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Differences in D2 dopamine receptor availability and reaction to novelty in socially housed male monkeys during abstinence from cocaine

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Abstract

Rationale—Studies in socially housed monkeys have demonstrated an influence of position in the social dominance hierarchy on brain dopamine D2 receptors and the reinforcing effects of cocaine that dissipates after long-term cocaine self-administration.

Objective—The aims of the study were to examine the effects of abstinence from cocaine on D2 receptors in socially housed monkeys and to extend behavioral characterizations to measures of reactivity to a novel object.

Materials and methods—Twelve socially housed male cynomolgus monkeys with extensive cocaine self-administration experience were used (average lifetime intakes ~270 and 215 mg/kg for dominant and subordinate monkeys, respectively). Abstinence lasted for approximately 8 months, after which D2 receptor availability was assessed using positron emission tomography and the D2 ligand [^{18}F]fluoroclebopride. Reaction to novelty was also assessed in these subjects as well as nine individually housed monkeys.

Results—During abstinence, D2 receptor availability in the caudate nucleus was significantly higher in dominant versus subordinate monkeys. Average latency to touch a novel object was also significantly higher in dominant monkeys compared to subordinates or individually housed monkeys. In socially experienced monkeys, a significant positive correlation was observed between caudate nucleus D2 receptor availability and latencies to touch the novel object.

Conclusions—Although chronic cocaine self-administration blunts the ability of social dominance to alter D2 receptor availability and sensitivity to the reinforcing effects of cocaine, this influence reemerges during abstinence. In addition, the data suggest that prior experience with social dominance can lead to longer latencies in reaction to novelty—a personality trait associated with low vulnerability to cocaine abuse.

Keywords

Social rank; Reaction to novelty; PET imaging; Vulnerability; Nonhuman primates

Earlier work in socially housed nonhuman primates found that dopamine (DA) D2 receptor availability, as assessed with positron emission tomography (PET), was higher in dominant

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monkeys compared to subordinate animals (Grant et al. 1998; Morgan et al. 2002). In one of these studies, D2 receptor availability increased by approximately 20% in monkeys that attained dominance but was unchanged in subordinates (Morgan et al. 2002). These changes in D2 receptor availability had behavioral consequences such that dominant monkeys self-administered significantly less cocaine compared to subordinate animals. Thus, it appears that the high D2 receptor levels "protected" the dominant monkeys from the reinforcing effects of cocaine which is consistent with data in humans and laboratory animals (Volkow et al. 1999; Thanos et al. 2001; Nader et al. 2006; Dalley et al. 2007).

These studies indicated that the position in the social hierarchy could influence vulnerability to the reinforcing effects of cocaine during early exposure; however, less is known about the influence of social rank in monkeys with extensive cocaine self-administration histories. In the group-housed monkeys described above, social rank-related differences in D2 receptor availability and cocaine self-administration were not observed once monkeys had self-administered cocaine for several years (Czoty et al. 2004). Thus, the influence of the social environment dissipated over time, ostensibly due to the indirect pharmacological effects of cocaine on D2 receptors. The primary goal of the present study was to examine whether social rank-related differences in D2 receptor availability would reemerge during abstinence from cocaine or, alternately, whether long-term cocaine exposure permanently changed the brain such that neuroplasticity related to social rank was no longer possible.

Another aim of this study was to examine the relationship between D2 receptor availability and measures of personality traits in cocaine-experienced monkeys. Preclinical studies have established a connection between aspects of personality and vulnerability to substance abuse (Dawe and Loxton 2004; Verdejo-Garcia et al. 2008). In laboratory animals, measures of various aspects of impulsivity, such as reaction to novelty, can predict sensitivity to abuse-related behavioral effects of psychostimulants (e.g., Piazza et al. 1989, 2000; Bardo et al. 1996; Perry et al. 2005; Dalley et al. 2007). High novelty seeking has generally been associated with lower subcortical D2 receptor availability, higher extracellular DA levels, and increased vulnerability to drug self-administration (Piazza et al. 1991; Hooks et al. 1991; Rouge-Pont et al. 1993; Dalley et al. 2007). In the present study, we assessed the relationship of reaction to novelty and D2 receptor availability in the caudate nucleus and putamen of cocaine-experienced socially housed monkeys; the latency to touch a novel object was compared with data from individually housed cocaine-naïve control monkeys. Based on the relationship between D2 receptor availability and measures of novelty seeking in rats, we hypothesized that dominant monkeys would be less reactive than subordinates (i.e., longer latencies to touch a novel object) and that social rank-related differences in reaction to novelty would parallel differences in D2 receptor availability.

Materials and methods

Subjects

Twenty-one adult male cynomolgus monkeys (*Macaca fascicularis*) served as subjects. Twelve of these monkeys had a history of being housed in groups of three or four for over 2 years (Czoty et al. 2004, 2005b). At the start of the present experiments, six monkeys lived in two social groups of three monkeys per group, and six monkeys were pair-housed with each other. All 12 had self-administered cocaine several days per week for more than 2 years under either a fixed-ratio (FR) schedule of cocaine presentation (Czoty et al. 2004) or a concurrent FR schedule of food and cocaine presentation (Czoty et al. 2005b). There were no differences in average lifetime or past-year cocaine intakes between dominant and subordinate monkeys, although the former was somewhat higher in dominant monkeys (Table 1). The remaining nine monkeys were individually housed and had no previous cocaine exposure. These animals were included in order to better assess the impact of social

housing on our primary behavioral endpoint (reactivity to a novel object). Each monkey was fitted with a nylon collar (Primate Products, Redwood City, CA, USA) and trained to sit calmly in a standard primate restraint chair (Primate Products) using a specially designed stainless steel pole that attached to the collar (Primate Products). Monkeys were weighed weekly and fed enough food daily (Purina Monkey Chow and fresh fruit and vegetables) to maintain body weights at approximately 95% of free-feeding levels. Body weights, which averaged 5.3 kg (SEM, 0.7 kg), did not change significantly during abstinence and were not different between dominant and subordinate monkeys. Water was available ad libitum in the home cage.

Monkeys lived in stainless steel cages (0.71×1.73× 1.83 m; Allentown Caging Equipment, Co., Allentown, NJ, USA) with removable wire mesh partitions that separated monkeys into quadrants (0.71×0.84×0.84 m). Socially housed monkeys were separated daily for several hours during operant behavioral sessions and feeding; partitions remained in place for individually housed monkeys. Social status had previously been determined for each monkey according to the outcomes of agonistic encounters using procedures similar to those described previously (see Kaplan et al. 1982; Czoty et al. 2005b, 2009). Briefly, two observers separately conducted several 15-min observation sessions per pen. Aggressive, submissive, and affiliative behaviors were recorded according to an ethogram described previously (see Table 1 in Morgan et al. 2000) utilizing Noldus Observer software (Noldus Information Technology; Wageningen, The Netherlands). In these focal group sessions, both initiators and recipients of behaviors were recorded. The monkey in each pen aggressing toward all others and submitting to none was ranked #1 (most dominant). The monkey designated most subordinate displayed a low frequency of aggressive behaviors and submitted to all other monkeys in the pen. In each pen of three monkeys, the #2-ranked monkey submitted to the most dominant monkey and aggressed toward the most subordinate monkey; thus, the hierarchies in pens that consisted of three monkeys were linear and transitive. For the present studies, #1-ranked monkeys were considered dominant (n=5), and all other monkeys were considered to be subordinate (n=7). Animal housing and handling and all experimental procedures were performed in accordance with the 2003 National Research Council *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* and were approved by the Animal Care and Use Committee of Wake Forest University. Environmental enrichment was provided as outlined in the Animal Care and Use Committee of Wake Forest University Non-Human Primate Environmental Enrichment Plan.

MR and PET imaging

An anatomical representation of the brain was acquired for each socially housed monkey using magnetic resonance imaging (MRI). Approximately 20 min prior to a scan, subjects were anesthetized with ketamine (15 mg/kg, i.m.) and transported to the MRI facility. Anesthesia was maintained during the scanning procedure with ketamine supplements when necessary. 3D spoiled gradient-recalled acquisition in steady state brain images were acquired (echo time 5, repetition time 45, flip angle 45, receiver bandwidth 15.6 kHz, field of view (FOV) 18 cm, 256×192 matrix, slice thickness 2 mm, number of excitations 3) with a 1.5-T GE Signa NR scanner (GE Medical Systems). T1-weighted whole brain images were used to anatomically define spherical regions of interest (ROIs), including the right and left caudate nucleus, putamen (0.5 mm radius), and cerebellum (0.8 mm radius), for later coregistration with PET images. Individually housed animals were not studied with PET.

During abstinence, PET scans were conducted in each monkey to measure D2 receptor availability using the D2 receptor radioligand [^{18}F]fluoroclebopride (FCP), which does not differentiate among subtypes of the D2-like superfamily (i.e., D_2, D_3, and D_4 receptors; Mach et al. 1996). The duration of abstinence from cocaine did not differ significantly

between dominant and subordinate monkeys (Table 1). Prior to each study, monkeys were anesthetized with 10 mg/kg ketamine and transported to the PET Center. Details regarding [^{18}F]FCP synthesis, the PET data acquisition protocol, blood sampling procedure, and metabolite analysis have been fully described previously (Mach et al. 1993a, b, 1996, 1997; Nader et al. 1999). Briefly, an arterial and a venous catheter were inserted by percutaneous stick for blood sampling and tracer injection, respectively. A paralytic agent (0.07 mg/kg vecuronium Br, i.v.) was administered and ventilation was maintained by a respirator throughout the 3-h PET scan. Supplemental doses of vecuronium (0.1 mg/h) were administered throughout the study. Body temperature was maintained at 40°C, and vital signs (heart rate, blood pressure, respiration rate, and temperature) were monitored throughout the scanning procedure.

Images were acquired on a General Electric Advance NXi PET scanner. In a single scan, the Advance NXi provided 35 transverse slices with a 4.25-mm center-to-center spacing over a 15.2-cm axial field of view. The transaxial resolution of the scanner ranges from 3.8 mm at the center of the FOV to 7.3 mm radial and 5.0 mm tangential at a radius of 20 cm when reconstructed with a ramp filter. Its axial resolution ranges from 4.0 mm at the center to 6.6 mm at a radius of 20 cm when reconstructed with a ramp filter. For more information on the performance of this scanner see DeGrado et al. (1994). At the start of the scan, approximately 5 mCi of [^{18}F]FCP was injected, followed by 3 ml of heparinized saline. Scans were conducted and images were registered to each subject's MRI (see Czoty et al. 2005a). Tissue–time–activity curves were generated for radiotracer concentrations in ROIs defined on each subject's co-registered MRI. Distribution volume ratios (DVR) for the caudate nucleus and putamen were calculated using the cerebellum as the reference region and the graphical method of Logan et al. (1996). Thus, the DVR served as an index of specific [^{18}F]FCP binding in each ROI.

Food-maintained responding

During abstinence from cocaine, eight monkeys received no other drugs. Three monkeys (C-6528, C-6628, and C-6629) received injections of the serotonin 1A receptor agonist 8-OH-DPAT (<0.4 mg/kg total over several weeks) prior to behavioral sessions in which they responded under a concurrent FR schedule of food and saline availability (Czoty et al. 2005b). Over several months, C-6526 had exposure to 4.7 mg/kg of the benzodiazepine midazolam under the concurrent schedule of food and midazolam availability (unpublished studies). At least 4.5 months passed after this drug exposure before the PET scan. During that time and for the duration of abstinence in all animals, monkeys participated in behavioral studies approximately once per week for the purpose of maintaining operant behavior after discontinuation of self-administration sessions. Each day, monkeys were separated by partitioning the cage into quadrants. Next, each monkey was seated in a restraint chair and placed into a ventilated, sound-attenuating chamber (1.5×0.74× 0.76 m; Med Associates, East Fairfield, VT, USA). During the session, 50 responses on the operant lever (FR50) resulted in delivery of a 1-g food pellet. Sessions lasted until 30 reinforcers had been obtained or 60 min had elapsed, whichever came first.

Response to novelty

During abstinence from cocaine in the socially housed monkeys and in all individually housed animals, latency to touch a novel object was determined. First, the monkey in the cage adjacent to the subject's home cage was removed, the partition was removed from between the cages, and the subject was moved to the adjacent cage. Next, the partition was replaced and the novel object, a box measuring 30.5×20.3×20.3 cm made of black Plexiglas, was placed in the monkey's empty home cage. Finally, the partition was again removed and the latency of the monkey to touch the object was recorded. If the monkey did not touch the

object within 15 min, a score of 900 s was assigned. All sessions were videotaped and scored by an observer blind to the monkey's social rank. While somewhat arbitrary, the 900-s maximum duration was based on preliminary data (A Bennett and P Pierre, unpublished) and was established prior to the start of this experiment.

Data analysis

DVRs in the caudate nucleus and putamen were compared between dominant and subordinate monkeys using *t* tests. Regarding novel object reactivity, because some dominant monkeys did not touch the object within 900 s and were thus assigned a score of 900, a (nonparametric) Kruskal–Wallis one-way analysis of variance (ANOVA) was used, followed by post hoc Mann–Whitney *U* tests. Finally, in the socially housed monkeys, correlations between latencies to touch the novel object and [^{18}F]FCP DVRs in the caudate nucleus and putamen were calculated using a (nonparametric) Spearman's rank correlation coefficient. In all cases, differences were considered statistically significant when $p<0.05$.

Results

PET imaging during abstinence

The average DVR in the caudate nucleus was significantly higher in dominant monkeys compared to subordinate monkeys ($t_{10}=2.96$, $p< 0.05$; Fig. 1). Dominant monkeys also had a higher average DVR in the putamen, but this difference did not reach statistical significance ($p=0.121$).

Food-maintained responding during abstinence

Mean (± SEM) numbers of reinforcers and mean (± SEM) response rates (responses per second) over the final five behavioral sessions before the monkeys' PET scans are shown in Table 1. Neither of these variables differed across ranks as determined with *t* tests.

Response to novelty

The Kruskal–Wallis ANOVA indicated a main effect of group on latency to touch the novel object ($K=8.73$, $p<0.05$). As shown in Fig. 2, the latencies of dominant monkeys to touch the novel object were significantly longer than those of subordinate (Mann–Whitney $U=3.00$, $p<0.05$) and individually housed monkeys (Mann–Whitney $U=2.00$, $p<0.01$). The latter two groups were not significantly different from each other. Moreover, in socially experienced monkeys, a significant positive correlation was observed between latency to touch the novel object and D2 receptor availability in the caudate nucleus (Fig. 3; Spearman rho=0.663, $p<0.05$) but not in the putamen (Spearman rho=0.4718, $p=0.122$).

Discussion

Previous research in monkeys has demonstrated that attainment of social dominance is associated with increases in D2 receptor availability in the basal ganglia and a lower sensitivity to the reinforcing effects of cocaine compared to subordinate monkeys (Morgan et al. 2002). The data further demonstrated an inverse relationship between D2 receptor availability and sensitivity to the reinforcing effects of cocaine, as seen in other studies in laboratory animals and humans (Volkow et al. 1999; Thanos et al. 2001; Nader et al. 2006; Dalley et al. 2007). After monkeys had self-administered cocaine for several years, D2 receptor availability in the caudate nucleus and putamen no longer differed between dominant and subordinate monkeys, despite continued social housing (Czoty et al. 2004). In the present study, rank-related differences in D2 receptor availability reemerged while monkeys remained socially housed during abstinence from cocaine self-administration. After approximately 8 months of abstinence from cocaine, the average D2 receptor

availability in the caudate nucleus of dominant monkeys was 26% higher than that of subordinates—a statistically significant effect. D2 availability in the putamen was 15% higher in dominant monkeys compared to subordinates, but variability across individuals was large enough to preclude statistical significance. These data provide evidence of neuroplasticity such that, despite several years of exposure to self-administered cocaine 5 days/week, brain D2 receptors remained responsive to environmental factors when cocaine exposure was discontinued. In addition, dominant monkeys were less reactive to novelty than subordinates, and this measure was positively correlated with D2 receptor availability in the caudate nucleus.

Our original study indicated that D2 receptor availability increased in monkeys that became dominant but was unchanged in subordinates (Morgan et al. 2002). We have conceptualized the dominance hierarchy as a continuum of social experience ranging from the unequivocal stress experienced by subordinate monkeys to environmental enrichment experienced by dominant animals (Nader and Czoty 2005). Thus, one interpretation of the present results is that the rank-related difference in D2 receptor availability observed after 8 months of abstinence was a result of exposure to environmental enrichment in dominant monkeys. At the outset of these experiments, we intended to assess this hypothesis more directly by determining the percentage change in individual monkeys' [^{18}F]FCP DVRs just before (i.e., Czoty et al. 2005b) and during abstinence. Unfortunately, this comparison was complicated by changes in social rank that occurred during abstinence for some monkeys. It is possible that the present results may be affected by individual differences in rates or extent of recovery from the decreases in D2 receptor availability that resulted from long-term cocaine self-administration, a phenomenon we previously demonstrated in individually housed rhesus monkeys (Nader et al. 2006). It is worth noting, however, that the average past-year cocaine intake of monkeys in the Nader et al. (2006) study was almost ten times higher than that of the monkeys in the present study (787.8±128.0 mg/kg versus 84.4±29.7 mg/kg). Although these issues complicate an understanding of the mechanisms through which dominant and subordinate monkeys came to differ in D2 receptor availability, after approximately 8 months of abstinence, dominant monkeys' DVRs were significantly higher than those of subordinates. The clinical relevance of this finding lies in the demonstration of plasticity of brain DA receptor systems driven by the environment, suggesting that the brain of a cocaine-dependent individual can remain responsive to positive changes in the environment.

An additional aim of these studies was to examine the relationship between social experience, D2 receptor availability, and reaction to novelty—a characteristic that has been associated with increased vulnerability to the reinforcing effects of abused drugs (e.g., Piazza et al. 1989, 2000; Bardo et al. 1996). In the present study, the average latency of dominant monkeys to touch a novel object placed in the home cage was significantly longer than that of subordinate and individually housed monkeys, suggesting that the experience of being dominant (i.e., environmental enrichment) decreased this measure of reaction to novelty. It is important to note that previous studies examined subjects' initial experiences with cocaine, whereas monkeys in the present studies had extensive experience self-administering cocaine. Thus, one important implication of these results is that the influence of social dominance on reaction to novelty was not eliminated due to the monkeys' history of cocaine intake. One alternative explanation is that individual differences may have predated social housing and influenced the establishment of eventual rank. That is, it is possible that monkeys who tend to display higher reactivity to novelty are more likely to become subordinate. Supporting this possibility, female cynomolgus monkeys' latencies to touch a novel object assessed prior to social housing were predictive of eventual social rank, and the direction of effects was similar to those observed in the present study (Riddick et al. 2009). In the present study, however, latencies of individually housed male monkeys were

low with little between-subject variability to suggest they could predict future social rank. In fact, when these monkeys were eventually placed into social groups, eventual rank was not predicted by latencies to touch the novel object (not shown). It should be noted, however, that in the present study, a direct comparison of monkeys with and without social experience may be confounded by experience self-administering cocaine. Factors underlying the difference between results in male and female monkeys remain to be explored but may be due to the relatively small sample size in the present study.

Considering that dominant monkeys had significantly higher caudate nucleus D2 receptor availability and higher latencies to touch the novel object, it is not surprising that the latter two measures were positively correlated. These data are consistent with PET data in humans that suggest an inverse relationship between novelty seeking and D2 receptor availability (Zald et al. 2008) and further support the link between D2 dopamine receptors and the temperamental variables reflected in laboratory assessments of various dimensions of impulsivity including novelty seeking. The radiotracer used in the present study, FCP, binds to the D_2, D_3, and D_4 subtypes of the D2 family of receptors; genetic studies have implicated these subtypes in mediating reaction to novelty and other measures related to impulsivity (e.g., Retz et al. 2003; Mufano et al. 2008). Moreover, Dalley and colleagues (2007) reported relatively lower D2 receptor availability in the nucleus accumbens of rats who were found to be more impulsive and subsequently self-administered greater amounts of cocaine. Although the cognitive processes measured by various laboratory tests of “impulsivity” and the overlap between these aspects of temperament as assessed in humans and animals is unclear (Dellu et al. 1996; Stoffel and Cunningham 2007), the predictive capacity of these measures suggests that they represent a reliable behavioral phenotype reflecting enhanced vulnerability to the abuse-related effects of psychostimulants. Moreover, the present and previous studies in socially housed monkeys (Morgan et al. 2002; Czoty et al. 2004, 2005b) demonstrate that these three characteristics can be influenced by environmental variables. Specifically, they support the intriguing hypothesis that social dominance is a form of environmental enrichment that can result in increases in D2 receptor availability, decreases in reaction to novelty (i.e., longer latencies to approach and touch a novel object), and decreases in sensitivity to the abuse-related effects of cocaine. To the clinician, these studies suggest that positive changes in a recovering drug abuser’s environment can be an effective component of substance abuse treatment.

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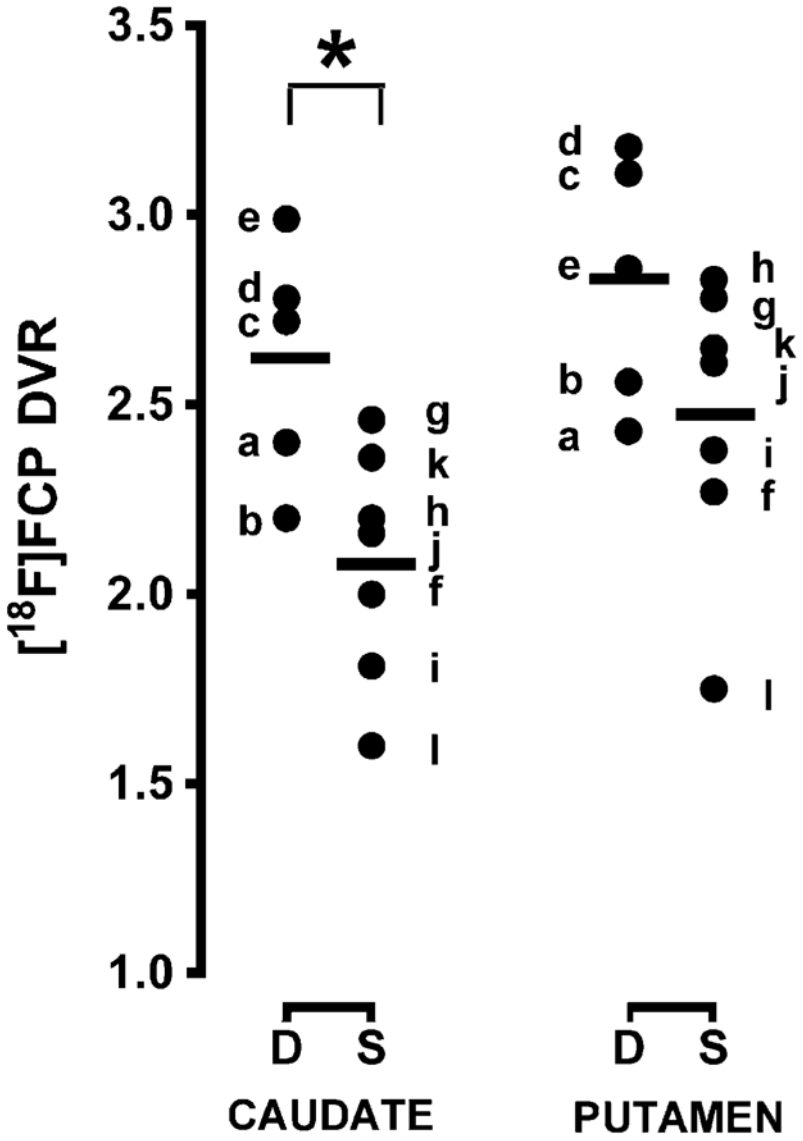

Fig. 1.

D2 receptor availability ([^{18}F]FCP DVR) in the caudate nucleus and putamen in five dominant (*D*) and seven subordinate (*S*) monkeys. *Letters* indicate individual monkeys (see Table 1). *Horizontal line* indicates the mean [^{18}F]FCP DVR. *p<0.05

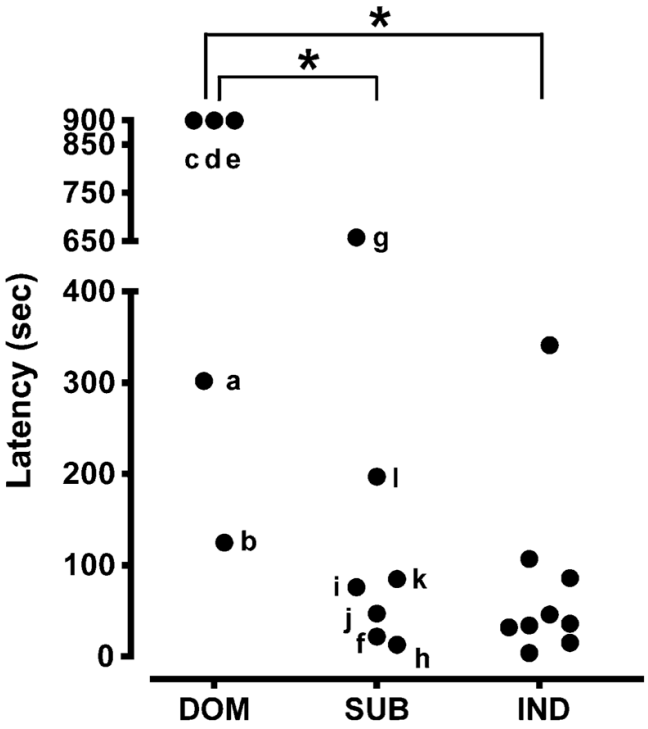

Fig. 2.
Latency in seconds to touch a novel object in five dominant (*DOM*), seven subordinate (*SUB*), and nine individually housed (*IND*) monkeys. *Letters* indicate individual monkeys (see Table 1), *$p<0.05$

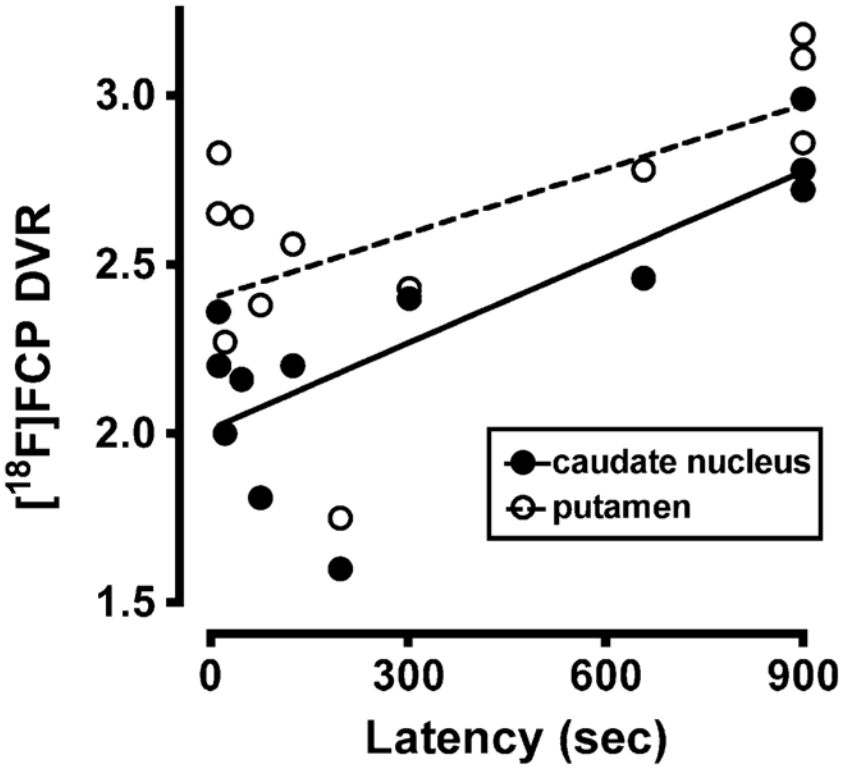

Fig. 3.

Relationship between D2 receptor availability ([^{18}F]FCP DVR) in the caudate nucleus or putamen and reaction to novelty (latency in seconds to touch a novel object) in socially housed monkeys

Table 1

Description of monkeys' cocaine histories (milligrams per kilogram), abstinence duration (days), and operant behavior during abstinence, according to social rank

Monkey	Lifetime intake (mg/kg)	Past-year intake (mg/kg)	Abstinence (days)	Mean reinforcers	Response rate (resp/sec)
Dominant					
C-6528 (a)	257.0	44.4	237	30.0	5.23
C-5386 (b)	267.4	80.8	266	30.0	5.64
C-6526 (c)	188.3	66.3	192	30.0	1.75
C-6626 (d)[a]	291.6	57.2	329	30.0	4.51
C-6628 (e)	365.5	121.0	232	30.0	2.77
Mean	273.9	73.9	251.2	30.0	3.98
SEM	63.9	29.5	25.4	0.0	0.83
Subordinate					
C-6625 (f)[a]	238.1	117.1	273	30.0	4.42
C-6525 (g)[a]	160.2	27.3	148	18.2	1.73
C-6529 (h)	202.5	50.7	126	30.0	3.72
C-6527 (i)[a]	219.5	103.4	131	29.6	3.31
C-6530 (j)	382.8	170.2	279	30.0	5.15
C-6214 (k)	98.6	93.6	340	30.0	3.67
C-6629 (l)	209.7	80.5	196	30.0	4.17
Mean	215.9	91.8	213.3	28.3	3.74
SEM	87.0	46.4	34.5	1.8	0.44

Letters are used to identify monkeys in the figures

[a]Indicate monkeys that held the opposite rank at initiation of abstinence

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