

## **Assessment of the Relative Reinforcing Strength of Cocaine in Socially Housed Monkeys Using a Choice Procedure**

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## Abstract

Position in the social hierarchy can influence brain dopamine function and cocaine reinforcement in nonhuman primates during early cocaine exposure. With prolonged exposure, however, initial differences in rates of cocaine self-administration between dominant and subordinate monkeys dissipate. The present studies used a choice procedure to assess the relative reinforcing strength of cocaine in group-housed cynomolgus monkeys with extensive cocaine self-administration histories. Responding was maintained under a concurrent fixed-ratio 50 schedule of food and cocaine (0.003-0.1 mg/kg per injection) presentation. Responding on the cocaine-associated lever increased as a function of cocaine dose in all monkeys. Although response distribution was similar across social rank when saline or relatively low or high cocaine doses were the alternative to food, planned post hoc analysis indicated that cocaine choice was significantly greater in subordinate monkeys when choice was between an intermediate dose (0.01 mg/kg) and food. When a between-session progressive-ratio procedure was used to increase response requirements for the preferred reinforcer (either cocaine or food), choice of that reinforcer decreased in all monkeys. The average response requirement that produced a shift in response allocation from the cocaine-associated lever to the food-associated lever was higher in subordinates across cocaine doses, an effect that trended toward significance ( $p=0.053$ ). These data indicate that despite an extensive history of cocaine self-administration, most subordinate monkeys were more sensitive to the relative reinforcing strength of cocaine than dominant monkeys.

Little is known about the factors that render certain people more susceptible to the addictive effects of drugs. Individual differences in vulnerability may be related to deficits in decision-making abilities, particularly regarding the choice to use drugs to the exclusion of alternative activities. Cocaine-dependent individuals have been characterized in laboratory studies as highly impulsive (Moeller et al., 2002; Coffey et al., 2003) and likely to make maladaptive decisions (Grant et al., 2000; Bechara et al., 2001; Heyman and Dunn, 2002). Since drug use occurs in a context in which many behavioral options exist, it is likely that perpetuation of drug taking and the transition from casual use to addiction is driven in part by overvaluing drug use relative to behaviors maintained by other reinforcers. Functional alterations in brain areas that participate in higher-order cognitive functions such as decision-making have been identified in brain imaging studies in cocaine users (Goldstein and Volkow, 2002; Rogers and Robbins, 2001), but it is largely unknown whether these deficits represent a pathological effect of chronic drug use or a predisposing trait that confers susceptibility to the addictive effects of drugs. Furthermore, little is known about the influence of environmental factors on cocaine choice.

Intravenous drug self-administration techniques in laboratory animals have proven to be valid models of human drug use (Griffiths et al., 1980; Mello and Negus, 1996). In the majority of preclinical studies, behavior is maintained by a single operant schedule of reinforcement, and a change in response rate or drug intake is interpreted as a change reinforcing effects of the drug. This model has well-documented predictive validity (Griffiths et al., 1980) and has been used to examine the influence of environmental and pharmacological variables on drug self-administration (e.g., Spealman and Goldberg, 1978; Johanson and Fischman, 1989; Woolverton and Nader, 1990). Recently, effects of social rank on cocaine reinforcement were examined in group-housed cynomolgus monkeys. Position in the dominance hierarchy was shown to influence response rate and cocaine intake (Morgan et al., 2002). Specifically, subordinate monkeys self-administered cocaine at significantly higher rates and had higher cocaine intakes compared to dominant monkeys when cocaine was available under a fixed-ratio (FR) 50

schedule. Formation of social hierarchies also resulted in significant differences in levels of DA D<sub>2</sub> receptor function (Morgan et al., 2002). These findings further supported the hypothesis that environmental variables can significantly impact the behavioral effects of abused drugs, including reinforcing effects (Barrett et al., 1989).

While monkeys' social rank significantly influenced cocaine reinforcement during initial exposure, long-term cocaine self-administration under an FR 50 schedule resulted in progressive increases in cocaine-maintained responding by dominant monkeys to the point that, after several years, no significant differences between dominant and subordinate monkeys were observed (Czoty et al., 2004). These findings suggested that with prolonged cocaine exposure, the impact of environmental variables (in this case dominance status) on certain measures of reinforcing effects was attenuated. Parallel changes in DA receptor function were observed (Czoty et al., 2004). One goal of the present study was to further evaluate the reinforcing effects of cocaine in socially housed monkeys with extensive experience self-administering cocaine.

While simple schedules of reinforcement have provided excellent predictive validity in drug self-administration studies, such procedures do not reflect the aspect of choice integral to human drug abuse. To characterize the influence of environmental and contextual variables on drug choice, procedures have been utilized that simultaneously schedule reinforcement on separate manipulanda, termed concurrent schedules (for review see Higgins, 1997). Unlike single-operant techniques, the dependent variable studied with concurrent schedules (percent of responses allocated to the drug-associated lever or percent of trials in which that lever was chosen) provides a measure of the reinforcing strength of a drug relative to a non-drug reinforcer. It is clear that measures of reinforcing strength and measures of reinforcing effects (e.g., ability to maintain responding under a simple schedule of reinforcement when substituted for cocaine) do not provide identical information (cf. Woolverton and Nader, 1990). Thus, the present studies describe cocaine self-administration under conditions of concurrent access to food reinforcement in socially housed monkeys in order to characterize the relative reinforcing

strength of cocaine as a function of social rank. In addition, relative reinforcing strength of cocaine was examined during systematic manipulation of the response requirements for food or cocaine.

## Materials and Methods

**Subjects.** Eleven adult male cynomolgus monkeys (*Macaca fascicularis*) served as subjects. All monkeys had self-administered cocaine several times per week for 2-5 years, and some had limited exposure to D<sub>1</sub> receptor agonists (Czoty et al., 2004). Each monkey was fitted with a nylon collar (Primate Products, Redwood City, CA) and trained to sit calmly in a standard primate restraint chair (Primate Products) using a specially designed stainless steel pole (Primate Products) that attached to the collar. Monkeys were weighed weekly and fed enough food daily (Purina Monkey Chow and fresh fruit) to maintain body weights at approximately 95% of free-feeding levels. Monkeys lived in 6 social groups of 2 or 3 monkeys per pen; each pen consisted of a stainless steel cage (Allentown Caging Inc, Allentown, NJ) with removable wire mesh partitions used to separate the monkeys into quadrants (approximately 0.33 m<sup>3</sup>) when necessary. Each quadrant was equipped with a spout from which water was continuously available. When the partitions were removed, the living space was approximately 2.3 m<sup>3</sup>.

Social status was determined for each monkey according to the outcomes of agonistic encounters as described previously (Kaplan et al., 1982; Morgan et al., 2000). Initially, aggressive, submissive and affiliative behaviors were recorded for individual monkeys in each pen during 45-min observation sessions. The animal that aggressed toward, and elicited submissive behaviors from, all others was designated the dominant monkey. The subordinate monkey received aggression from all others and rarely aggressed. Stability of the hierarchies in each pen was confirmed daily by visual inspection. For example, when a peanut was offered by a technician, the dominant animal typically threatened other monkeys in the pen and retrieved

the peanut, whereas the subordinate animal typically moved to the rear of the pen and engaged in submissive behaviors and vocalizations. Ranks did not change during the present study.

**Catheter Implantation.** Each monkey was prepared with a chronic indwelling venous catheter and subcutaneous vascular access port (Access Technologies, Skokie, IL) under sterile surgical conditions. Anesthesia was induced with ketamine (15 mg/kg) and butorphanol (0.025 mg/kg) and maintained with ketamine supplements. A catheter was inserted into a major vein (femoral, internal or external jugular, brachial) to the level of the vena cava. The distal end of the catheter was passed subcutaneously to a point slightly off the midline of the back, where an incision was made. The end of the catheter was attached to the vascular access port which was placed in a pocket formed by blunt dissection. To prolong patency, each port and catheter was filled with a solution of 50% heparinized saline (500 U/ml) at the end of each experimental session.

**Self-administration procedure.** Each day monkeys were separated by partitioning the living space into quadrants. Next, each monkey was seated in a restraint chair and placed into a ventilated, sound-attenuating chamber (1.5 x 0.74 x 0.76 m; Med Associates, East Fairfield, VT). The back of the animal was cleaned with 95% EtOH and betadine and the port was connected to an infusion pump (Cole-Parmer, Inc. Chicago, IL) located outside the chamber via a 20-gauge Huber Point Needle (Access Technologies). The pump was operated for approximately 3 sec to fill the port and catheter with the dose of cocaine available for the session. Two retractable response levers (5 cm wide) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm above each lever. Levers were positioned to be easily within reach of the monkey seated in the primate chair. A food receptacle located between the levers was connected with a tygon tube to a pellet dispenser (Gerbrands Corp., Arlington, MA) located on the top of the chamber for delivery of 1-g banana-flavored food pellets (P.J. Noyes Co., Lancaster, NH).

Prior to catheter implantation, monkeys were trained to respond under an FR 50 schedule of food presentation, with each pellet delivery followed by a 10-sec timeout (TO). During these sessions, either lever was extended and only the lights above that lever were illuminated. Sessions lasted until 30 pellets had been obtained or 60 min had elapsed. When responding was reliably maintained on either lever and maximal food reinforcement was received consistently, catheters were implanted as described above. When experiments resumed, concurrent exposure to cocaine and food was begun. For approximately half of the monkeys, completion of an FR 50 on the left lever activated the infusion pump, producing an injection of 0.03 mg/kg cocaine, while responding on the right lever continued to be maintained by food presentation. For the other monkeys, the reinforcers on each lever were reversed (i.e., the lever associated with cocaine was counterbalanced across monkeys). As during training, a 10-sec TO followed each reinforcer (food and drug). Initially, levers were presented individually for several consecutive sessions until monkeys consistently earned the maximum number of available reinforcers. Subsequently, levers were presented simultaneously and responding was maintained under a concurrent FR 50 schedule of food presentation and cocaine injection. Under this condition, 50 consecutive responses on either lever produced the appropriate reinforcer; responses on the alternate lever reset the response requirement. The session ended after 30 total reinforcers had been earned or 60 min had elapsed. Saline and several doses of cocaine (0.003-0.1 mg/kg per injection) were examined under these conditions. Each dose was available for at least 5 consecutive sessions and until responding was deemed stable (% injection-lever responding  $\pm 15\%$  of the mean of 3 consecutive sessions with no trend; if these criteria were not met within approximately 20 sessions, the mean of the last 5 days was used). Doses were tested in random order in each monkey. (-)Cocaine HCl (National Institute on Drug Abuse, Bethesda, MD) was dissolved in sterile saline. Different doses were studied by changing the drug concentration prepared in 250 ml of saline. Injections consisted of approximately 1.5 ml of drug solution over 10 sec.



After completion of the cocaine dose-response curve, the schedule was changed to a concurrent FR 50 food, progressive-ratio (PR) cocaine schedule, and the lowest cocaine dose that resulted in >80% cocaine choice was studied. Under the PR schedule, the response requirement was increased across days until preference for cocaine decreased to <20%. To accomplish this, the response requirement for a cocaine injection was increased from 50 to 100 for a minimum of four sessions and until responding again stabilized. If cocaine choice was still >20% of the total responses, the response requirement was increased further to 200, then to 400, 800 and 1600 in a similar stepwise fashion, until an FR value was reached at which fewer than 20% of the total responses were emitted on the injection lever. For statistical analyses, the linear increment (e.g. FR 50 = 1, FR 100 = 2, etc.) was used to compare dominant and subordinate monkeys rather than the FR value. A similar experiment was conducted in which the highest dose of cocaine that resulted in <20% cocaine choice under the initial FR 50 food, FR 50 cocaine condition was studied. Under these conditions, the response requirement for food was increased similarly until >80% of the responses were made on the injection lever.

**Data analysis.** The primary dependent variables examined were cocaine choice, defined as the percent of responses on the injection lever (calculated by dividing the total number of injection-lever responses by the total responses on both levers x 100), and the number of injections and food pellets earned in each session. Data are presented as averages ( $\pm$  SEM) across monkeys. Choice data, and the number of injections and food reinforcers were initially analyzed using repeated-measures two-way analyses of variance (ANOVA) with social rank and cocaine dose as factors. Because previous studies of self-administration under a simple (FR 50) schedule of reinforcement indicated that response rates and cocaine intakes differed significantly according to social rank when 0.01 and 0.03 mg/kg cocaine doses, but not higher or lower doses, were available (Morgan et al., 2002), ANOVAs were followed by planned t-tests were conducted to compare dominant monkeys and subordinates when these doses

were the alternative to food. Effects of social rank on response distribution under the concurrent FR 50 food, PR cocaine schedule were analyzed using a repeated-measures two-way ANOVA. In all cases, differences were considered significant at the 95% level of confidence ( $p < 0.05$ ).

## Results

**Effect of dose on cocaine choice.** When cocaine injections and food pellets were concurrently available under identical FR 50 schedules of reinforcement, cocaine choice increased significantly as a function of dose ( $F_{4,36}=38.50$ ,  $p<0.0001$ ; Fig. 1a). On average, fewer than 20% of responses were emitted on the injection lever when saline or 0.003 mg/kg per injection cocaine was the alternative to food, and nearly 100% of responses were emitted on the injection lever when the available cocaine dose was 0.03 or 0.1 mg/kg per injection. The main effect of social rank and the interaction only approached significance ( $F_{1,9}=3.25$ ,  $p=0.105$ ;  $F_{4,36}=2.46$ ,  $p=0.063$ , respectively), likely due to similarity between dominant monkeys and subordinates during availability of saline and three of the four doses tested. However, planned post-hoc t-tests revealed that when 0.01 mg/kg per injection was available for self-administration, cocaine choice was significantly greater in subordinate compared to dominant monkeys ( $t_9=2.27$ ,  $p<0.05$ ). At this dose, four of six subordinates emitted >90% of responses on the injection lever, whereas >80% injection-lever responding was observed in only one of five dominant monkeys.

The relationship between cocaine dose and number of injections earned was characterized by an inverted-U shaped dose-effect curve (Fig. 1b). A significant effect on number of injections was observed for cocaine dose ( $F_{4,36}=18.13$ ,  $p<0.0001$ ), but not social rank, with no interaction. Post-hoc analysis revealed no differences between ranks. Number of food reinforcers earned decreased significantly as the available cocaine dose increased ( $F_{4,36}=39.62$ ,  $p<0.0001$ ; Fig. 1c). Although neither the effect of social rank nor the interaction achieved statistical significance ( $F_{1,9}=2.79$ ,  $p=0.129$ ;  $F_{4,36}=2.176$ ,  $p=0.091$ , respectively),

planned post-hoc t-tests revealed that dominants and subordinates differed significantly in food reinforcers earned when 0.01 mg/kg cocaine was the alternative ( $t_9=2.32$ ,  $p<0.05$ ).

**Effect of increasing response requirement.** At cocaine doses at which >80% of responses were emitted on the injection lever under the concurrent FR 50 condition, progressively increasing the response requirement for cocaine injections resulted in a shift in distribution of responding to the food lever (Fig. 2). Eventually, an FR value was reached at which less than 20% of responses were emitted on the injection lever. In most monkeys, the ratio value required to produce this shift in response allocation increased with cocaine dose (Fig. 3). That is, cocaine choice persisted to higher FR values when larger cocaine doses were available; increases in response requirements more readily shifted responding to the food lever when lower cocaine doses were the alternative to food. This result was reflected in a significant main effect of cocaine dose on final FR increment ( $F_{3,27}=13.28$ ,  $p < 0.0001$ ). The average FR values were higher in subordinates across cocaine doses, an effect that trended toward significance ( $F_{1,9}=4.95$ ,  $p=0.053$ ). No significant interaction between rank and cocaine dose was observed.

**Effect of increasing food response requirement.** Sensitivity to increasing the response requirement for food reinforcement was assessed at the highest cocaine dose at which <20% cocaine choice was observed when response requirements for cocaine and food were equal (FR 50). For 9 of 11 monkeys, this distribution occurred when either 0.003 or 0.01 mg/kg per injection served as the alternative to food (Table 1). It was necessary to decrease the cocaine dose to 0.001 mg/kg per injection for C-6217 to achieve this response allocation. C-6214 was not tested in this experiment since no cocaine dose produced less than 20% injection-lever responding. Regardless of the dose at which monkeys were tested, increasing the response requirement for food shifted the distribution of responding to the injection lever. The

FR value at which responding on the injection lever exceeded 20% differed across animals, but was not related to social rank (Table 1).

## Discussion

The present study was designed to examine the relative reinforcing strength of cocaine in socially housed monkeys using a choice procedure. When cocaine and food were available as reinforcers at equal response requirements, cocaine choice increased as a function of available cocaine dose as reported previously (Woolverton and Balster, 1981; Nader and Woolverton, 1991, 1992; Paronis et al., 2002; Negus, 2003). Considering the similarity in response distribution across social rank when saline or relatively low or high cocaine doses served as the alternative to food, the non-significance of a main effect of social rank as determined by ANOVA was not unexpected. Several observations suggested that subordinate monkeys were more sensitive to the relative reinforcing strength of cocaine under limited conditions. First, a planned comparison between dominant and subordinate monkeys' response allocations during availability of an intermediate cocaine dose (0.01 mg/kg per injection) revealed a significant difference. Moreover, subordinate but not dominant monkeys allocated a greater proportion of responses to the injection lever on average when 0.01 mg/kg per injection cocaine was available as the alternative to food compared to when saline served as the alternative. Finally, when response requirements for a preferred dose of cocaine were systematically increased, higher FR values were required to shift response allocation in subordinates, an effect that trended toward significance ( $p=0.053$ ). The data suggest that, in monkeys with extensive histories of cocaine self-administration, subtle differences may exist in the relative reinforcing strength of cocaine; differences in choice were limited to an intermediate cocaine dose.

There is unequivocal evidence that social status exerts a profound impact on nonhuman primate physiology (e.g. Grant et al., 1998; Kaplan and Manuck, 1999; Kaplan et al., 2002) and

can influence the behavioral effects of dopaminergic drugs. For example, effects of *d*-amphetamine on aggression are more profound in dominant than subordinate squirrel monkeys (Miczek and Gold, 1983; Martin et al., 1990). Recently, these observations were extended to DA D<sub>2</sub> receptors and cocaine self-administration in cynomolgus monkeys (Morgan et al., 2002). Environmental variables associated with the attainment of dominance produced alterations in D<sub>2</sub> receptor function that attenuated the reinforcing effects of cocaine during initial exposure to the drug (modeling the “acquisition” phase of human cocaine abuse). Once monkeys had developed a long history of cocaine self-administration, modeling the “maintenance” phase of cocaine abuse, neither differences in D<sub>2</sub> receptor function nor differences in the reinforcing effects of cocaine had persisted (Czoty et al., 2004), suggesting that chronic exposure to self-administered cocaine had reversed the initial effects of social housing on D<sub>2</sub> receptors and the reinforcing effects of cocaine.

Preclinical studies have shown that measures of reinforcing effects (e.g., response rates maintained by FR schedules) do not provide identical information as measures of reinforcing strength (Woolverton and Johanson, 1984). For example, procaine has been shown to maintain higher rates of responding than cocaine under simple schedules of reinforcement (Woolverton and Balster, 1979), but was not preferred over cocaine in choice studies (Johanson and Aigner, 1981). The converse can also be true. The high affinity DA uptake inhibitor PTT (2beta-propanoyl-3beta-(4-tolyl)-tropane) can maintain significantly lower rates of responding under simple schedules compared to cocaine (Nader et al., 1997; Birmingham et al., 1998; Lile et al., 2000), but when studied under choice conditions can be chosen with equal frequency to cocaine (Lile et al., 2002). Thus, the fact that response rates maintained by cocaine under simple schedules no longer differed according to social rank (Czoty et al., 2004) did not preclude social rank-related differences in relative reinforcing strength of cocaine compared to food.

In the present studies, the relative reinforcing strength of a cocaine was similar across social rank when saline or relatively high or low cocaine doses served as the alternative to food.

However, a significant difference was observed between dominant and subordinate monkeys when an intermediate dose of cocaine was available. This result is consistent with other findings indicating that individual differences in measures of reinforcement are most prominent at lower drug doses. Previous studies in rodents (Piazza et al., 1989) have shown that animals characterized as high responders in a locomotor assay are more likely to self-administer low doses of amphetamine than are animals initially characterized as low responders; group differences dissipate at higher doses. Subordinate monkeys displayed similar characteristics to high-responding rats in that monkeys that had higher locomotor scores in an open field tended to become subordinate (Morgan et al., 2000) and were more sensitive to the reinforcing effects of cocaine during initial exposure (Morgan et al., 2002). Moreover, the present data are consistent with the findings of Goeders and colleagues (for review see Goeders, 2002), who demonstrated that exposure to uncontrollable footshock or corticosterone injections increased rats' sensitivity to the reinforcing effects of low, but not higher, cocaine doses. These effects were observed during early exposure to cocaine, but not during the maintenance phase (Goeders, 2002). Consistent with differences in maintenance vs. initial exposure to drug reinforcement, we recently reported that subordinate and dominant monkeys no longer differed in cocaine self-administration under an FR schedule (Czoty et al., 2004). In the present study, however, subtle differences in the relative reinforcing strength of cocaine were observed under limited conditions in monkeys with an extensive history of cocaine self-administration, further supporting a distinction between measures of reinforcing effects and reinforcing strength.

Studies in nonhuman primates using concurrent schedules of food and cocaine availability have consistently demonstrated that monkeys allocate responding according to the relative reinforcing strength of the available reinforcers. When food was available as an alternative to cocaine, predictable changes in cocaine choice were observed with manipulations of the amount of food or drug presented or the number of responses required for their presentation (Woolverton and Balster, 1981; Nader and Woolverton, 1991, 1992; Anderson et

al., 2002; Paronis et al., 2002; Negus, 2003). In the present studies, increasing response requirements was less able to shift responding to the food lever in subordinates regardless of cocaine dose, an effect that trended toward statistical significance ( $p = 0.053$ ). Future studies should examine differences in cocaine choice between dominant and subordinate monkeys during initial exposure to cocaine, to address whether long-term cocaine self-administration diminishes differences in the relative reinforcing strength of cocaine, as was previously observed for the reinforcing effects of cocaine (Morgan et al., 2002; Czoty et al., 2004).

In summary, the present findings suggest that the ability of social rank to influence cocaine choice in monkeys with extensive histories of cocaine self-administration is limited and evident primarily at an intermediate cocaine dose. However, cocaine choice did not differ at lower or higher cocaine doses, and differences in responsiveness to changes in response requirements were subtle. Future work will be needed to determine whether there are differences in models of relapse to cocaine abuse in this homologous animal model and whether potential cocaine treatments differentially affect cocaine choice according to social rank.

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## Footnotes

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## Legends for Figures

**Fig. 1.** Cocaine choice according to social rank. Data are represented as mean  $\pm$  SEM.

Ordinate, cocaine dose. Values above S indicate data obtained when saline was the alternative to food. Abscissa, (a) % injection-lever responding; (b) drug injections earned; (c) food reinforcers earned. \*,  $p < 0.05$  vs. dominant monkeys.

**Fig. 2.** Effects of increasing cocaine FR on cocaine choice (left, 0.03 mg/kg per injection; right, 0.1 mg/kg per injection) in individual dominant (top) and subordinate monkeys (bottom).

Ordinate, response requirement for cocaine. Abscissa, % injection-lever responding. Open circles represent average ( $\pm$  SEM) response distribution when saline was the alternative to food.

**Fig. 3.** FR increments (left abscissa) and response requirements (right abscissa) that resulted in  $<20\%$  responding on the cocaine-associated lever, as determined under the between-session progressive-ratio schedule. Ordinate, cocaine dose.

**Table 1.** Highest dose of cocaine producing <20% injection-lever responding and response requirement at which allocation of responding was shifted such that >20% of responses were emitted on the injection lever.

	<u>cocaine (mg/kg)</u>	<u>FR value</u>
<i>Dominant</i>		
C-6528	0.01	200
C-5386	0.003	200
C-6530	0.03	100
C-6629	0.01	400
C-6625	0.003	100
<i>Subordinate</i>		
C-6626	0.003	400
C-6217	0.001	200
C-6216	0.01	100
C-6214	<i>a</i>	--
C-6627	0.003	200
C-6529	0.003	400

*a*, no cocaine dose produced <20% injection-lever responding

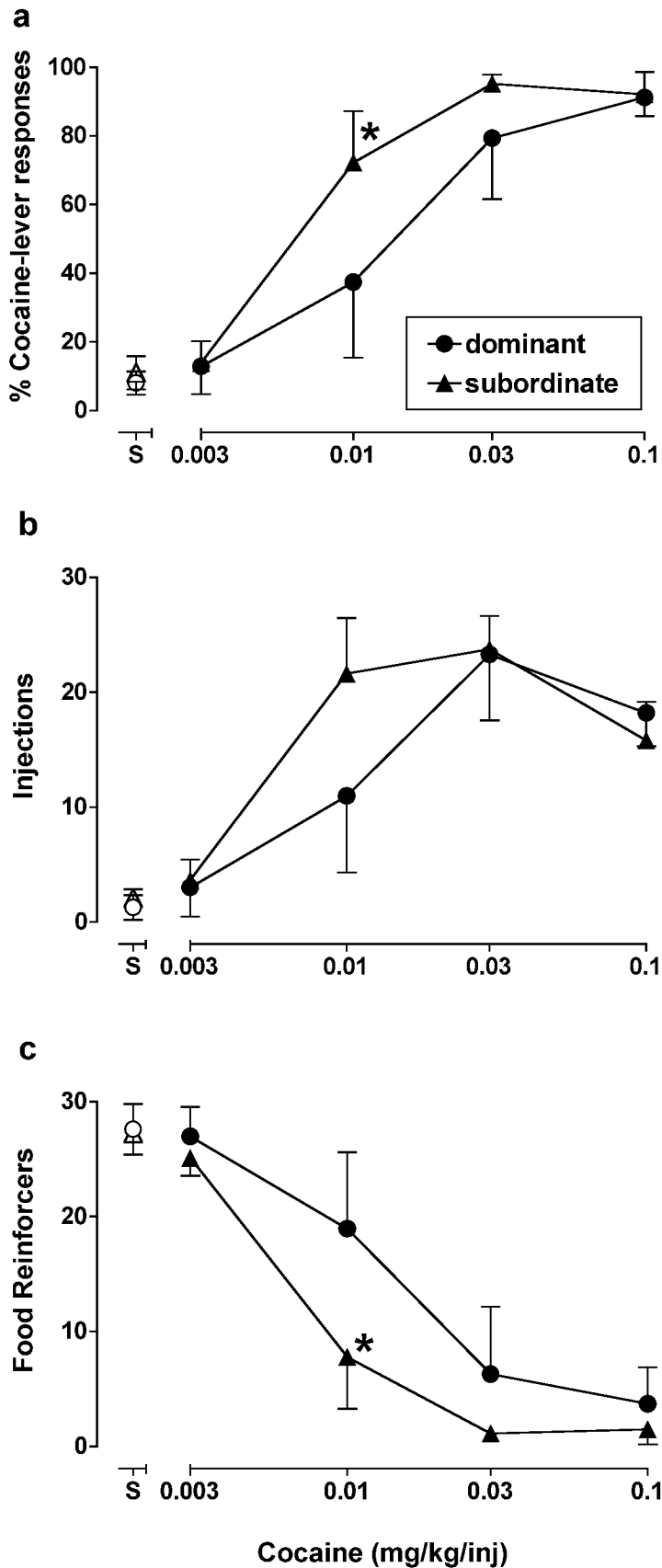


Figure 1.



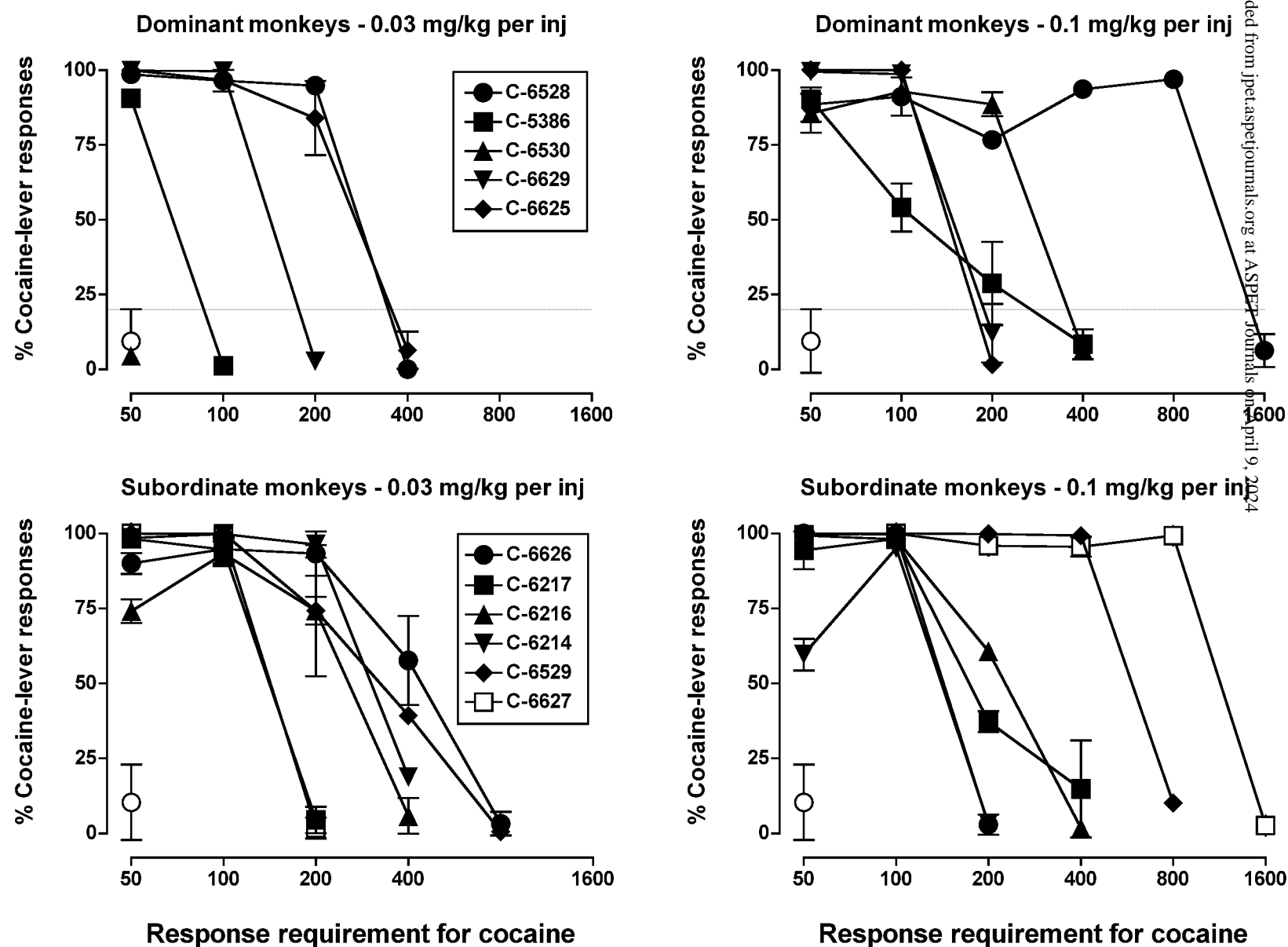


Figure 2

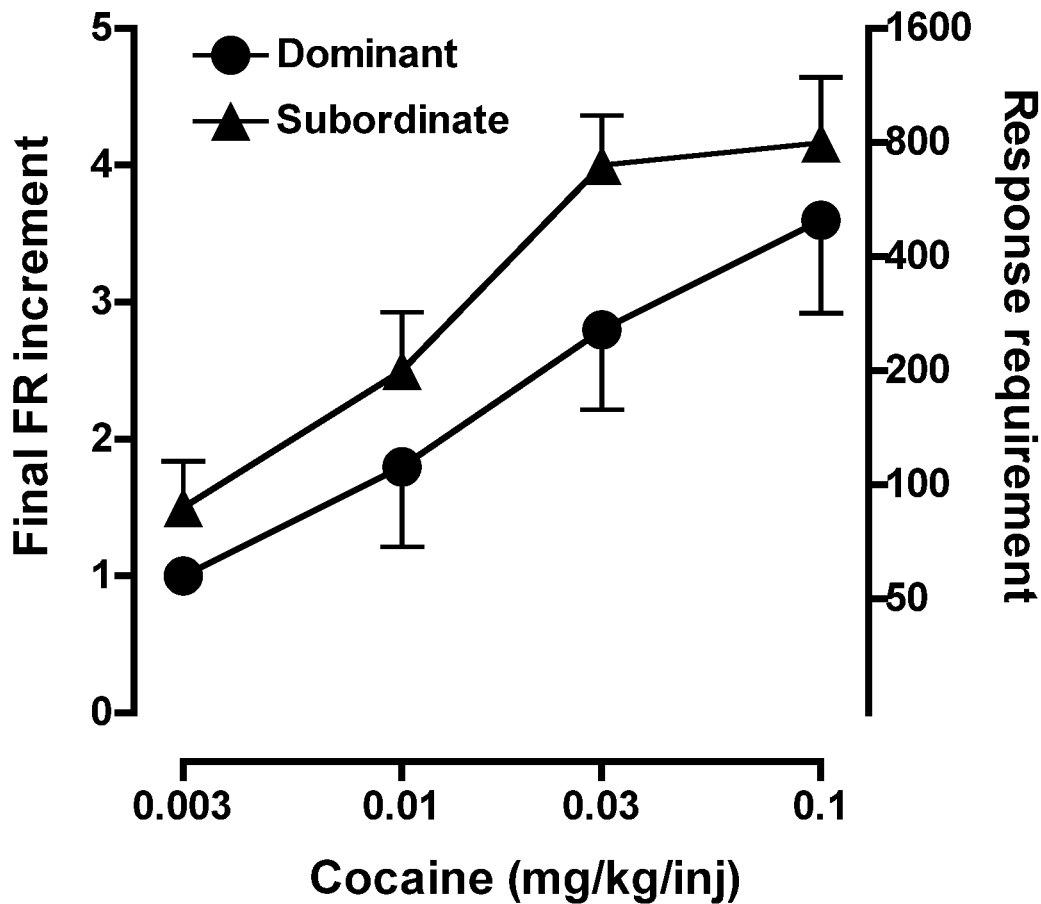


Figure 3