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Striatal dopamine D2 receptor availability predicts the thalamic and medial prefrontal responses to reward in cocaine abusers three years later

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Abstract

Low levels of dopamine (DA) D2 receptor availability at a resting baseline have been previously reported in drug addicted individuals and have been associated with reduced ventral and dorsal prefrontal metabolism. The reduction in DA D2 receptor availability along with the reduced ventral frontal metabolism is thought to underlie compromised sensitivity to non-drug reward, a core characteristic of drug addiction. We therefore hypothesized that variability in DA D2 receptor availability at baseline will covary with dynamic responses to monetary reward in addicted individuals. Striatal DA D2 receptor availability was measured with [^{11}C]raclopride and positron emission tomography and response to monetary reward was measured (an average of 3 years later) with functional magnetic resonance imaging in seven cocaine addicted individuals. Results show that low DA D2 receptor availability in the dorsal striatum was associated with decreased thalamic response to monetary reward; while low availability in ventral striatum was associated with increased medial prefrontal (Brodmann Area 6/8/32) response to monetary reward. These preliminary results, that need to be replicated in larger sample sizes and validated with healthy controls, suggest that resting striatal DA D2 receptor availability predicts variability in functional responses to a non-drug reinforcer (money) in prefrontal cortex, implicated in behavioral monitoring, and in thalamus, implicated in conditioned responses and expectation, in cocaine addicted individuals.

Keywords

fMRI; PET; striatal dopamine D2 receptor availability; thalamus; prefrontal cortex; cocaine addiction; monetary reward

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Introduction

Striatal decrease in dopamine (DA) D2 receptor availability in drug abusers may reflect neuroadaptations secondary to supraphysiological dopaminergic stimulation from repeated drug abuse (Volkow et al., 2004). Using functional magnetic resonance imaging (fMRI), we have recently reported compromised prefrontal cortical sensitivity to monetary reward in cocaine addicted individuals (Goldstein et al., 2007a). Given a significant association between resting glucose metabolism in the ventral and dorsal prefrontal cortex (PFC) and baseline striatal DA D2 receptor availability in drug abusers (cocaine, methamphetamine and alcoholic) (Volkow et al., 2001; Volkow et al., 1993b; Volkow et al., 2007b), we interpreted these fMRI results to reflect reduced cortical sensitivity to non-drug rewards in addiction that may in part reflect alterations in DA release and DA D2 receptor availability (Volkow et al., 2007a). However, a direct association between a dynamic (i.e., in response to a challenge) reward-related response of the PFC (and other regions comprising the striato-thalamic-prefrontal cortical circuit previously implicated in drug addiction) with baseline DA D2 receptor availability in drug addicted individuals remains to be demonstrated.

In the current preliminary study we therefore correlated blood oxygen level dependent (BOLD) fMRI responses to a monetary incentive task with DA D2 receptor availability [obtained at a resting baseline with [^{11}C]raclopride and positron emission tomography (PET), a mean of 3 years prior to the fMRI study] in cocaine addicted individuals. We tested the hypothesis that response to monetary reward in the PFC (and other regions in the striato-thalamic-prefrontal cortical circuit) is significantly associated with striatal DA D2 receptor availability in cocaine addicted individuals.

Methods

Participants

Data were available for seven active cocaine addicted subjects (5 males and 2 females, all African-American, see Table 1 for demographics) that had participated in two previously published neuroimaging studies (Goldstein et al., 2007a;Volkow et al., 2006a;Volkow et al., 2006b). Participants met inclusion criteria at both studies, as verified by physical, neurological and psychiatric examinations. In brief, subjects were free of neuropsychiatric (other than drug abuse or dependence), cardiovascular, or endocrinological diseases, in addition fulfilling DSM-IV criteria for current cocaine dependence or abuse. All subjects were active users for at least the previous 6 months (free-base or crack, at least “four grams” a week; see Table 1 for other drug use variables). Current use of marijuana, barbiturates, amphetamines, or opiates was denied and corroborated by pre-scan urine tests. Written informed consent was obtained for all subjects after procedures were carefully explained and in compliance with the local Institutional Review Board.

PET data

PET scans were performed with a CTI 931 scanner (Siemens, Knoxville, TN). Subjects were scanned after intravenous injection of [^{11}C]raclopride, a relatively low affinity DA D2/D3 receptor radioligand. Details of the procedures for positioning, arterial and venous catetherization, and quantification of the radiotracer have been previously described (Volkow et al., 1993b). Briefly, the 60-minute dynamic scans were started immediately after intravenous injection of 4–10 mCi of [^{11}C]raclopride (specific activity > 0.25 Ci/μmol at time of injection). During the study, subjects lay with eyes open in the PET camera, the room was dimly lit, and noise was kept to a minimum. Regions of interest (ROIs) in the [^{11}C]raclopride images were obtained for the dorsal (caudate, putamen) and ventral striatum and for the cerebellum, used to control for non-specific binding. For every subject, these

three striatal ROIs were initially selected on an averaged scan (activity from 10 to 60 minutes) and were then projected to the dynamic scans, as previously described (Volkow et al., 1993b). The time-activity curves for [^{11}C]raclopride in the striatum and the cerebellum and the time-activity curves for unchanged tracer in plasma were used to calculate distribution volumes by using a graphical analyses technique for reversible systems (Logan et al., 1990). The parameter Bmax/Kd, obtained as the ratio of the distribution volume in the striatum to that in the cerebellum minus 1, was used as the model parameter of DA D2 receptor availability. This PET data was obtained a mean of 3.3 ± 1.2 years before the fMRI data.

fMRI Activation Paradigm

After training, subjects performed a sustained attention task under three blocked monetary incentive conditions ($0.45, $0.01, or $0.00). Specifically, subjects either responded (pressed a button) or refrained from responding during a trigger stimulus (red square), depending on the preceding instructional stimulus [adapted from (Thut et al., 1997)]. There were 18 trials, nine pairs of press and no-press, for each of the monetary conditions that repeated six times/blocks [see details in (Goldstein et al., 2007a; Goldstein et al., 2007b; Goldstein et al., 2007c)]. Accuracy and reaction time were collected throughout the task (Table 1). To simulate real-life incentive motivation, the subjects received up to $50 for this task, depending on performance accuracy. This was a relatively substantial amount of money because it doubled the subjects' total earnings during the complete study day. Subjects were aware of the reward contingencies throughout the task. The task was presented by means of MRI-compatible goggles. Upon task completion, subjects rated their level of interest and excitement in the three monetary conditions using two visual analogue scales (range: 0 to 7, boring to interesting and dull to exciting) and the mean of these two ratings was used as an indirect measure of self-reported task motivation (Table 1).

fMRI Data Processing and Image Analysis

MRI scanning was performed on a 4-T whole-body MRI scanner (Varian, Palo Alto, CA/ Siemens, Berlin). The BOLD responses were measured with a T2*-weighted single-shot gradient-echo echoplanar imaging sequence (TE=20, TR=3500 msec, 4-mm slice thickness, 1-mm gap, typically 33 coronal slices, field of view=20 cm, 64×64 matrix size, 90° flip angle, 200-kHz bandwidth with ramp sampling, 91 time points, and four dummy scans). Padding was used to minimize motion, which was inside the accepted threshold of 1-mm maximum displacement (32% of the voxel size) and 1° rotation, as determined immediately after each run (Caparelli et al., 2003). A T1-weighted three-dimensional modified equilibrium Fourier transform sequence (Lee et al., 1995) was used for structural imaging; all MRI images were inspected to rule out gross morphological brain abnormalities.

All time series were converted into the SPM99 format (Wellcome Department of Cognitive Neurology, London). A six-parameter rigid body transformation (three rotations, three translations) was used for image realignment to correct for head motion. The realigned data sets were normalized to the Talairach frame with a 12-parameter affine transformation (Ashburner et al., 1997) by using a voxel size of 3×3×3 mm^3. An 8-mm full-width half-maximum Gaussian kernel was used to smooth the data. A general linear model (Friston et al., 1995) and a box-car design convolved with a canonical hemodynamic response function were used to calculate the activation maps. The time series were band-pass filtered with the hemodynamic response function as a low-pass filter and a 1/750-second cut-off frequency as a high-pass filter. For each subject, three contrasts were created (45¢, 1¢, or 0¢ vs. baseline averaged across all six task runs).

Statistical Analyses

Three voxel-based (whole brain) simple correlations between BOLD fMRI responses (each monetary contrast vs. fixation baseline) and DA D2 receptor availability in the bilateral[1] caudate, putamen and ventral striatum (i.e., Bmax/Kd values in each of these three ROIs were used as seed values) were performed (for a total of nine analyses). In all whole-brain analyses, statistical threshold was set at $p<.05$ cluster-level corrected (minimum $Z=2.5$ or $T=4.03$) with a minimum of 5 contiguous voxels (135 mm^3). Because we performed nine correlation analyses, we further applied a Bonferroni correction to protect against Type I error (i.e., nominal significance level was set at $p\leq.006$ corrected).

For descriptive purposes, we also conducted correlations between all demographics and task-related performance variables with DA D2 receptor availability (Table 1) and with selected BOLD fMRI ROIs (here the cluster maxima voxel was used). To protect against Type I error, nominal significance was set at a family-wise level of $p<.01$ for these exploratory correlations.

Results

Statistically significant correlations between DA D2 receptor availability and fMRI BOLD responses to monetary reward (45¢) were observed and included the PFC and thalamus as a priori hypothesized (Table 2 and Figure 1). Specifically, thalamic BOLD fMRI responses to the highest monetary reward (45¢) correlated positively with DA D2 receptor availability in the caudate (Figure 1A) with a similar trend for the putamen (data not shown). The BOLD fMRI signal in the supramarginal gyrus showed a similar correlation with DA D2 receptor availability in the putamen. Further, fMRI response to this highest monetary reward in the right dorsal superior medial frontal gyrus [Brodmann Area (BA) 6/8/32] correlated negatively with DA D2 receptor availability in the ventral striatum (Figure 1B). These correlations (Figure 1) were still detected after holding constant (with partial correlations) the time delay between fMRI and PET and years of cocaine use ($r>|.95|$, $p<.01$). These correlations were not observed for the low monetary reward (1¢) or during non-reward (0¢).

Correlation analyses also showed a trend for a positive association between the ventral striatum DA D2 receptor availability and reaction time during all task conditions (Table 1). However, these correlations did not survive the family-wise correction. Finally, there was a trend for a negative correlation between BOLD responses in the right dorsal superior medial frontal gyrus ROI with reaction time during the highest monetary reward condition (45¢, $R=-0.78$; $p<0.05$). Similar trends were not observed for any of the other variables in Table 1 with this PFC or the thalamic ROI in this sample.

Discussion

The current results demonstrate, for the first time, significant relationships between DA D2 receptor availability in the dorsal and ventral striatum and fMRI BOLD responses to monetary reward in cocaine addicted individuals. Specifically, a negative correlation was observed between the dorsal superior medial frontal gyrus [BA 6/8/32, overlapping with the rostral cingulate zone as defined by (Ridderinkhof et al., 2004)] and DA D2 receptor availability in the ventral striatum, such that the lower the ventral striatal DA D2 receptor availability, the higher this PFC region's responsiveness to monetary reward. Given that cocaine addicted individuals demonstrate reduced DA D2 receptor availability (Volkow et al., 2004), decreased baseline prefrontal metabolism (Volkow et al., 1993b) and reduced

[1]There were no significant differences in DA D2 receptor availability between both hemispheres (paired $t<0.1$, $p>0.9$); values were therefore averaged for all analyses.

PFC sensitivity to monetary reward (Goldstein et al., 2007a), the direction of this correlation was unexpected. However, previous studies similarly reported a *negative* correlation between DA D2 receptor availability in the ventral striatum (where the nucleus accumbens is located) and fMRI BOLD response to alcohol-related cues in a more ventral PFC region (encompassing the medial PFC and rostral anterior cingulate cortex) in alcoholic subjects but not in healthy controls (Heinz et al., 2004). Our results extend this negative correlation to a secondary *non-drug* reinforcer. It is possible that the cocaine addicted individuals with lower ventral striatal DA D2 receptor availability are also the ones who activate this PFC region, frequently implicated in performance monitoring to feedback (Ridderinkhof et al., 2004), possibly to compensate for their reduced sensitivity to monetary reinforcement or for their increased impulsivity. In support of this interpretation are the associations with reaction time during the task: faster performance was associated with both higher PFC response to monetary reward and lower DA D2 ventral striatal receptor availability. Note that although in our study these correlations did not reach nominal significance level, other studies have recently linked dopamine synthesis (Landau et al., 2009) and dopamine binding potential (Cervenka et al., 2008) with cognitive performance including reaction times. It is also possible that cocaine addicted subjects with low DA D2 receptor availability, who may also have lower PFC glucose metabolism at baseline (Volkow et al., 1993b), generate a greater dynamic change when challenged than those with higher DA D2 receptor availability and higher baseline prefrontal metabolism.

In contrast, positive correlations were observed for the thalamus such that the higher the DA D2 receptor availability in the dorsal striatum (significant for the caudate and with a similar trend for the putamen), the higher the thalamic responses to monetary reward. The thalamus, a key target for brain's DA (Sanchez-Gonzalez et al., 2005), has a major role in conditioned reinforcement and reward expectation. For example, we have previously observed greater thalamic metabolic responses when methylphenidate, a stimulant drug that similarly to cocaine blocks the DA transporters, was expected as compared to when it was unexpected (Volkow et al., 2003). Similarly, animal experiments show greater thalamic metabolism when cocaine is administered in a drug-conditioned place than when it is administered in the home-cage to "addicted" rats (Knapp et al., 2002) or when comparing contingent vs. non-contingent cocaine administration in non human primates (Porrino et al., 2002). Moreover, we also showed that in cocaine abusers, but not in controls, intravenous methylphenidate significantly increased DA in the thalamus and this increase was proportional to the intensity of the craving elicited by methylphenidate (Volkow et al., 1997). Therefore, the currently reported correlation suggests dopaminergically modulated thalamic involvement in monetary reward expectation in the cocaine addicted individuals.

Clearly the current results need to be replicated in larger sample sizes of both addicted and healthy control individuals. Specifically, inclusion of a control group would allow to directly link these results to a general relationship between DA D2/D3 receptor availability and reward processing [note that recent study showed a positive correlation between neural activity of the dopaminergic midbrain during reward anticipation (as measured with fMRI) and reward-related DA D2 receptor availability in the ventral striatum in 10 healthy volunteers (Hakyemez et al., 2008)], or highlight whether these findings are specific to cocaine addiction. A further limitation of this report is the time elapsed between the PET and the fMRI studies, which was on average 3 years. Although stability of the PET measures is quite high [test-retest studies (with up to 19 months follow-up) report low variability of [^{11}C]raclopride binding potential (7.9% variability) or distribution volume (6–8% change) and high intraclass correlations (0.81 – 0.90) in the striatal dopaminergic system between the two separate measures (Hietala et al., 1999; Schlösser et al., 1998; Uchida et al., 2009; Volkow et al., 1993a)], test-retest measures have not been done in cocaine abusers and these

are likely to vary as a function of the drug histories. Thus, the current results need to be replicated performing the PET and fMRI measurements during the same time frame.

To summarize, pending replication in larger studies in addicted individuals as compared to healthy controls that undergo PET-fMRI during the same time frame, our results suggest that PFC and thalamic responses to monetary reward in cocaine addicted individuals could be modulated by DA D2 receptor availability in the ventral and dorsal striatum, respectively. The relevance of results to choice behaviour, especially for the drug and drug-related stimuli vis-à-vis alternative reinforcers [e.g., (Martinez et al., 2007)], needs to be explored in future studies.

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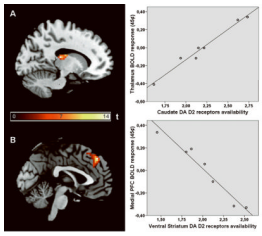

Figure 1.
Localization (left) and scatterplot (right) of the correlations between (A) caudate DA D2 receptor availability (as seed value) and thalamic (cluster maxima at x=9, y=−11, z=14) BOLD fMRI response and between (B) ventral striatum DA D2 receptor availability (as seed value) and medial prefrontal cortex (cluster maxima at x=0, y=43, z=39) BOLD fMRI response to monetary reward (45¢) in seven cocaine addicted individuals. Statistical threshold: p<.05 cluster-level corrected (minimum Z=2.5 or T=4.03). Minimum cluster size: 5 contiguous voxels (135 mm^3). For display purposes, threshold was set at p<0.01 uncorrected.

Table 1

Sample descriptives including demographics, history of cocaine use and behavioral task variables (motivation, reaction time and accuracy) and their correlations with dopamine (DA) D2 receptor availability (Bmax/Kd) in the caudate, putamen and ventral striatum.

						Correlations (R) with DA D2 receptors level(Bmax/Kd)		
General, drug use and behavioral variables	**N**	**Min**	**Max**	**Mean**	**SD**	**Putamen**	**Caudate**	**V. Striatum**
Age	7	37	54	43.9	5.6	−0.39	−0.43	−0.41
Years of education	7	8	16	12.43	2.57	−0.16	−0.42	0.46
Age of onset for cocaine use	7	20	45	28.43	9.09	0.17	0.8	−0.18
Years of cocaine use	7	4	23	15.43	6.70	−0.55	−0.61	−0.01
Number of days of cocaine use per week in the past 30 days	7	1	7	3.64	2.34	0.16	0.08	0.80*
Number of days since the last cocaine use	7	1	10	2.86	3.48	0.65	0.81*	0.35
Longest period of cocaine abstinence (days)	7	0	1825	435.71	667.95	0.35	0.35	−0.11
Cocaine Selective Severity Assessment (Sum of 18-items)	7	8	38.5	15.93	10.67	−0.39	−0.47	−0.33
Cocaine Craving Questionnaire (Sum of 5 questions)	7	0	38	22.00	12.88	−0.39	−0.47	−0.07
Self-report of motivation for 0¢ condition	7	0.5	6.5	4.43	2.30	0.15	0.43	−0.27
Self-report of motivation for 1¢ condition	7	0.5	6.5	4.43	2.30	0.15	0.43	−0.27
Self-report of motivation for 45¢ condition	7	2	6.5	4.79	1.80	0.13	0.41	−0.33
Mean Reaction Time during the 0¢ condition	7	0.22	0.38	0.3034	0.0483	0.54	0.43	0.83*
Mean Reaction Time during the 1¢ condition	7	0.21	0.37	0.3040	0.0498	0.43	0.31	0.77*
Mean Reaction Time during the 45¢ condition	7	0.22	0.36	0.3034	0.0447	0.46	0.30	0.86*
Mean Accuracy for the 0¢ condition	7	92.59	99.07	95.77	2.56	0.04	0.04	−0.22
Mean Accuracy for the 1¢ condition	7	93.83	100	96.61	2.12	0.23	0.41	−0.18
Mean Accuracy for the 45¢ condition	7	95.37	100	97.29	1.66	0.26	0.40	0.02
DAD2 Putamen	7	1.59	3.18	2.61	0.53	-	0.92**	0.35
DAD2 Caudate	7	1.62	2.73	2.20	0.38		-	0.06
DAD2 V. Striatum	7	1.46	2.52	2.02	0.36			-

*p<0.05

**p<0.005

Table 2

Significant positive (+) and negative (−) correlations (Pearson coefficient) between dopamine (DA) D2 receptor availability (Bmax/Kd) in the caudate, putamen and ventral striatum (as seed values) and fMRI BOLD response to monetary reward (45¢, 1¢, 0¢) in seven cocaine addicted individuals.

Condition	ROI	BA	Correlation	Size	x	y	z	t	Z	p-value
Caudate DAD2										
45¢	Thalamus		+0.99	87	9	−11	14	13.84**	4.14	<0.001
	Lingual gyrus	17	+0.97	41	−12	−78	7	9.22*	3.66	0.018
Putamen DAD2										
45¢	Supramarginal gyrus	40	+0.95	99	50	−39	41	10.98**	3.87	<0.001
	Thalamus		+0.97	45	12	−14	15	9.03*	3.63	0.014
1¢	Cuneus	31	−0.97	52	6	−48	33	9.26*	3.67	0.013
Ventral Striatum DAD2										
45¢	Superior Medial Frontal gyrus	6/8/32	−0.98	55	0	43	39	9.86*	3.74	0.006
1¢	Insula/Superior Temporal gyrus	13/22	+0.97	13	45	−14	3	8.96*	3.63	0.008
0¢	Globus Pallidum		+0.95	36	21	−3	−5	6.94*	3.30	0.028

* cluster-level corrected p<0.05

** cluster-level corrected p<0.005

Note: the nominal significance level was p<.006 corrected; the other correlations are reported for completeness.

Note: the x y z coordinates represent the cluster maxima. There were no significant correlations for conditions 0¢ and 1¢ in the caudate, and 0¢ in the putamen at the selected significance threshold.