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SOCIAL DOMINANCE IN FEMALE MONKEYS: DOPAMINE RECEPTOR FUNCTION AND COCAINE REINFORCEMENT

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Abstract

Background—Brain imaging and behavioral studies suggest an inverse relationship between dopamine (DA) D2/D3 receptors and vulnerability to cocaine abuse, though most research has utilized males. For example, male monkeys that become dominant in a social group have significant elevations in D2/D3 receptor availability and are less vulnerable to cocaine reinforcement.

Methods—DA D2/D3 receptor availability was assessed in female cynomolgus monkeys (n=16) using positron emission tomography (PET) while they were individually housed, 3 months after stable social hierarchies had formed and again when individually housed. In addition, PET was used to examine changes in DA transporter (DAT) availability following social hierarchy formation. After imaging studies were complete, monkeys were implanted with indwelling intravenous catheters and self-administered cocaine (0.001–0.1 mg/kg/injection) under a fixed-ratio 30 schedule of reinforcement. Acquisition of cocaine reinforcement occurred when response rates were significantly higher than when saline was self-administered.

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AUTHOR CONTRIBUTIONS

M.A.N., S.H.N., P.W.C. and N.V.R. designed the experiments. N.V.R., R.W.G and B.L.B. performed the behavioral studies, including intravenous catheterization. H.D.G. analyzed the PET data, J.R.K. assisted with the social housing manipulations, P.K.G., H.M.L.D., D.M. and S.G. were involved in the synthesis of both radiotracers and B.A.R. was responsible for the statistical analyses. The manuscript was written by M.A.N. with assistance from S.H.N., P.W.C., R.W.G, B.L.B. and J.R.K.

Results—Neither DAT nor D2/D3 receptor availability in the caudate nucleus and putamen was predictive of social rank, but both significantly changed following formation of social hierarchies. D2/D3 receptor availability significantly increased in females that became dominant, while DAT availability decreased in subordinate females. Dominant female monkeys acquired cocaine reinforcement at significantly lower doses than subordinate monkeys.

Conclusions—Based on these findings, the relationship between D2/D3 receptor availability and vulnerability to cocaine reinforcement appears opposite in females and males. These data indicate that the social environment profoundly affects the DA system, but does so in ways that have different functional consequences for females than males.

Keywords

Dopamine; vulnerability; PET imaging; social rank; females; sex differences

INTRODUCTION

Drug abuse continues to be a major public health problem worldwide (1), with an estimated 1.6 million Americans confirming current cocaine use (2). Within the European Union, 56% of all countries reporting on cocaine trends documented increases (1). Although several novel avenues are being considered, at present there are no FDA-approved treatments for cocaine addiction (3–4). There is evidence of sex differences in vulnerability to cocaine abuse (5), with women initiating drug use at earlier ages, progressing to dependence faster and being more vulnerable to physical, mental, and social consequences of abuse (6–7). However, female subjects are underrepresented in both preclinical and clinical research. The present study used female cynomolgus monkeys in a unique animal model that incorporated social behavior, brain imaging using positron emission tomography (PET), and cocaine self-administration in an effort to enhance our understanding of the etiology of drug abuse with the goal of developing novel treatment approaches. An additional goal of the present study was to extend earlier work in socially housed male subjects to female monkeys.

Brain dopamine (DA) mediates the reinforcing effects of cocaine (8). Research using male subjects (human, monkey and rodent) suggests a relationship between DA D2/D3 receptors and psychostimulant reinforcement, such that individuals with lower measures experienced greater reinforcement (8–11). For example, D2/D3 receptor availability was assessed in male monkeys while they were individually housed and again after 3 months of social housing (9). While initial D2/D3 receptor availability was not predictive of eventual social rank, it significantly increased in monkeys that became dominant in the social group. Consistent with findings reported in men, the increases in D2/D3 receptor availability were associated with lower rates of cocaine self-administration; there is, at present, little evidence of such a relationship in females. The three primary objectives of the present study were to: 1) determine whether dominant females, like their male counterparts, had higher D2/D3 receptors and reduced rates of cocaine self administration; 2) assess DA transporter (DAT) availability following the establishment of dominance hierarchies; and 3) evaluate changes in D2/D3 receptor availability after returning the females from social to individual housing conditions.

In animal models, housing conditions, social rank, individual differences and personality traits can profoundly influence the reinforcing effects of cocaine (9,11–15). We hypothesized that dominant male monkeys were protected from cocaine reinforcement because they were living in an enriched environment (2,16). Whereas same-sex social groups involving female macaques also form linear hierarchies (17,18), dominant females seem to aggress towards their subordinate cagemates with greater intensity than is observed among males (19,20). Thus, it remains to be determined whether attainment of a dominant

social position among female monkeys is similarly associated with environmental enrichment and subsequent decreases in cocaine reinforcement compared to female monkeys that become subordinate in the social group. Because estrogen can affect DA levels (21,22) and menstrual cycle phase can influence D2/D3 receptor availability (23), all PET imaging was conducted in the follicular phase in which D2/D3 receptor availability is reliably lower relative to the luteal phase, which we hypothesized would allow for increases or decreases due to social rank formation.

MATERIALS AND METHODS

Subjects

The subjects were 16 experimentally naïve adult female cynomolgus monkeys (*Macaca fascicularis*), imported from Indonesia (Institute Pertanian Bogor, Bogor, Indonesia), 8–18 years old. Monkeys lived in stainless steel cages (0.71 × 1.73 × 1.83 m; Allentown Caging Equipment, Co., Allentown, NJ) with removable wire mesh partitions that separated monkeys into quadrants (0.71 × 0.84 × 0.84 m). During social housing, monkeys were separated and individually housed for 1–2 hrs each day for feeding. One monkey died of natural causes prior to operant training bringing the total number of subjects to 15. Each monkey was fitted with an aluminum collar (Primate Products, Redwood City, CA) and trained to sit calmly in a standard primate chair (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. Water was available *ad libitum* in the homecage. Menstrual cycle phase was assessed by daily vaginal swabs (18,23) and was approximately 28 days. The first day of bleeding was indicative of menses and was counted as day 1 of the cycle. We considered days 2–10 the follicular phase and days 19–28 the luteal phase of the menstrual cycle. Behavioral studies were conducted in both menstrual cycle phases, while PET imaging studies were conducted only in the follicular phase; this was confirmed by measuring plasma progesterone concentrations (Biomarkers Core Laboratory, Yerkes National Primate Research Center, Atlanta, GA). Progesterone levels < 4 ng/ml were indicative of follicular phase. Animal housing, 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 Wake Forest University Non-Human Primate Environmental Enrichment Plan.

Social rank determination

Social status was determined using the outcome of agonistic encounters (17). From weeks 2–12 of social housing, two observers separately conducted 3 observations/week per pen, for a total of 34–36 observation sessions per pen (18). Winners of fights were considered dominant to losers; linear and transitive hierarchies existed in each pen. Eight monkeys were designated as dominant (ranked #1 or #2) and 7 were subordinate (ranked #3 or #4), as was done previously in males (9). Body weights, age and social rank did not correlate (18).

Cerebrospinal fluid (CSF) concentrations

To assess concentrations of the DA metabolite homovanillic acid (HVA), CSF was collected by a cervical puncture from 12 monkeys, once during the follicular phase and once during the luteal phase of a single menstrual cycle while the animals were anesthetized with 10 mg/kg (i.m.) ketamine (18). Four monkeys were not cycling regularly at this time, so two samples were taken 2 weeks apart. When it was determined subsequently that HVA concentrations did not differ across menstrual cycle phase (Table S1), data from the two samples were averaged for each monkey, including those that were not cycling, and were

considered individually housed CSF HVA baselines (n=16). Following social housing, CSF was collected from all monkeys during the follicular phase. For statistical purposes, reporting HVA pre- vs. post-social housing utilized a 2-way repeated measures ANOVA with all pairwise multiple comparison post hoc analyses (Tukey test).

PET imaging

A structural magnetic resonance imaging (MRI) study was conducted in each monkey under ketamine (15–20 mg/kg, i.m.) anesthesia with a 1.5-Tesla 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 (Cd), putamen (Pt), both at 0.5 cm diameter and cerebellum (Cb; 0.8 cm diameter), for later co-registration with PET images. PET studies used the DAT radioligand [^{18}F]fluorobenzylchlorotropane (FCT) (24) and the D2/D3 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) (25). Each monkey was scanned with both tracers while individually housed and after 3 months of social housing. The #1- and #4-ranked monkeys were scanned a third time after return to individual housing. For half the monkeys, D2/D3 PET studies were conducted before DAT. Body temperature was maintained at 40° C and vital signs were monitored throughout the scanning procedure (see 23). PET scans were acquired using a Siemens/CTI Concorde Primate microPET P4 scanner specifically designed for small-animal imaging, with approximately 2 mm resolution. At the start of the scan, approximately 5 mCi of [^{18}F]FCP or [^{18}F]FCT was injected, followed by 3 ml of heparinized saline. Tissue-time-activity curves were generated for radiotracer concentrations in each ROI and distribution volume ratios (DVR) for the Cd and Pt were calculated using the Cb as the reference region.

Surgery

Each monkey was prepared with a chronic indwelling venous catheter and subcutaneous vascular port (Access Technologies, Skokie, IL) under sterile surgical conditions, as described previously (26). Prior to each drug self-administration session, the back of the animal was cleaned with chlorhexidine acetate solution and 95% EtOH and the port was connected to the infusion pump located outside the chamber via a 22-gauge Huber Point Needle (Access Technologies).

Cocaine self-administration

The apparatus consisted of a ventilated, sound-attenuating chamber (1.5 × 0.74 × 0.76 m; Med Associates, East Fairfield, VT) designed to accommodate a primate chair. Two response keys (5 cm wide) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm above each response key and a food receptacle was located between the response keys. Each monkey was trained to respond on the left or right key, under a 30-response fixed-ratio (FR 30) schedule of reinforcement. Under these conditions, a food pellet was delivered after the 30th response, followed by a 10-s timeout. Sessions ended after 15 reinforcers or 60 min, whichever occurred first. The light above the response key signaled food availability; only one key was active during a session.

After catheter implantation, food-maintained responding was re-established and saline was substituted for food pellets for at least 5 consecutive sessions and until responding was deemed extinguished (i.e., mean response rate decreased by at least 80% of food-reinforced responding for 3 consecutive sessions with no trends in responding). After re-establishing food-maintained responding, different doses of cocaine HCl (National Institute on Drug Abuse, Bethesda, MD, dissolved in sterile 0.9% saline) were substituted for the food pellets in ascending order from 0.001 mg/kg/injection increasing in half log units to 0.1 mg/kg/

injection; each dose was available for at least 5 sessions and until responding was deemed stable (response rate mean ±20% with no trends for 3 consecutive sessions). Sessions ended after 30 injections or 60 min, whichever occurred first. Each dose was available days 2–10 (early to mid) of the follicular phase for at least 5 consecutive sessions. Food-maintained responding was reestablished during the late follicular to early luteal phase (typically days 11–18). If cocaine self-administration was not acquired during the previous follicular phase, the same dose of cocaine was made available during the mid- to late-luteal phase (days 19–26). Until acquisition occurred, new doses were always introduced in the follicular phase. There was a return to food-maintained responding, for at least 3 sessions, between different cocaine doses. The lowest cocaine dose at which response rates were significantly higher than responding leading to saline injections was defined as the acquisition dose. A cocaine dose was operationally defined as reinforcing by using two-tailed t-tests comparing 3-day mean response rates for a given cocaine dose to mean response rates when saline was available.

Statistical analysis

To determine if there were differences in the rate of acquisition between dominant and subordinate monkeys, a log-rank analysis of Kaplan-Meier survival curves was computed. To evaluate the entire cocaine dose-response curve, the primary dependent variables were response rate (total responses divided by session length) and cocaine intake (total intake in mg/kg per session). Food-maintained response rates and reinforcers (raw data) were analyzed with separate two-tailed, unpaired t-tests. Two-tailed, paired t-tests, within dominant and subordinate rank, were performed on response rate and intake measures to determine if there was an effect of menstrual phase at each dose tested. Because there were no significant effects of menstrual cycle phase, averages from both phases at each cocaine dose for response rates and intake were analyzed using a 2-way repeated-measures analysis of variance (ANOVA), followed by post-hoc analysis using all pairwise multiple comparison procedures (Tukey test). To perform the 2-way ANOVA, the raw data for intake was transformed (log10) due to unequal variances and post-hoc multiple comparison procedures were performed (Tukey test). In all cases, differences were considered statistically significant at $p<0.05$.

RESULTS

Behavioral and neurochemical profiles of socially housed females

Animals were individually housed for 27 months, during which various unconditioned behaviors and neurotransmitter metabolite levels were assessed for later use as potential predictors of social rank (18). After acquiring all individually housed baseline measures, monkeys were randomly assigned to social groups of 4 monkeys per pen. Social rank significantly ($F_{1,31} = 5.94$, $P<0.05$) affected CSF measures of HVA. When individually housed, future subordinate monkeys had higher concentrations at baseline compared to future dominant monkeys that trended towards significance ($t_{14} = 2.06$, $P=0.052$). The difference in HVA concentrations was significant ($t_{14} = 2.29$, $P<0.05$) once these social ranks were attained (Fig. 1A). Examining just the most dominant (#1-ranked) and most subordinate (#4-ranked) monkeys (Fig. 1B) confirmed significantly higher HVA concentrations in the subordinate monkeys ($t_6 = 2.48$, $P<0.05$).

Social rank and dopamine receptor function

PET scans were performed prior to and following 3 months of social housing. For both [^{18}F]FCT and [^{18}F]FCP, there was a high level of uptake in the Cd and Pt and low levels in the Cb. DAT availability in the Cd and Pt was differentially affected by social housing, with a significant interaction between Rank and Housing ($F_{1,31} = 4.67$, $P<0.05$; $F_{1,31} = 4.97$,

P<0.05, respectively). Post-hoc tests indicated that when monkeys were individually housed, DVRs for [^{18}F]FCT (Table 1) in the Cd (t_{14} = 0.54, P=0.60) and Pt (t_{14} = 1.62, P=0.12) did not predict eventual social rank. After social housing, subordinate monkeys had significant decreases in [^{18}F]FCT DVRs in the Cd (t_7 = 2.79, P<0.05) and in the Pt (t_7 = 2.52, P<0.05); DAT DVRs did not change in monkeys that became dominant (Table 1, Fig. 2). When individually housed, there was a significant correlation between age and DAT DVR in the Pt (r=−0.60, P<0.05); this effect was lost after social housing.

Housing conditions also affected D2/D3 receptor availability in the Cd ($F_{1,31}$ = 5.87, P<0.05), but not in the Pt [$F_{1,31}$ = 4.11, P=0.06) (Table 2). Post-hoc tests indicated that when monkeys were individually housed, DVRs for [^{18}F]FCP (Table 2) in the Cd did not predict eventual social rank (t_{14}=0.83, P=0.42), but that DVRs significantly increased in monkeys that became dominant (t_7 = 2.54, P<0.05). Comparing between social groups, the [^{18}F]FCP DVRs in the Cd were significantly higher in dominant compared to subordinate monkeys (t_7 = 2.32, P<0.05; Table 2 and Figs. 2 and 3). All monkeys were returned to individual housing for 3 months and the plasticity of D2/D3 receptor function was examined by repeat scans in the most dominant and most subordinate monkeys. Individually housed D2/D3 receptor availability in the Cd was not different pre- vs. post-social housing in dominant (t_3 = 2.18, P=0.12) and subordinate (t_3 = 0.85, P=0.46) monkeys (Table 2). During individual housing, there was not a significant correlation between age and D2/D3 DVR in the Cd and Pt.

Social rank and cocaine self-administration

Once PET scans were completed monkeys were returned to their original social groups and tested in operant behavioral sessions in which lever pressing was maintained under an FR 30 schedule of food reinforcement. There were no differences in baseline rates of responding between dominant and subordinate monkeys (t_{13} = 0.68, P=0.51). When saline was substituted for food, there were no group differences in rates of extinguished responding (Table 3). Ascending doses of cocaine were sequentially substituted for food in each monkey and acquisition of cocaine reinforcement was examined. Dominant female monkeys acquired cocaine reinforcement at significantly lower cocaine doses compared to subordinate monkeys (log rank test for equality of survival curves, $\chi 2$ = 5.63, P<0.05), indicating a greater sensitivity to the reinforcing effects of cocaine (Fig. 4). Cocaine acquisition occurred in the follicular phase in 11 of the 15 monkeys. Of the four monkeys that acquired in the luteal phase, one was #1-ranked, two were #2-ranked and one was #4-ranked. Because there were no menstrual cycle differences, data for each dose in each phase were averaged (Fig. 5). Examination of complete cocaine dose-response curves showed that, for both dominant and subordinate monkeys, response rates ($F_{5,84}$ = 4.22; P<0.005) and cocaine intake ($F_{4,69}$ = 53.18; P<0.001) varied significantly as a function of cocaine dose (Fig. 5). Post-hoc tests revealed significantly higher response rates (Fig. 5A) in dominant monkeys compared to subordinate animals when 0.003 mg/kg cocaine was available for self-administration (t_1 =2.89, P<0.05). Cocaine intake increased monotonically as a function of dose in all monkeys and was not different in dominant and subordinate monkeys (Fig. 5B).

DISCUSSION

The present findings extend earlier work in male subjects (humans, monkeys and rodents) to female monkeys demonstrating the powerful role of social environment and alterations within the DA system, specifically DAT and D2/D3 receptor availability on vulnerability to cocaine reinforcement. Previous research has shown that male monkeys that become dominant show significant increases in DA D2/D3 receptor availability, which resulted in lower measures of cocaine reinforcement (9). The major finding of the present study was

that dominant female monkeys showed significant increases in D2/D3 receptor availability following social rank formation but they were more vulnerable to cocaine reinforcement. These within-subject findings are the first to describe intravenous cocaine self-administration in socially housed female monkeys and identify significant sex differences in the relationship between D2/D3 receptor availability and drug abuse.

Indirect measures of DA activity revealed a significant relationship between CSF HVA concentrations and social rank, such that dominant monkeys had a lower average HVA concentration compared to subordinate monkeys. These findings are consistent with studies in humans (27) showing lower concentrations of CSF HVA were associated with greater aggression in dominant females. Whether CSF HVA accounts for the sex differences in cocaine reinforcement remains to be determined; these measures were not previously obtained in individually or socially housed male monkeys (9). The present study also extended earlier work (28) to include presynaptic DA measures by showing that DAT availability, while not predictive of eventual social rank, significantly decreased in female monkeys that became subordinate. These findings suggest that becoming socially subordinate is not similar to remaining individually housed.

Consistent with effects observed in male monkeys, D2/D3 receptor availability significantly increased in females that became dominant. This increase was related to the social hierarchy, because returning the most dominant (rank #1) and the most subordinate (rank #4) monkeys to their original individual-housing condition resulted in equivalence of D2/D3 receptor measures. The relationship between the three measures of DA neurotransmission appears orderly. Subordinate monkeys have higher CSF concentrations of HVA, consistent with higher extracellular DA compared to dominant females; the lower DAT availability in subordinates is also consistent with that hypothesis. The lower D2/D3 receptor availability in subordinate monkeys may also be indicative of higher synaptic concentrations of DA, as hypothesized for subordinate male monkeys (9, 16). In contrast to the considerable literature in males suggesting an inverse relationship between D2/D3 receptor availability and abuse potential of stimulants (8–11), results from the present study suggest a direct relationship between D2/D3 receptor availability and cocaine reinforcement in female monkeys. That is, females with higher D2/D3 receptor availability were more vulnerable to cocaine reinforcement than monkeys with lower D2/D3 receptor measures.

There were some procedural differences between studies that preclude direct sex comparisons in terms of behavior and brain imaging. The present self-administration studies were designed to model vulnerability – to determine the lowest cocaine dose that functioned as a reinforcer. While we found significant differences in response rates, especially at the lower cocaine doses, we did not observe differences in cocaine intake. In contrast, male subordinate monkeys had higher cocaine intakes compared to dominant male monkeys (9). For the males, doses were tested in random order, rather than in ascending order as in the present study, which may account for the differences in cocaine intake between males and females (see 29). Nonetheless, the present study clearly showed that dominant females were more vulnerable to cocaine reinforcement compared to subordinates. It is important to note that even under conditions in which there are no differences in baseline cocaine self-administration between dominant and subordinate monkeys, environmental manipulations can produce drastically different effects depending on the monkey's social rank (30). As it relates to D2/D3 receptor availability, different PET cameras were used in males and females. In the males, the spatial resolution at the time was only 9 mm and the DVR for dominant males in the basal ganglia was 3.04. The values obtained in females were much higher (Table 1). While it would have been ideal to test both sexes at the same time, the relationship between D2/D3 receptor availability and social rank is similar in males and females.

The inverse relationship between D2/D3 receptor availability and vulnerability to drug abuse has been hypothesized to be related to DA dysregulation (8,31). HVA concentrations have been shown to parallel measures of DA in the striatum (32); thus, the lower HVA concentrations in dominant, more vulnerable monkeys, compared to subordinates, provides support for a hypodopaminergic system. However, the direct relationship between D2/D3 receptor availability and vulnerability in females is opposite to that observed in males and suggests that D2/D3 receptor changes alone may not be sufficient to alter sensitivity to cocaine reinforcement. Earlier work in male monkeys has shown that chronic cocaine exposure decreased D2/D3 receptor measures (10,33,34) and increased DAT densities in monkeys (35) and humans (36). Thus in males, high D2/D3 and low DAT availability should lead to less vulnerability and treatment strategies that elevate D2/D3 receptor availability and/or decrease DAT availability should be advantageous. However, this strategy may not be beneficial in females, although additional research in females is required to better understand sex differences in the mechanisms mediating vulnerability to drug abuse (37).

There is evidence for an inverse relationship between D2/D3 receptor availability and several addictive behaviors, including obesity (38). In the present study, subordinate monkeys had lower D2/D3 receptor availability, which is consistent with other research showing that subordinate female macaques consume more low-fat and high-fat diets and gain more weight compared to dominant female monkeys (39,40). However, the fact that dominant female monkeys were more sensitive to cocaine reinforcement compared to subordinates is at odds with the hypothesis that all addictive behaviors have a similar etiology (41,42). One possibility is that the berry-flavored pellets were a stronger reinforcer in subordinate monkeys compared to dominant animals and that substituting cocaine for these berry-flavored pellets resulted in cocaine being a relatively weaker reinforcer in the subordinate monkeys, a process termed reward devaluation (43,44). However, there were no rank-related differences in food-maintained responding. A second possibility is that the low rates of cocaine self-administration by the subordinate monkeys represent “stronger” cocaine reinforcement. The use of simple fixed-ratio schedules does not allow for comparisons of reinforcing strength (45). However, the experimental design did allow for an unequivocal assessment of acquisition of cocaine reinforcement and indicated that dominant female monkeys were more vulnerable to cocaine reinforcement. Future studies involving food-cocaine choice would address the issue of whether the reinforcing strength of cocaine was different in socially housed females (26).

While we noted sex differences in our socially housed monkeys, we did not observe significant effects of menstrual cycle phase on cocaine reinforcement. This was surprising considering the evidence for changes in D2/D3 receptor availability across the menstrual cycle phase (23). One possibility is that we were primarily focusing on early vulnerability and that menstrual cycle differences have been noted under conditions of longer access to cocaine (46). There have been findings of sex differences in cocaine reinforcement in rats (46,47), monkeys (46,49) and people (50) and a recent study in human smokers has shown sex differences in DA D2/D3 receptor availability in men vs. women (51). The present study confirms the importance of social and environmental factors on brain DA receptor function and on the consequences of these variables on vulnerability to cocaine abuse (52,53). Considering that the majority of research on cocaine addiction occurs in males, the observations of sex differences in neurobiological consequences, as well as etiology and symptoms suggest different treatment strategies would be effective in women compared to men and reinforce the importance of studying both males and females with the goal of individualized treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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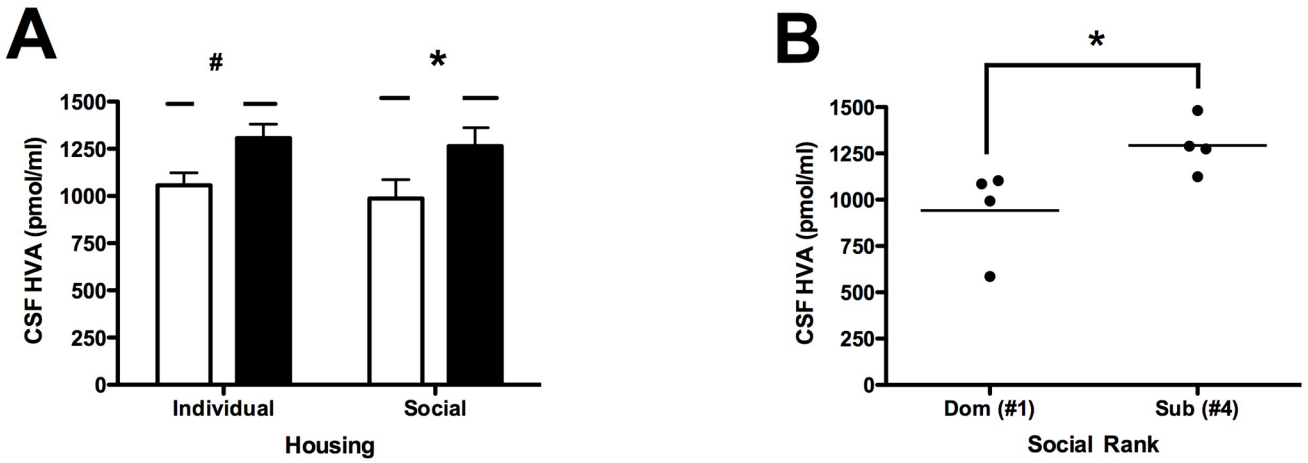

Figure 1.

A. CSF HVA concentrations in female cynomolgus monkeys as a function of eventual social rank while individually housed and following stable social group formation. For these data, #1 and #2 ranked monkeys (open bars) are considered dominant while #3 and #4 ranked monkeys (filled bars) are considered subordinate (n=8/group). ***B***. Post-social housing HVA concentrations in #1 and #4 ranked female monkeys (n=4/group). Symbols represent individual subject data; horizontal lines represent group means. All samples were obtained in the follicular phase. # p=0.052; * $p < 0.05$.

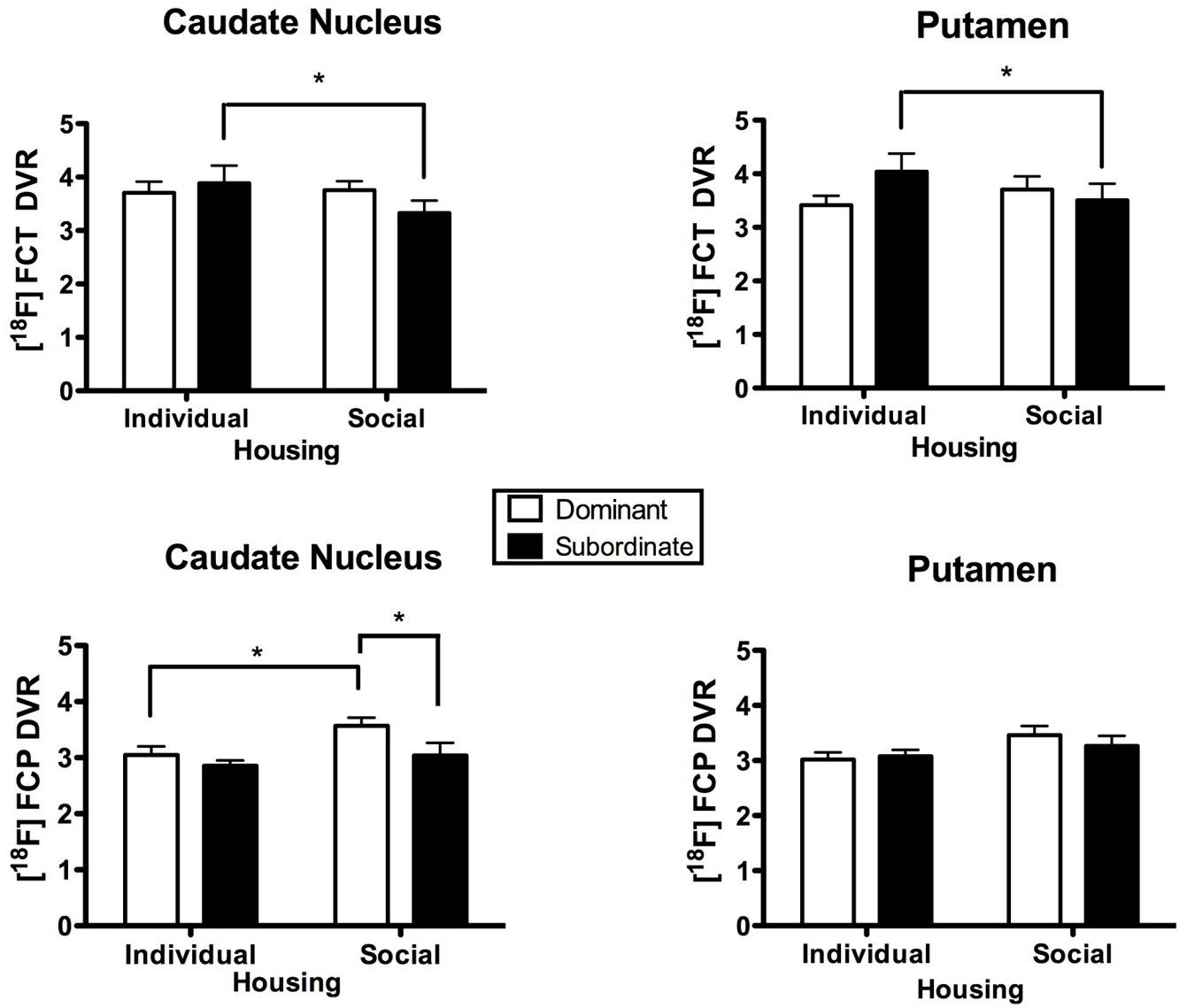

Figure 2.

[^{18}F]FCT (top panel) and [^{18}F]FCP (bottom panel) distribution volume ratios (DVRs) change as a function of social rank in the caudate nucleus (left panels) and putamen (right panels). Panels show the mean DVR values for dominant (ranks #1 and #2) and subordinate (ranks #3 and #4) monkeys (n=8/group), while they were individually and socially housed.

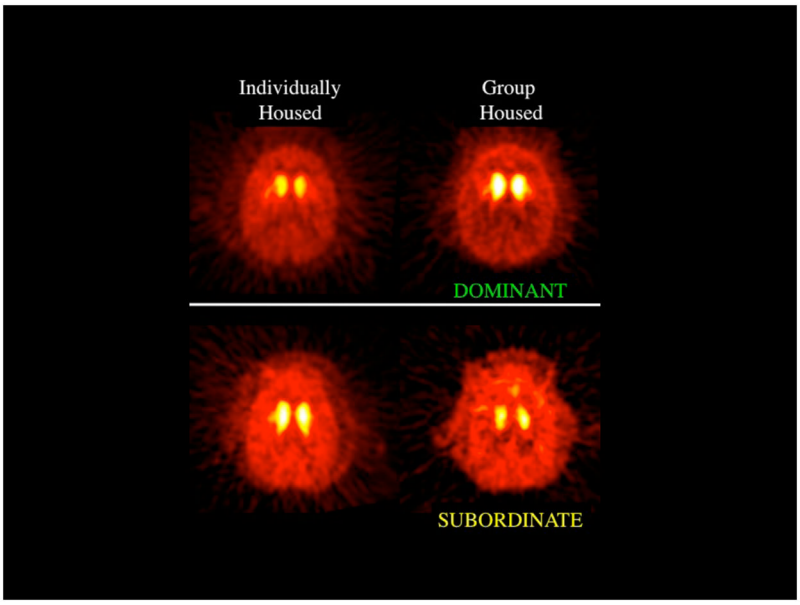

Figure 3.
Measures of dopamine D2/D3 receptor availability increase in dominant female monkeys. Normalized, co-registered PET images (percent injected dose per ml) of [^{18}F]FCP binding in the midbrain (caudate nucleus and putamen) of a dominant and a subordinate monkey, while individually housed and socially housed.

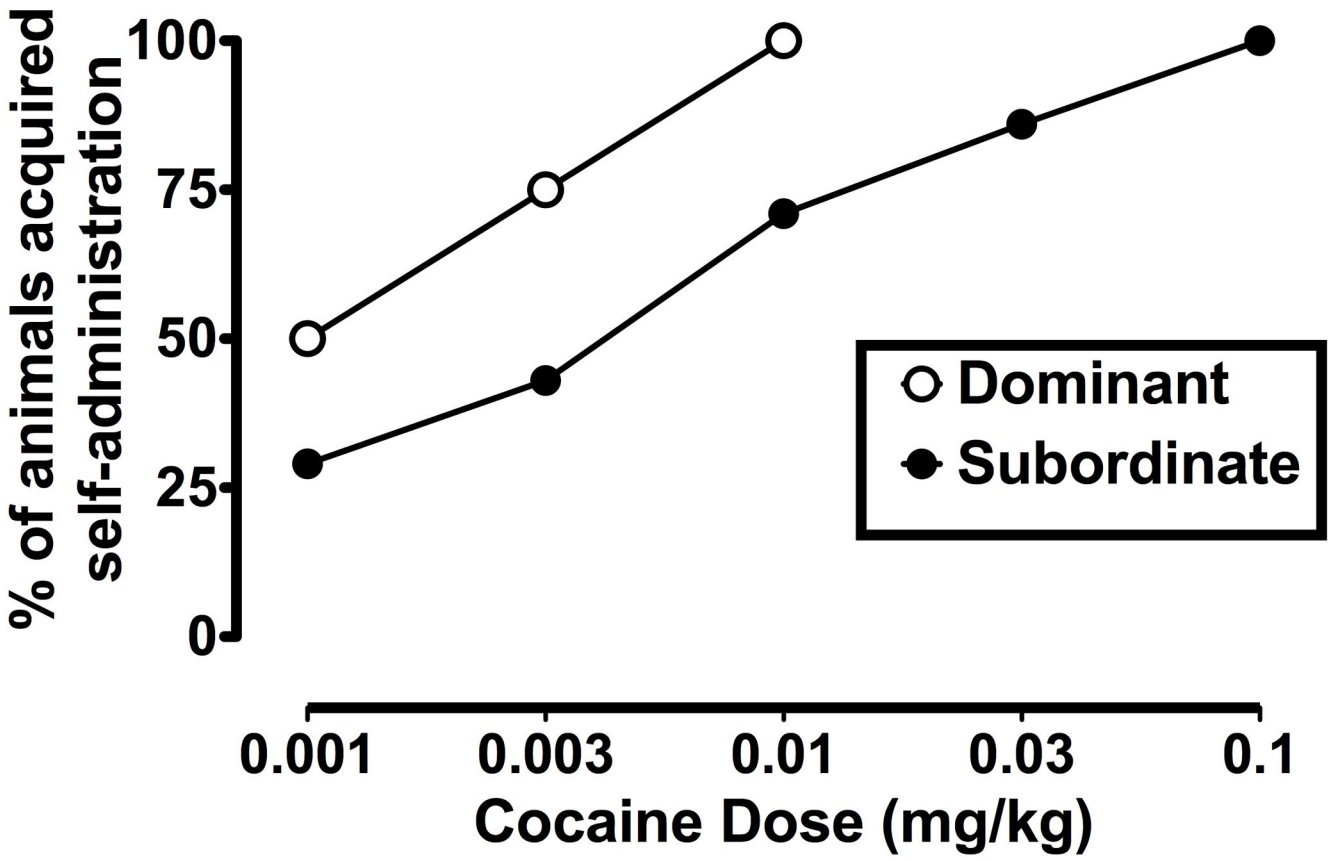

Figure 4.

Dominant female monkeys acquire cocaine reinforcement at lower doses than subordinate monkeys. Percentage of dominant (open symbols) and subordinate (closed symbols) monkeys that reached criteria to acquire cocaine self-administration at various doses of cocaine available under an FR 30 schedule of reinforcement.

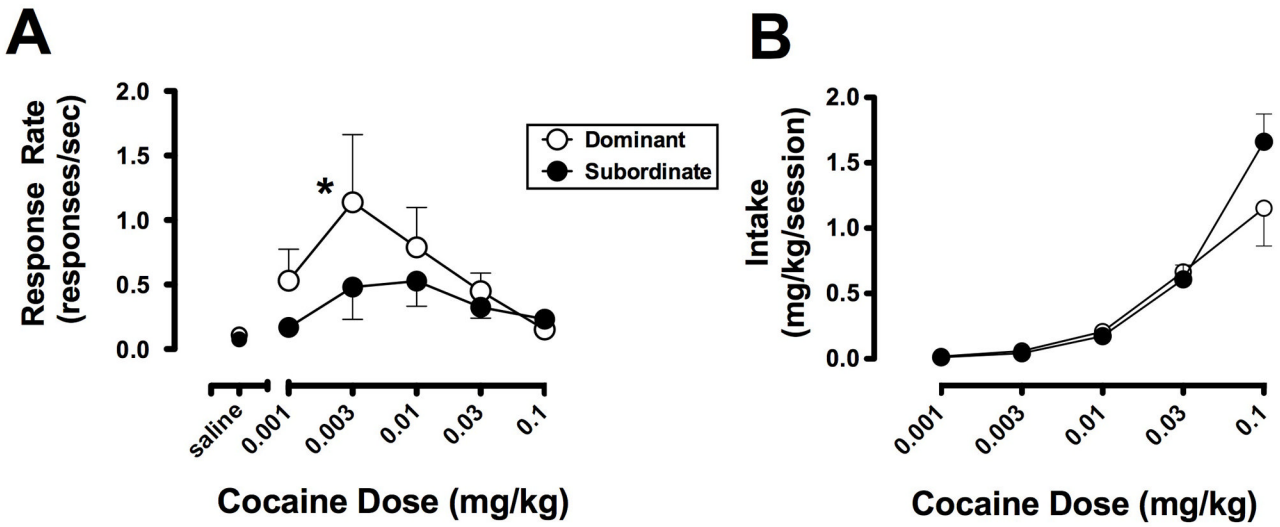

Figure 5.

Reinforcing effects of cocaine are greater in dominant female monkeys compared to subordinate animals. ***A.*** Mean (±SEM) rate of responding (responses/sec) when saline or various doses of cocaine were available per session for dominant (ranks #1 and #2, open symbols, n=8) and subordinate (ranks #3 and #4, closed symbols, n=7) monkeys. ***B.*** Mean (±SEM) cocaine intake (mg/kg/session). Each dose was available for at least 5 sessions and until responding was stable; data represent the mean of the last 3 days of availability for each animal. Data from follicular and luteal phases were averaged for each monkey. * $p <$ 0.05 between dominant and subordinate monkeys at that particular dose.

Table 1

Dopamine Transporter Availability in Female Monkeys

[^{18}F]FCT distribution volume ratios in the Caudate Nucleus[a]					
Social Rank [b]		**Individually housed**	**Individually housed [Mean ± SEM]**	**Socially housed**	**Socially housed [Mean ± SEM] (% Chng)[c]**
Dominant	1	4.13 ± 0.28	3.71 ± 0.21	3.69 ± 0.23	3.76 *± 0.16 (+3.1 ± 6.14%)*
	2	3.28 ± 0.08		3.83 ± 0.26	
Subordinate	3	4.09 ± 0.54	3.89 ± 0.33	3.61 ± 0.32	3.33 *± 0.23*** *(−13% ± 4.3%)*
	4	3.69 ± 0.42		3.05 ± 0.32*	

[^{18}F]FCT distribution volume ratios in the Putamen[a]					
Social Rank [b]		**Individually housed**	**Individually housed [Mean ± SEM]**	**Socially housed**	**Socially housed [Mean ± SEM] (% Chng)[c]**
Dominant	1	3.81 ± 0.18	3.42 ± 0.17	3.62 ± 0.12	3.71 *± 0.25 (+10.4 ± 9.6%)*
	2	3.02 ± 0.08		3.80 ± 0.51	
Subordinate	3	4.22 ± 0.53	4.04 ± 0.34	3.87 ± 0.27	3.51 *± 0.31** *(−12.3% ± 6.3%)*
	4	3.87 ± 0.47		3.14 ± 0.54	

[a] Data represent mean (± 1 SEM) distribution volume ratios (DVRs)

[b] For individually housed scans these numbers represent eventual social rank

[c] percent change from individually housed DVRs

* $p < 0.05$ significant change from individually housed

** $p < 0.01$ significant change from individually housed

Table 2

Dopamine D2/D3 Receptor Availability in Female Monkeys

[^{18}F]FCP distribution volume ratios in the Caudate Nucleus[a]							
Social Rank[b]		**Individually housed**	**Individually housed [Mean ± SEM]**	**Socially housed**	**Socially housed Mean ± SEM (% Chng)[c]**	**Return to Individual Housing**	**Individually housed (% Chng)[d]**
Dominant	1	3.18 ± 0.20	3.05 ± 0.16	3.78 ± 0.24	3.57 *± 0.14*[*§] *(+18.7% ± 6.4)*	3.51 ± 0.22	*−6.4 ± 6.7*
	2	2.92 ± 0.25		3.36 ± 0.09			
Subordinate	3	2.94 ± 0.14	2.86 ± 0.10	3.16 ± 0.38	3.04 *± 0.22 (+6.71% ± 7.7)*		
	4	2.78 ± 0.14		2.93 ± 0.29		3.01 ± 0.26	*+4.0 ± 7.3*

[^{18}F]FCP distribution volume ratios in the Putamen[a]							
Social Rank[b]		**Individually housed**	**Individually housed [Mean ± SEM]**	**Socially housed**	**Socially housed Mean ± SEM (% Chng)[c]**	**Return to Individual Housing**	**Individually housed (% Chng)[d]**
Dominant	1	3.09 ± 0.19	3.01 ± 0.13	3.50 ± 0.34	3.46 *± 0.17 (+16.4% ± 7.6)*	3.14 ± 0.39	*−10.4 ± 7.2*
	2	2.94 ± 0.19		3.42 ± 0.13			
Subordinate	3	3.19 ± 0.19	3.11 ± 0.13	3.41 ± 0.31	3.27*± 0.18 (+6.13% ± 7.2)*		
	4	3.04 ± 0.20		3.12 ± 0.21		3.22 ± 0.18	*+4.9 ± 9.2*

[a] Data represent mean (± 1 SEM) distribution volume ratios (DVRs)

[b] For individually housed scans these numbers represent eventual social rank

[c] percent change from individually housed DVRs

[*] p< 0.05 significant change from individually housed

[§] p< 0.05 significant difference between dominant and subordinate monkeys

Table 3

Baseline response rates in socially housed female monkeys.

Food-Maintained Responding Prior to Cocaine Acquisition					
Social Rank		**Response Rate (resp/sec)**	**Response Rates [Mean ± SEM]**	**# Pellets**	**# Pellets [Mean ± SEM]**
Dominant	1	0.74 ± 0.25	0.75 ± 0.17	14.20 ± 0.83	14.0 *± 0.56*
	2	0.75 ± 0.27		13.80 ± 0.79	
Subordinate	3	1.09 ± 0.28	0.91 ± 0.18	15.00 ± 0.00	15.0 *± 0.0*
	4	0.78 ± 0.26		15.00 ± 0.00	

Saline-Maintained Responding Prior to Cocaine Acquisition					
Social Rank		**Response Rate (resp/sec)**	**Response Rates [Mean ± SEM]**	**# Injections**	**# Injections [Mean ± SEM]**
Dominant	1	0.19 ± 0.09	0.11 ± 0.05	16.50 ± 5.94	10.0 *± 3.72*
	2	0.03 ± 0.01		3.58 ± 1.29	
Subordinate	3	0.10 ± 0.03	0.09 ± 0.01	10.33 ± 3.21	9.2 *± 1.44*
	4	0.08 ± 0.01		8.42 ± 1.26	

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