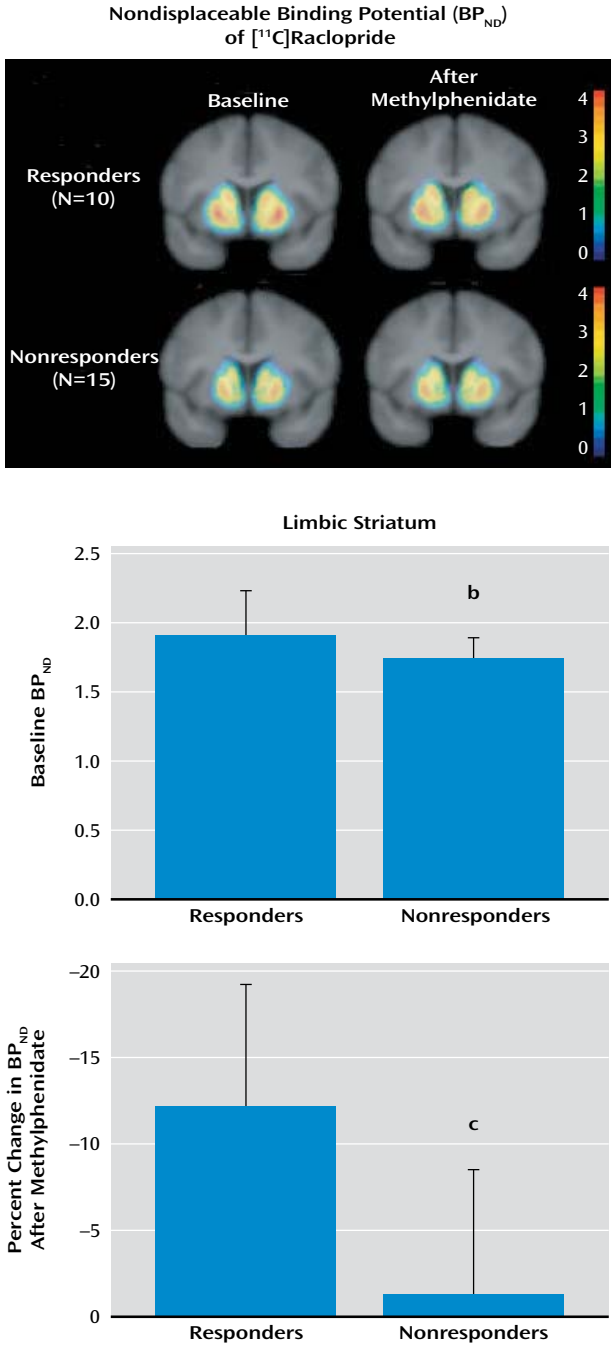
Response to treatment among the cocaine-dependent patients was measured as the amount of voucher money earned, since this outcome measure depends on continuous cocaine-free urine samples and reflects the degree of abstinence obtained. As shown in Figure 1, the response to treatment among the cocaine-dependent subjects was bimodal, which is a frequent finding in studies using this treatment modality (24, 25). Thus, the response to treatment was analyzed by comparing the group of cocaine abusers who clustered on the left portion of the graph (nonresponders, N=15) with those on the right (responders, N=10). Of the 10 responders, nine experienced continued recovery at 6 months past the start of treatment; the remaining subject provided 100% cocaine-negative urine samples until week 11, then moved and was not available for follow-up in person (although by telephone reported continued abstinence). Of the 15 nonresponders, none achieved sustained abstinence. No differences in age, tobacco smoking, or amount of cocaine use before study entry were seen between the responders and nonresponders (p>0.2 in all cases, see supplemental data). However, the duration of cocaine use was longer for the nonresponders (mean=17 years, SD=8) than for the responders (mean=11 years, SD=8) (t=2.34, df=23, p=0.03).

FIGURE 1. Rewards Earned and Number of Negative Urine Samples for 25 Cocaine-Dependent Patients Who Received 12 Weeks of Treatment With Contingency Management and Positive Reinforcement



[a] Range, $0.00 to $977.50. This outcome showed a bimodal distribution and was used to classify subjects as responders or nonresponders.
[b] Range, 0 to 36. The values are the mean and standard deviation for each group.
[c] Significant difference between groups (t=8.41, df=23, p<0.0001, two-tailed test).

FIGURE 2. Pretreatment PET Scan Images[a] and Measures of Dopamine Transmission in the Limbic Striatum of Cocaine-Dependent Patients Who Did or Did Not Respond to 12 Weeks of Behavioral Treatment



[a] Binding of [11C]raclopride, a radioligand that provides quantitative information about striatal dopamine type 2 and type 3 ($D_{2/3}$) receptor binding. Methylphenidate increases extracellular dopamine so that fewer $D_{2/3}$ receptors are available to bind to [11C]raclopride; the dose of methylphenidate was 60 mg p.o. The color bar shows the values for BP_{ND}.
[b] Significant difference between groups (t=2.10, df=13, p=0.05, two-tailed test).
[c] Significant difference between groups (t=3.90, df=13, p<0.001, two-tailed test).

Comparison of PET Data for Responders and Nonresponders

Figure 2 shows the average BP_{ND} (calculated per voxel) in the baseline condition and following methylphenidate in the treatment responders and nonresponders. The primary analysis for this study was for the limbic striatum, and the values were greater for the responders than for the nonresponders for both BP_{ND} (responders: mean=1.94, SD=0.27; nonresponders: mean=1.75, SD=0.17) and the change in BP_{ND} (responders: mean=–12.1%, SD=6.9; nonresponders: mean=–1.3%, SD=6.7). As shown in Figure 2, this effect was more pronounced for change in BP_{ND} than for baseline BP_{ND}.

TABLE 2. Pretreatment PET Scan Measures of Dopamine Transmission in Cocaine-Dependent Patients Who Did or Did Not Respond to 12 Weeks of Behavioral Treatment

	Responders (N=10)		Nonresponders (N=15[a])		Two-Tailed Unpaired t Test		
PET Measure and Region of Interest	Mean	SD	Mean	SD	t	df	p
Baseline nondisplaceable binding potential (BP_{ND}) of [^{11}C]raclopride							
Limbic striatum	1.94	0.27	1.75	0.17	2.07	23	0.05
Anterior caudate	2.11	0.31	1.96	0.17	1.60	23	0.12
Posterior caudate	1.40	0.26	1.32	0.19	0.84	23	0.40
Anterior putamen	2.51	0.34	2.26	0.20	2.26	23	0.03
Posterior putamen	2.59	0.39	2.39	0.20	1.74	23	0.09
Change in BP_{ND} in response to 60 mg of methylphenidate (%)							
Limbic striatum	–12.1	6.8	–1.3	6.7	3.85	22	<0.001
Anterior caudate	–8.5	10.7	–2.6	9.9	1.40	22	0.18
Posterior caudate	–9.4	10.9	–0.3	7.8	2.23	22	0.04
Anterior putamen	–7.4	11.2	–1.9	6.0	1.56	22	0.13
Posterior putamen	–11.0	7.9	–6.7	5.8	1.51	22	0.15

[a] N=14 for change in BP_{ND}.

An exploratory analysis was performed to compare the values in the remaining regions (Table 2). While some of these values were lower in the nonresponders than in the responders, the results did not survive correction for multiple observations.

Comparison of PET Data Before and After Treatment

Of the 25 cocaine-dependent subjects, 15 returned for PET scans after 12 weeks of treatment, and nine of them were treatment responders. The data comparing BP_{ND} and change in BP_{ND} before and after treatment in the responders (Table 3) show no significant differences. Comparisons for the six nonresponders also showed no significant differences in the before and after conditions ($p>0.5$ in all cases, data not shown). Notably, a post hoc analysis of the treatment responders and the healthy comparison subjects also showed no difference in BP_{ND} or change in BP_{ND} ($p>0.10$ in all cases) 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 $D_{2/3}$ receptor binding (BP_{ND}) and presynaptic dopamine release (change in BP_{ND} after methylphenidate administration). 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 than did 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). Creating lesions in the nucleus accumbens of 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 produced 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, some not seeking treatment (10) and some who were seeking treatment (reported here), low dopamine release in the limbic striatum was associated with the choice to consume cocaine over alternative reinforcers. In each case, the subjects with low dopamine transmission made the nonadaptive choice between competing rewards. Our previous study in the laboratory gave subjects a choice between a low dose of cocaine (6 mg) and $5, and the choice was weighted toward the money, since the street value of this dose of cocaine was less than $5. In the present study, subjects came to the clinic in search of treatment and could earn money for pursuing their goal. Therefore, in both the nontreatment and treatment studies, the more adaptive response was 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, relative to comparison subjects, as indicated by four different findings: 1) lower

TABLE 3. Pre- and Posttreatment PET Scan Measures of Dopamine Transmission in Nine Cocaine-Dependent Patients Who Responded to 12 Weeks of Behavioral Treatment

PET Measure and Region of Interest	Before Treatment		After Treatment		Two-Tailed Paired t Test (df=8)	
	Mean	SD	Mean	SD	t	p
Baseline nondisplaceable binding potential (BP_{ND}) of [^{11}C]raclopride						
Limbic striatum	1.95	0.28	2.02	0.36	0.41	0.70
Anterior caudate	2.11	0.33	2.34	0.31	1.46	0.17
Posterior caudate	1.42	0.27	1.50	0.31	1.12	0.28
Anterior putamen	2.52	0.36	2.77	0.33	1.50	0.15
Posterior putamen	2.61	0.40	2.90	0.41	1.52	0.20
Change in BP_{ND} in response to 60 mg of methylphenidate (%)						
Limbic striatum	–11.8	7.2	–10.6	11.5	0.26	0.80
Anterior caudate	–8.0	11.4	–4.5	12.7	0.53	0.60
Posterior caudate	–9.4	10.9	–9.9	14.9	1.53	0.65
Anterior putamen	–6.3	11.3	–4.3	10.1	0.38	0.70
Posterior putamen	–9.5	6.9	–11.1	9.5	0.35	0.73

baseline $D_{2/3}$ receptor binding (BP_{ND}) of the postsynaptic neurons (9, 10, 15, 16), 2) lower presynaptic dopamine release (change in BP_{ND}) (9, 10), 3) lower presynaptic neuronal stores of dopamine (28), and 4) lower baseline levels of endogenous dopamine (29). In the present study we investigated the association between dopamine transmission and response to treatment, and these results show that a positive response is associated with higher $D_{2/3}$ receptor binding and greater methylphenidate-induced dopamine release than occur in those for whom treatment fails. These findings suggest that increasing striatal dopamine transmission would be the most appropriate strategy for converting treatment nonresponders to responders, by either increasing $D_{2/3}$ receptors or increasing presynaptic 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). On the basis of those data and the findings from the present study, it can be surmised that increasing $D_{2/3}$ receptors would improve treatment response, but this technology is unlikely to translate into human use in the near future.

Another approach is to increase presynaptic dopamine release. A number of previous clinical trials have investigated medications that increase striatal dopamine transmission, and while some showed success, others did not (31). One reason for this inconsistency may be that medications that are known to increase dopamine transmission in the nonaddicted brain may have a minimal effect in the addicted brain, as shown by this study. Notably, Schmitz et al. (32) reported that treatment of cocaine abusers with contingency management and L-dopa/carbidopa, which would be expected to improve dopamine transmission by increasing presynaptic stores in the striatum, resulted in a greater response to treatment than occurred with placebo. Another approach may be to increase dopamine transmission by targeting other receptor systems, such as the kappa or acetylcholine receptors (for reviews, see references 33 and 34). Together, these findings strongly suggest that the combination of pharmacology addressing 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 presynaptic 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 comparison subjects before treatment, suggesting that presynaptic dopamine was largely intact in the responders to begin with. Among the nonresponders, 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.

Previous studies using functional MRI 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 response to treatment. 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 a review, see reference 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.

On the basis of 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 change in BP_{ND} were significantly lower in the nonresponders. However, if we had used correction for multiple observations (which would have been necessary if our hypothesis had included all regions), only the finding for change in BP_{ND} would have reached significance. It is interesting that 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 the effect of change in BP_{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 presynaptic dopamine release (6), studies have shown that receptor internalization or dimerization plays a key role (7, 38, 39).

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

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