Social dominance in monkeys: dopamine D_2 receptors and cocaine self-administration

Drake Morgan[1], Kathleen A. Grant[1], H. Donald Gage[2], Robert H. Mach[1,2], Jay R. Kaplan[3], Osric Prioleau[1], Susan H. Nader[1], Nancy Buchheimer[2], Richard L. Ehrenkaufer[2] and Michael A. Nader[1,2]

[1] *Department of Physiology and Pharmacology,* [2]*Department of Radiology,* [3]*Departments of Pathology (Comparative Medicine) and Anthropology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA*

Correspondence should be addressed to M.A.N. (mnader@wfubmc.edu)

Published online: 22 January 2002, DOI: 10.1038/nn798

Disruption of the dopaminergic system has been implicated in the etiology of many pathological conditions, including drug addiction. Here we used positron emission tomography (PET) imaging to study brain dopaminergic function in individually housed and in socially housed cynomolgus macaques ($n = 20$). Whereas the monkeys did not differ during individual housing, social housing increased the amount or availability of dopamine D_2 receptors in dominant monkeys and produced no change in subordinate monkeys. These neurobiological changes had an important behavioral influence as demonstrated by the finding that cocaine functioned as a reinforcer in subordinate but not dominant monkeys. These data demonstrate that alterations in an organism's environment can produce profound biological changes that have important behavioral associations, including vulnerability to cocaine addiction.

Drug abuse is a significant public health problem. With regard to cocaine use in the United States, the annual number of new users rose between 1994 and 1998 from 500,000 to over 900,000 ("1999 National Household Survey on Drug Abuse," Substance Abuse and Mental Health Services Administration, 2000). Although some of these new cocaine users will eventually become addicted, not all will. Unfortunately, little is known about the biological substrates and environmental influences underlying this differential vulnerability[1], and ethical considerations make it impossible to study in humans. One purpose of the present study was to develop an animal model of vulnerability to drug abuse that incorporates the assessment of social behavior, the noninvasive brain imaging technique PET, and cocaine self-administration in socially housed monkeys. Such a model could identify variables that would aid in the characterization and treatment of individuals vulnerable to drug abuse.

Certain environmental conditions, such as availability of alternative reinforcers[2] or living in an 'enriched' environment[3], alter the reinforcing effects of drugs, particularly cocaine[4]. Many of these stimuli also produce changes in dopaminergic function[5,6], a neurotransmitter system whose dysregulation is linked to cocaine's abuse potential[7]. In particular, the dopamine D_2 family of receptors is related to cocaine's effects[8]. Thus, there is a clear potential for interaction between particular environmental events, the actions of dopamine, and the reinforcing effects of cocaine.

A profound environmental influence on dopaminergic function is the particular housing conditions of animals and the dominance rank among socially housed animals[6,9–12]. It is unclear whether these observed differences reflect a neurobiological predisposition that determines dominance rank (a trait marker), or a neurobiological alteration induced by the attainment of dominance rank (a state marker). Our hypothesis that D_2 receptor binding potential is related to environmental influences and associated with vulnerability to the abuse-related effects of cocaine[13] was confirmed by the findings that there were differential changes in binding potential across social ranks, and that the dominant monkeys were less vulnerable to the reinforcing effects of cocaine compared to subordinate animals.

Results

Behavioral profiles of socially housed monkeys

For the first 1.5 years of the study, the monkeys were individually housed and various hormonal measures (such as cortisol, testosterone) and behavioral measures (such as locomotor activity) were obtained[14], as well as initial PET scans. Monkeys were subsequently assigned to social groups of four. Consistent with previous research, the dominant monkeys engaged in significantly more aggressive behaviors (1.9 versus 0 episodes/h) and were submitted to more often than were the subordinate monkeys (3.0 compared to 0.1 episodes/h). Conversely, subordinate monkeys received aggression and submitted more often (3.6 and 3.5 episodes/h) than did dominant monkeys (0.1 and 0 episodes/h). Percentage of time engaged in various affiliative behaviors also depended on social rank. For example, dominant monkeys were groomed more often (12.1% versus 4.9% of the time), whereas the subordinate monkeys spent more time alone (27.8% versus 14.8% of the time; for details, see ref. 14).

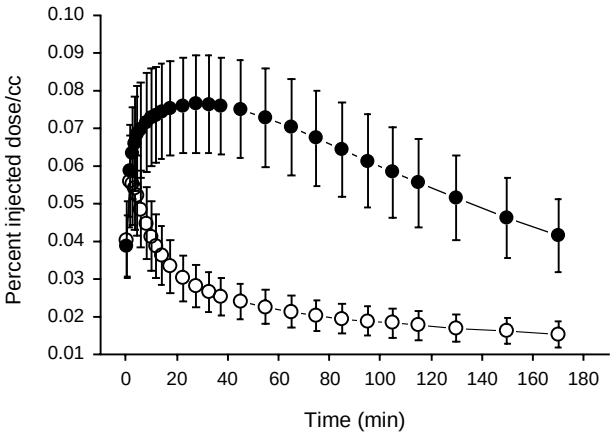

Fig. 1. [^{18}F]FCP has high uptake and linear rate of washout in the basal ganglia (BG; black symbols) relative to the cerebellum (Cb; white symbols). Each point is the mean (± 1 s.d.) value determined from 20 individually housed monkeys.

Social rank and dopaminergic functioning

Monkeys were first scanned using PET imaging while individually housed and again after they were placed in social groups and a stable social hierarchy was established. During all PET scans, there was a high level of uptake of [^{18}F]fluoroclebopride (FCP) and a linear rate of washout from the region of interest (ROI), the basal ganglia (**Fig. 1**). In the reference region, the cerebellum, there was a low level of [^{18}F]FCP uptake and high rate of washout. After three months of social housing, dominant monkeys (rank 1) had significantly higher D_2 receptor distribution volume ratios (DVRs) compared to subordinate (rank 4) monkeys (**Table 1**). These data replicate previous findings[12] showing a greater than 20% higher DVR in dominant monkeys compared to subordinate monkeys. Importantly, these findings extended the previous data from female to male monkeys, and demonstrate that this difference is apparent after only three months of social housing compared to three years in the previous study. In addition, the longitudinal design of the present experiment allowed the comparison of the same ROIs obtained while individually and socially housed, and revealed a significant change in [^{18}F]FCP binding only in the eventual dominant monkeys (**Table 1**). That is, the significant interaction between housing condition and social rank ($F_{2,39} = 8.88$, $p = 0.002$) demonstrates that the DVR of dominant monkeys increased from a mean of 2.49 to a mean of 3.04, an increase of approximately 22%, whereas the mean DVR of subordinate monkeys was not altered (means of 2.40 and 2.49) as a function of housing condition (**Fig. 2**). The latter findings are similar to previous results showing low between-study variability with this PET ligand[15].

This measure of dopaminergic function suggests that, rather than a predisposing trait, the changes were a consequence of becoming the dominant monkey in a social group (**Fig. 3**). Previously examined neuroendocrine markers, such as cortisol and testosterone levels, were similarly not predictive of eventual social rank[14]. In contrast, high levels of locomotor activity in individually housed monkeys were associated with eventual social subordination[14]. Age or weight of the monkeys did not correlate with D_2 binding (all p values > 0.05) during either housing condition, indicating no relationship between these characteristics and dopaminergic function.

Social rank and cocaine self-administration

Subordinate monkeys reliably self-administered cocaine across several doses, with the entire dose–effect curve characterized as an inverted U-shaped function (**Fig. 4**, left, black symbols). There was a significant interaction between dose and social rank ($F_{4,134} = 3.54$, $p < 0.01$), and further analyses showed that subordinate monkeys self-administered more 0.01 and 0.03 mg/kg cocaine injections than saline. In contrast, in the dominant monkeys, cocaine failed to maintain responding higher than saline, and therefore did not function as a reinforcer (**Fig. 4**, left, white symbols). During these sessions, subordinate monkeys had significantly higher intakes compared to dominant monkeys (**Fig. 4**, right; significant interaction between dose and social rank, $F_{3,107} = 10.59$, $p < 0.0001$). A dose-dependent increase in cocaine intake occurred for the dominant monkeys, suggesting that these animals were not avoiding cocaine altogether, but their total intakes were significantly below those of subordinate monkeys. Correlation analyses indicated that social rank was inversely related to the number of reinforcers obtained per session ($r^2 = 0.62$, $p = 0.01$) and to cocaine intake ($r^2 = 0.55$, $p = 0.02$). These data demonstrate a resistance to the reinforcing effects of cocaine in the dominant monkeys, and, conversely, show an increased vulnerability in the subordinate monkeys.

Discussion

The major findings from these studies were that environmental conditions produced a relatively quick alteration in the dopaminergic system of socially housed dominant but not subordinate monkeys and that this difference was associated with a differential vulnerability to the reinforcing effects of cocaine. These findings emerged from a design using a combination of several experimental methods including repeated PET imaging in individually and socially housed monkeys to study changes in brain DA function, the evaluation of social interactions in monkeys, and the study of intravenous cocaine self-administration in socially housed animals.

Whereas the present study represents the first examination of intravenous drug self-administration in socially housed monkeys, there have been several studies examining other behavioral effects of psychomotor stimulants in similarly housed monkeys[16–19]. These experiments have demonstrated differential effects of cocaine and d-amphetamine as a function of social rank[19]. Several rodent studies have examined the influence of housing conditions (individual versus social) on cocaine and amphetamine self-administration, although the results have been contradictory[3,4,20–22]. Differences in intravenous self-administration of

Table 1. Dopaminergic characteristics of monkeys.

Social rank[a]	[^{18}F]FCP distribution volume ratios		
	Individually housed	Socially housed	Percent change
1	2.49 ± 0.08	3.04 ± 0.23[b,c]	+22.0 ± 8.8
2	2.58 ± 0.13	2.99 ± 0.13	+16.7 ± 6.0
3	2.58 ± 0.13	2.88 ± 0.30	+13.4 ± 15.3
4	2.40 ± 0.06	2.49 ± 0.10	+3.9 ± 5.3

Mean ± s.e.m. [^{18}F]FCP DVR as determined with PET imaging in male cynomolgus monkeys as a function of social rank while individually and socially housed. [a]For individually housed scans, these numbers represent eventual social rank. [b]Significantly higher than individually housed 'dominants.' [c]Significantly higher than socially housed subordinates.

cocaine across social ranks of rats or monkeys had not been previously explored. The present study provides experimental evidence in monkeys that individual differences in susceptibility to cocaine abuse within a population may be mediated by social dominance rank.

In the present study, the higher levels of [^{18}F]FCP binding in dominant monkeys could have resulted from increased levels of D_2 receptors and/or decreases in the basal levels of synaptic dopamine. Previous rodent studies have examined the neurochemical changes within the dopamine system as a consequence of housing conditions[6,9–11]. For example, rats reared in isolation or in 'environmentally impoverished' conditions have increased synaptic levels of dopamine and/or increased efflux of dopamine in response to particular environmental events (for example, after exposure to stressful stimuli) when compared to socially housed rodents or those living in 'enriched' environments. Concurrent decreases in D_2 responsivity and D_2 receptor levels have been observed in individually housed rats. Taken together with the present findings, these results suggest that individually housed monkeys and socially subordinate animals have relatively high levels of synaptic dopamine (that is, dopaminergic hyperactivity). We would suggest that after social housing, the dominant animals return to a 'normal' state of dopamine function, presumably as the result of being in control of environmental events such as social contact, mobility through the environment, and food and sexual resources. The ability to control resources may induce neurochemical changes that are reflected in the over 20% increase in D_2 receptor DVR and a decrease in vulnerability to the reinforcing effects of cocaine in the dominant animals. This latter finding is even more striking when one considers that in nonhuman primate models, cocaine functions as a reinforcer in nearly all individually housed subjects.

The dopaminergic system is centrally involved in the neurochemical pathology of various psychiatric and neurodegenerative diseases involving the basal ganglia[13,23–25]. The link between dopaminergic functioning and behavioral processes has been extensively studied in the field of drug abuse[26–28]. Importantly, individual differences in dopaminergic function can result in varying degrees of susceptibility to drug abuse[29,30]. The most well studied animals in this respect are the high- and low-responders (HR and LR, respectively) to novelty as measured by locomotion in an open field. LR rats are less likely to acquire amphetamine self-administration compared to HR rats[31], similar to our findings that low locomotor levels in monkeys predicted 'resistance' to the reinforcing effects of cocaine (also see ref. 14). Neurobiologically, HR rats have higher basal, cocaine-stimulated and stress-induced dopamine levels, and have lower D_2 receptor levels in the nucleus accumbens[32]. Using extracellular single-neuron recordings, HR rats have higher basal firing rates of dopamine neurons in the ventral tegmental area and decreased sensitivity to D_2 receptor stimulation compared to LR rats; these differences in firing rates are associated with differences in sensitivity to cocaine's reinforcing effects[33]. These data suggest that a hyperactive dopamine system is characteristic of a drug-prone phenotype.

There is an extensive literature describing the involvement of D_2-like receptors in modulating cocaine's reinforcing effects using direct-acting agonists and antagonists in several animal models of cocaine abuse[34–36]. Consistent with these animal studies, PET data obtained in non–drug abusing humans suggests that levels of D_2 receptors predict the subjective effects of stimulants[37]. In particular, individuals with low

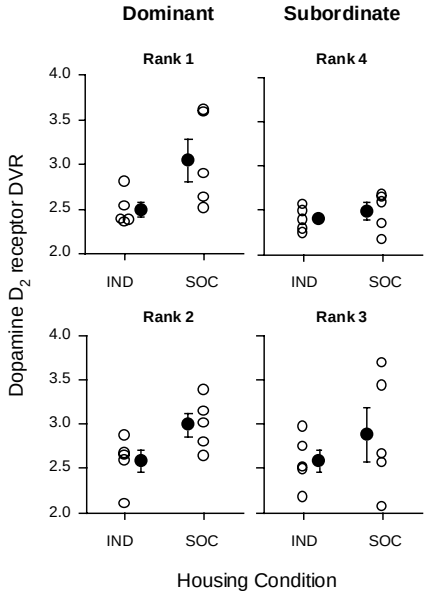

Fig. 2. [^{18}F]FCP binding potential changes as a function of social rank. Panels show the mean and individual [^{18}F]FCP DVR values for monkeys with different social ranks, while they were individually (IND) and socially (SOC) housed.

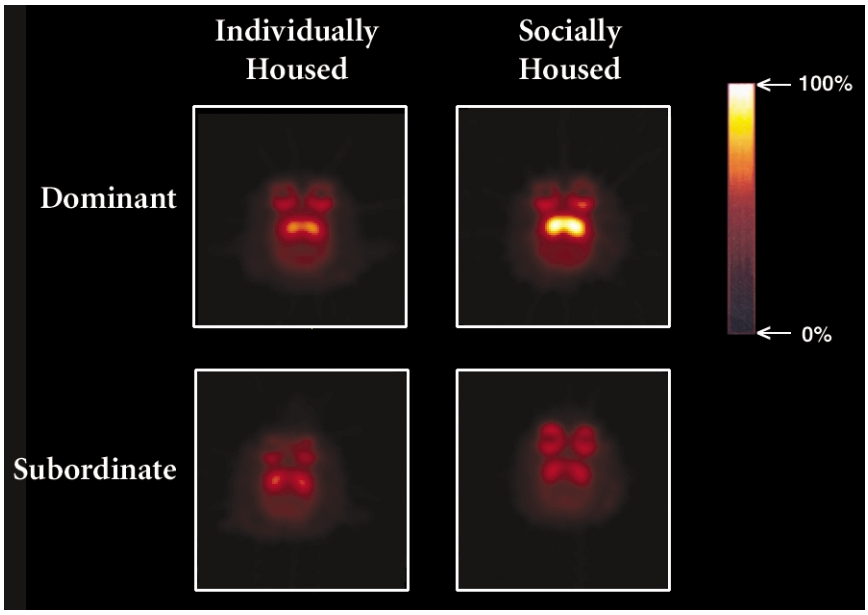

Fig. 3. [^{18}F]FCP binding potential increases in dominant monkeys. Normalized, co-registered PET images (percent injected dose per ml) of [^{18}F]FCP binding in the basal ganglia of a dominant and a subordinate monkey, while individually housed and socially housed.

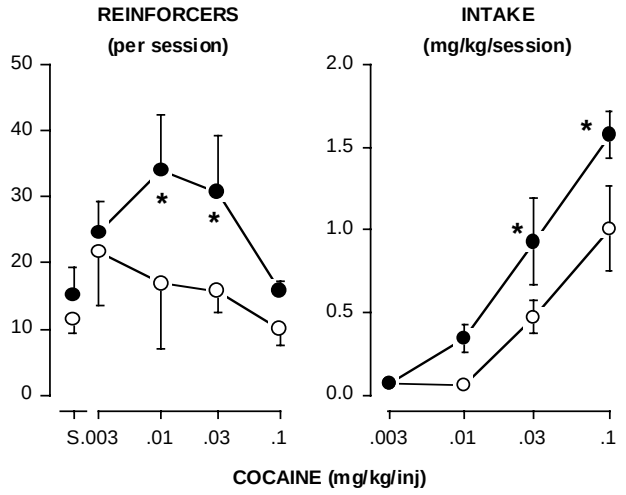

Fig. 4. Reinforcing effects of cocaine are greater in subordinate monkeys compared to dominant animals. Left, mean number of intravenous injections (either saline or various doses of cocaine) per session for 5 dominant (rank 1 and 2, white symbols) and 4 subordinate (rank 3 and 4, black symbols) monkeys. Right, mean intake per session for dominant (white symbols) and subordinate (black symbols) monkeys. Each dose was available for at least 7 sessions and until responding was stable. Data represent the mean of the last 3 days of availability for each animal. Asterisk indicates a statistically significant difference ($p < 0.05$) from dominant monkeys at that particular dose, and from the appropriate saline point.

D_2 receptor DVRs reported that methylphenidate was more pleasurable and less aversive than did individuals with high D_2 DVRs. This behavioral and biological phenotype is similar to the one defined in the present study, and suggests that environmental events (such as becoming a particular social rank) may be as important as biological predispositions in determining vulnerability to drug abuse. It is not clear, however, whether changes or differences in extracellular dopamine or the D_2 receptors themselves are contributing to the differences in cocaine reinforcement.

The present study demonstrates that social context can have profound effects on brain dopaminergic function in adult, nonhuman primates. Furthermore, these neurobiological alterations in D_2 receptor levels or availability produced by an environmental change can lead to qualitatively different behavioral phenotypes. In the present study, this difference manifested as dominant monkeys being resistant to cocaine's effects, while subordinate monkeys were shown to be susceptible to the reinforcing effects of cocaine. The promise of this model, specifically for vulnerability to drug abuse but more generally to any behavioral phenotype, lies in the ability to use brain-imaging techniques to identify individual neurobiological characteristics associated with a particular social or environmental state, so that the course of related diseases and treatment can be followed and ultimately altered.

METHODS

Subjects. Twenty experimentally naive adult male cynomolgus monkeys (*Macaca fascicularis*) were purchased from a commercial vendor (Primate Products, Miami, Florida, or Biomedical Resources Foundation, Houston, Texas). The monkeys were bred in captivity and, after weaning, were primarily individually housed. At the start of the study, monkeys lived in cages (Allentown Caging, Allentown, New Jersey) equipped with removable metal partitions, providing four compartments each containing 11.5 cubic feet of space and a water spigot. Throughout the experiment, monkeys were weighed weekly and maintained at approximately 95% of their free-feeding body weight by limited access to Purina Monkey Chow (100–120 g/day). In addition, monkeys received a multiple vitamin tablet and fresh fruit approximately 2–3 times per week. At the time of the first PET scans, monkeys weighed an average of 5.0 kg (range, 3.8–7.6 kg) and were approximately 4.8 years old (range, 3.4–6.4 years old). Approximately 8 months (range, 5–12 months) after the first PET scan and after at least 3 months of social housing, the second PET scan was conducted, at which point the monkeys weighed ~5.2 kg (range, 4.4–7.8 kg). The experimental manipulations described in this manuscript were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the NIH, and with the approval of the Institutional Animal Care and Use Committee.

Behavioral profiles of socially housed monkeys. Monkeys were individually housed for approximately 10 months before the initial PET scans. The monkeys were placed into social groups of four after initial PET scans were completed. Approximately 20 behavioral observation sessions, to measure various aggressive, submissive and affiliative behaviors, were conducted per pen at regular intervals over the next 3 months[14]. Dominance rank was determined by the outcomes of dyadic agonistic encounters. That is, the monkey that aggressed toward and typically elicited submission from all others was designated as the first-ranking monkey. The monkey that aggressed toward all except the first-ranking monkey was designated the second-ranking monkey, and so on. In each pen, a linear hierarchy formed where the relationships between monkeys were transitive.

Social rank and dopaminergic function. Monkeys were first scanned with the D_2 radioligand [^{18}F]FCP while individually housed and again after they were placed in social groups and a stable social hierarchy was established. The average time between scans was 8 months (range, 4.5–12.1 months). All animals in a particular pen were scanned before beginning the next pen and the order of scanning as a function of social rank was randomly determined. Details regarding the PET data acquisition protocol, blood sampling procedure, and metabolite analysis have been fully described[15,38–39]. Briefly, monkeys were initially anesthetized with 8 mg/kg ketamine, maintained on isoflurane anesthesia (1.5%), administered a paralytic (0.07 mg/kg vecuronium bromide), and prepared with percutaneous arterial and venous catheters. Although it is possible that ketamine-induced changes in dopamine levels can alter tracer kinetics when injected during a PET study[40], we previously demonstrated that under the present conditions, this dose of ketamine does not alter the DVR values obtained with [^{18}F]FCP[15].

PET scans were obtained with a Siemens/CTI ECAT 951/31 PET scanner, which has been described elsewhere[15,38,39]. The effective resolution (full width at half maximum) of the PET scanner was 9 mm in all axes for the reconstructed image after filtering (Hanning filter with a 0.4-cycle/pixel cutoff; resolution determined experimentally using a line source).

ROI determinations were made from frame 13 (25–30 minutes post-injection acquisition frame) of the 26 dynamically acquired emission frames, as this frame occurs at the time that the basal ganglia uptake reaches a plateau, providing good whole brain anatomic definition and sufficient contrast of the basal ganglia versus the rest of the brain. ROIs for both basal ganglia and cerebellar regions were determined using the isocontour mode. For the basal ganglia, an isocontour threshold of 95% was set. For the cerebellum, a reference region with low D_2 receptor density, an isodensity contour of 65–85% was routinely used. The use of set isocontour levels for ROI determination insures that the ROIs are easily and reproducibly defined. The narrow range of 95% was used for the basal ganglia, as it selects the highest 5% of the pixel activities in the slice, thus minimizing the errors due to partial volume effect. In contrast, using an isocontour level of 65–85% in the cerebellum generates a fairly large region of nearly uniform tracer concentration. For all studies, the first 4 frames (0–4 min) were used for registration. The individual housing scan from each monkey was registered to the social housing scan and the ROI from the social housing scan placed onto the individual housing scan, ensuring that identical ROIs were used[41]. This method of defining

ROIs resulted in the same overall effects as using other methods (e.g. separate ROIs for each scan or ROIs from the summed scans). Time–activity curves were generated by the ECAT software by placing the isocontour regions determined from frame 13 over the same region in each of the 26 frames. The ROI value is the average of all pixels contained within the ROI, for each time frame. In the basal ganglia, right and left sides were determined separately, then averaged. The distribution volumes (DV) for these regions were determined using the linear portion of the Logan plot[42], which in all cases included the last 80 min of the PET scan. DVR was used as a metric of specific binding.

At the start of the scan, approximately 4 mCi of [^{18}F]FCP was injected, followed by 3 ml of heparinized saline. Tracer doses of FCP were injected (2.39 ± 0.35 μg), and the mass of FCP was not different across groups. There was no relationship between injected mass and binding potential.

Surgery. After the second PET scan, each monkey was surgically prepared under sterile conditions with a vascular access port (Model GPV, Access Technologies, Skokie, Illinois), implanted under ketamine (15 mg/kg) and butorphanol (0.025 mg/kg) anesthesia. An incision was made near the femoral or jugular vein, and the catheter was inserted into the vein for a distance calculated to terminate in the vena cava. The distal end of the catheter was threaded subcutaneously to an incision made slightly off the midline of the back. The vascular access port was placed within a pocket formed by blunt dissection near the incision. The port and catheter were then flushed with a 50% dextrose/saline solution containing heparin (500 Units/ml). Antibiotic (25 mg/kg kefzol, BID; Cefazolin sodium, Marsam Pharmaceuticals, Cherry Hill, New Jersey) was administered prophylactically for 7–10 days beginning on the day of the surgery.

Cocaine self-administration. Monkeys were first trained to respond with food as the reinforcer, and subsequently, saline and increasing doses of cocaine were made available for self-administration. Each morning (5–7 days/week), monkeys from each pen were individually housed by partitioning the cage into four quadrants. Next, each monkey was seated in a primate chair (Primate Products) and the chair was wheeled to the operant chamber (Med Associates, East Fairfield, Vermont). The back of the animal was cleaned with 95% ethyl alcohol and betadine, and a 20 gauge Huber Point Needle (Access Technologies) was inserted into the port, connecting the infusion pump to the catheter. The pump was operated for approximately 3 s, filling the port and catheter with the dose of cocaine available during the experimental session. During the session, a fixed number of responses on the response lever (for example, a fixed ratio of 30) resulted in presentation of a banana pellet or activation of the infusion pump for 10 seconds. Each condition (saline or each dose of cocaine availability) was available for at least 7 consecutive sessions and until responding was stable (±15% of the mean for the last 3 sessions). There was a return to food-reinforced responding after evaluating a cocaine dose. In some social groups, the hierarchy changed while the cocaine dose-response curves were being determined. Because the effects of changes in rank, as well as cocaine exposure, on D_2 binding potential were not assessed, only self-administration data obtained during the time in which we were confident that the monkey's rank was not different from when the PET scans were conducted was included in the analysis. Thus, data from 9 monkeys that were evaluated with 4 doses of cocaine and saline, whose rank did not change across the period of the study, were evaluated.

Statistical analysis. For purposes of PET image analysis, animals with a rank of 1 or 4 were considered dominant or subordinate, respectively, whereas those ranking 2 or 3 were considered intermediate, and their data were combined ($n = 5$ for each rank). Data were analyzed with a 3 (rank: dominant, intermediate and subordinate) by 2 (housing: individual and social) repeated measures ANOVA using commercially available software. Because of the smaller number of animals tested for acquisition of cocaine self-administration ($n = 9$), animals were considered either dominant (rank of 1 or 2, $n = 5$) or subordinate (rank of 3 or 4, $n = 4$). A repeated-measures ANOVA with dose (5 levels including saline) as the within-subject variable and social rank (that is, dominant and subordinate) as the between-subject variable was conducted. Pairwise comparisons for all analyses were made using the student Neuman–Keuls test. Correlation coefficients were computed using the same software package. Differences were considered statistically significant when $p < 0.05$.

Acknowledgements

We would like to thank C.S. Carter for comments on the manuscript; C. Hubbard, T. Moore and J. Lile for assistance with handling the monkeys; R. Kuhner for conducting the PET scans; and E. Nicks and P. Warren for assistance analyzing the social behavior data. This research was supported by the National Institute on Drug Abuse Grant DA-10584.

RECEIVED 7 AUGUST; ACCEPTED 12 DECEMBER 2001

1. Leshner, A. I. Vulnerability to addiction: new research opportunities. *Am. J. Med. Genet.* **96**, 590–591 (2000).
2. Nader, M. A. & Woolverton, W. L. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. *Psychopharmacology* **105**, 169–174 (1991).
3. Schenk, S., Lacelle, G., Gorman, K. & Amit, Z. Cocaine self-administration in rats influenced by environmental conditions: implications for the etiology of drug abuse. *Neurosci. Lett.* **81**, 227–231 (1987).
4. LeSage, M. G., Stafford, D. & Glowa, J. R. Preclinical research on cocaine self-administration: environmental determinants and their interaction with pharmacological treatment. *Neurosci. Biobehav. Rev.* **23**, 717–741 (1999).
5. Schultz, W., Tremblay, L. & Hollerman, J. R. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb. Cortex* **10**, 272–284 (2000).
6. Bowling, S. L., Rowlett, J. K. & Bardo, M. T. The effect of environmental enrichment on amphetamine-stimulated locomotor activity, dopamine synthesis and dopamine release. *Neuropharmacology* **32**, 885–893 (1993).
7. Hurd, Y. L., Svensson, P. & Ponten, M. The role of dopamine, dynorphin, and CART systems in the ventral striatum and amygdala in cocaine abuse. *Ann. NY Acad. Sci.* **877**, 499–506 (1999).
8. Volkow, N. D., Fowler, J. S. & Wang, G. J. Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *J. Psychopharmacol.* **13**, 337–345 (1999).
9. Blanc, G. *et al.* Response to stress of mesocortico-frontal dopaminergic neurones in rats after long-term isolation. *Nature* **284**, 265–267 (1980).
10. Rilke, O., May, T., Oehler, J. & Wolffgramm, J. Influences of housing conditions and ethanol intake on binding characteristics of D2, 5-HT1A, and benzodiazepine receptors of rats. *Pharmacol. Biochem. Behav.* **52**, 23–28 (1995).
11. Hall, F. S. *et al.* Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacol. Biochem. Behav.* **59**, 859–872 (1998).
12. Grant, K. A. *et al.* Effect of social status on striatal dopamine D2 receptor binding characteristics in cynomolgus monkeys assessed with positron emission tomography. *Synapse* **29**, 80–83 (1998).
13. Blum, K., Cull, J.G., Braverman, E. R. & Comings, D. E. Reward deficiency syndrome. *Am. Scientist* **84**, 132–145 (1996).
14. Morgan, D. *et al.* Predictors of social status in cynomolgus monkeys (*Macaca fascicularis*) after group formation. *Am. J. Primatol.* **52**, 115–131 (2000).
15. Nader, M. A. *et al.* PET imaging of dopamine D2 receptors with [^{18}F]fluoroclebopride in monkeys: effects of isoflurane- and ketamine-induced anesthesia. *Neuropsychopharmacology* **21**, 589–596 (1999).
16. Crowley, T. J., Stynes, A. J., Hydinger, M. & Kaufman, I. C. Ethanol, methamphetamine, pentobarbital, morphine, and monkey social behavior. *Arch. Gen. Psychiatry* **31**, 829–838 (1974).
17. Crowley, T. J. *et al.* Cocaine, social behavior, and alcohol-solution drinking in monkeys. *Drug Alcohol Depend.* **29**, 205–223 (1992).
18. Martin, S. P., Smith, E. O. & Byrd, L. D. Effects of dominance rank on d-amphetamine-induced increases in aggression. *Pharmacol. Biochem. Behav.* **37**, 493–496 (1990).
19. Miczek, K. A. & Gold, L. H. d-Amphetamine in squirrel monkeys of different social status: effects on social and agonistic behavior, locomotion, and stereotypes. *Psychopharmacology* **81**, 183–190 (1983).
20. Bozarth, M. A., Murray, A. & Wise, R. A. Influence of housing conditions on the acquisition of intravenous heroin and cocaine self-administration in rats. *Pharmacol. Biochem. Behav.* **33**, 903–907 (1989).
21. Phillips, G. D. *et al.* Isolation rearing enhances the locomotor response to cocaine and a novel environment, but impairs the intravenous self-administration of cocaine. *Psychopharmacology* **115**, 407–418 (1994).
22. Boyle, A. E., Gill, K. J., Smith, B. R. & Amit, Z. Differential effects of an early housing manipulation on cocaine-induced activity and self-administration in laboratory rats. *Pharmacol. Biochem. Behav.* **39**, 269–274 (1991).
23. Verhoeff, N. P. Radiotracer imaging of dopaminergic transmission in neuropsychiatric disorders. *Psychopharmacology* **147**, 217–249 (1999).

24. Calabresi, P., De Murtas, M. & Bernardi, G. The neostriatum beyond the motor function: experimental and clinical evidence. *Neuroscience* **78**, 39–60 (1997).
25. Wang, G. J. *et al.* Brain dopamine and obesity. *Lancet* **357**, 354–357 (2001).
26. Piazza, P. V. & Le Moal, M. The role of stress in drug self-administration. *Trends Pharmacol. Sci.* **19**, 67–74 (1998).
27. Volkow, N. D. *et al.* Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am. J. Psychiatry.* **147**, 719–724 (1990).
28. Volkow, N. D. *et al.* Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* **14**, 169–177 (1993).
29. Piazza, P. V. & LeMoal, M. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu. Rev. Pharmacol. Toxicol.* **36**, 359–378 (1996).
30. Lucas, L. R. *et al.* Neurochemical characterization of individual vulnerability to addictive drugs in rats. *Eur. J. Neurosci.* **10**, 3153–3163 (1998).
31. Piazza, P. V., Deminiere, J.-M., Le Moal, M. & Simon, H. Factors that predict individual vulnerability to amphetamine self-administration. *Science* **245**, 1511–1513 (1989).
32. Piazza, P. V., Deroche-Gamonent, V., Rouge-Pont, F. & Le Moal, M. Vertical shifts in self-administration dose-response functions predict a drug-vulnerable phenotype predisposed to addiction. *J. Neurosci.* **20**, 4226–4232 (2000).
33. Marinelli, M. & White, F. J. Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. *J. Neurosci.* **20**, 8876–8885 (2000).
34. Nader, M. A., Green, K. L., Luedtke, R. R. & Mach, R. H. The effects of benzamide analogues on cocaine self-administration in rhesus monkeys. *Psychopharmacology* **147**, 143–152 (1999).
35. Caine, S. B., Negus, S. S. & Mello, N. K. Effects of dopamine D(1-like) and D(2-like) agonists on cocaine self-administration in rhesus monkeys: rapid assessment of cocaine dose-effect functions. *Psychopharmacology* **148**, 41–51 (2000).
36. Khroyan, T. V., Barrett-Larimore, R. L., Rowlett, J. K. & Spealman, R.D. Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. *J. Pharmacol. Exp. Ther.* **294**, 680–687 (2000).
37. Volkow, N. D. *et al.* Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *Am. J. Psychiatry* **156**, 1440–1443 (1999).
38. Mach, R. H. *et al.* Comparison of two fluorine-18 labeled benzamide derivatives that bind reversibly to dopamine D2 receptor: *in vitro* binding studies and positron emission tomography. *Synapse* **24**, 322–333 (1996).
39. Mach, R. H. *et al.* Use of positron emission tomography to study the dynamics of psychostimulant-induced dopamine release. *Pharmacol. Biochem. Behav.* **57**, 477–486 (1997).
40. Laruelle, M. Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J. Cereb. Blood Flow Metab.* **20**, 423–451 (2000).
41. Woods, R. P. *et al.* Automated image registration: I. General methods and intrasubject, intramodality validation. *J. Comput. Assist. Tomogr.* **22**, 141–152 (1998).
42. Logan, J. *et al.* Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-cocaine PET studies in human subjects. *J. Cereb. Blood Flow Metab.* **10**, 740–747 (1990).